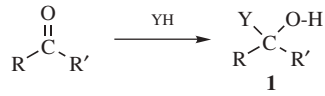
CHAPTER 16

Addition to Carbon–Hetero Multiple Bonds

MECHANISM AND REACTIVITY

The reactions considered in this chapter involve addition to the carbon–oxygen, carbon–nitrogen, and carbon–sulfur double bonds, and the carbon–nitrogen triple bond. The mechanistic study of these reactions is much simpler than that of the additions to carbon–carbon multiple bonds considered in Chapter 15.[1] Most of the questions that concerned us there either do not arise here or can be answered very simply. Since C=O, C=N, and C≡N bonds are strongly polar, with the carbon always the positive end (except for isocyanides, see p. 1466), there is never any doubt about the *orientation* of unsymmetrical addition to these bonds. Nucleophilic attacking species always go to the carbon and electrophilic species to the oxygen or nitrogen. Additions to C=S bonds are much less common,[2] but in these cases the addition can be in the other direction.[3] For example, thiobenzophenone ($Ph_2C{=}S$), when treated with phenyllithium gives, after hydrolysis, benzhydryl phenyl sulfide (Ph_2CHSPh).[4]



1

[1]For a discussion, see Jencks, W.P. *Prog. Phys. Org. Chem.* ***1964***, *2*, 63.

[2]For reviews of thioketones and other compounds with C=S bonds, see Schaumann, E., in Patai, S. *Supplement A: The Chemistry of Double-Bonded Functional Groups*, Vol. 2, pt. 2, Wiley, NY, ***1989***, pp. 1269–1367; Ohno, A. in Oae, S. *Organic Chemistry of Sulfur*, Plenum, NY, ***1977***, pp. 189–229; Mayer, R., in Janssen, M.J. *Organosulfur Chemistry*, Wiley, NY, ***1967***, pp. 219–240; Campaigne, E., in Patai, S. *The Chemistry of the Carbonyl Group*, pt. 1, Wiley, NY, ***1966***, pp. 917–959.

[3]For a review of additions of organometallic compounds to C=S bonds, both to the sulfur (*thiophilic addition*) and to the carbon (*carbophilic addition*), see Wardell, J.L.; Paterson, E.S., in Hartley, F.P.; Patai, S. *The Chemistry of the Metal-Carbon Bond*, Vol. 2, Wiley, NY, ***1985***, pp. 219–338, 261–267.

[4]Beak, P.; Worley, J.W. *J. Am. Chem. Soc.* ***1972***, *94*, 597. For some other examples, see Schaumann, E.; Walter, W. *Chem. Ber.* ***1974***, *107*, 3562; Metzner, P.; Vialle, J.; Vibet, A. *Tetrahedron* ***1978***, *34*, 2289.

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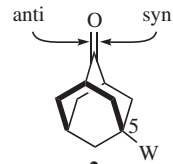
In addition of YH to a ketone to give **1** the product has a stereogenic carbon, but unless there is chirality in R or R′ or YH is optically active, the product must be a racemic mixture because there is no facial bias about the carbonyl. The same holds true for C=N and C=S bonds, since in none of these cases can chirality be present at the heteroatom. The stereochemistry of addition of a single YH to the carbon–nitrogen triple bond could be investigated, since the product can exist in (*E*) and (*Z*) forms (p. 183), but these reactions generally give imine products that undergo further reaction. Of course, if R or R′ *is* chiral, a racemic mixture will not always arise and the stereochemistry of addition can be studied in such cases. Cram's rule (p. 168) allows us to predict the direction of attack of Y in many cases.[5] However, even in this type of study, the relative directions of attack of Y and H are not determined, but only the direction of attack of Y with respect to the rest of the substrate molecule.



2

On p. 1023, it was mentioned that electronic effects can play a part in determining which face of a carbon–carbon double bond is attacked. The same applies to additions to carbonyl groups. For example, in 5-substituted adamantanones (**2**) electron-withdrawing (-*I*) groups W cause the attack to come from the syn face, while electron-donating groups cause it to come from the anti face.[6] In 5,6-disubstituted norborn-2-en-7-one systems, the carbonyl appears to tilt away from the π-bond, with reduction occurring from the more hindered face.[7] An *ab initio* study of nucleophilic addition to 4-*tert*-butylcyclohexanones attempted to predict π-facial selectivity in that system.[8]

The mechanistic picture is further simplified by the fact that free-radical additions to carbon–heteroatom double bonds are not as prevalent.[9] In most cases, it

[5]For a discussion of such rules, see Eliel, E.L. *The Stereochemistry of Carbon Compounds*, McGraw-Hill, NY, ***1962***, pp. 68–74. For reviews of the stereochemistry of addition to carbonyl compounds, see Bartlett, P.A. *Tetrahedron* ***1980***, *36*, 2, 22; Ashby, E.C.; Laemmle, J.T. *Chem. Rev.* ***1975***, *75*, 521; Goller, E.J. *J. Chem. Educ.* ***1974***, *51*, 182; Toromanoff, E. *Top. Stereochem.* ***1967***, *2*, 157.

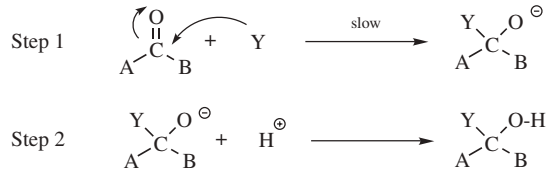
[6]Cheung, C.K.; Tseng, L.T.; Lin, M.; Srivastava, S.; le Noble, W.J. *J. Am. Chem. Soc.* ***1986***, *108*, 1598; Laube, T.; Stilz, H.U. *J. Am. Chem. Soc.* ***1987***, *109*, 5876.

[7]Kumar, V.A.; Venkatesan, K.; Ganguly, B.; Chandrasekhar, J.; Khan, F.A.; Mehta, G. *Tetrahedron Lett.* ***1992***, *33*, 3069.

[8]Yadav, V.K.; Jeyaraj, D.A. *J. Org. Chem.* ***1998***, *63*, 3474. For a discussion of models, see Priyakumar, U.D.; Sastry, G.N.; Mehta, G. *Tetrahedron* ***2004***, *60*, 3465.

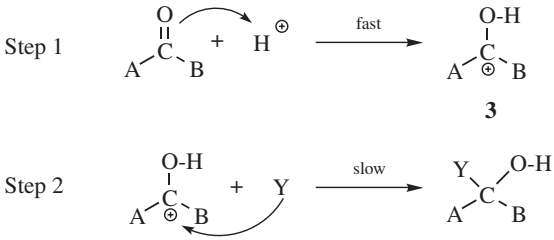
[9]An example is found in **16-31**. For other examples, see Kaplan, L. *J. Am. Chem. Soc.* ***1966***, *88*, 1833; Drew, R.M.; Kerr, J.A. *Int. J. Chem. Kinet.* ***1983***, *15*, 281; Fraser-Reid, B.; Vite, G.D.; Yeung, B.A.; Tsang, R. *Tetrahedron Lett.* ***1988***, *29*, 1645; Beckwith, A.L.J.; Hay, B.P. *J. Am. Chem. Soc.* ***1989***, *111*, 2674; Clerici, A.; Porta, O. *J. Org. Chem.* ***1989***, *54*, 3872; Cossy, J.; Pete, J.P.; Portella, C. *Tetrahedron Lett.* ***1989***, *30*, 7361.

is the nucleophile that forms the first new bond to carbon, and these reactions are regarded as *nucleophilic additions*, which can be represented thus (for the C=O bond, analogously for the others):



The electrophile shown in step 2 is the proton. In almost all the reactions considered in this chapter, the electrophilic atom is either hydrogen or carbon. Note that step 1 is exactly the same as step 1 of the tetrahedral mechanism of nucleophilic substitution at a carbonyl carbon (p. 1255), but carbon groups (A, B = H, alkyl aryl, etc.) are poor leaving groups so that substitution does not compete with addition. For carboxylic acids and their derivatives (B = OH, OR, NH_2, etc.) much better leaving groups are available and acyl substitution predominates (p. 1254). It is thus the nature of A and B that determines whether a nucleophilic attack at a carbon–heteroatom multiple bond will lead to substitution or addition.

It is also possible for the heteroatom (oxygen in a carbonyl) to react as a base, attacking the electrophilic species. This species is most often a proton and the mechanism is

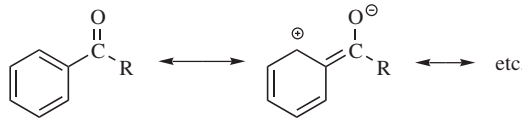


3

Whether the nucleophile attacks the carbon or the heteroatom attacks the electrophilic species, the rate-determining step is usually the one involving nucleophilic attack. It may be observed that many of these reactions can be catalyzed by both acids and bases.[10] Bases catalyze the reaction by converting a reagent of the form YH to the more powerful nucleophile Y^- (see p. 490). Acids catalyze it by converting the substrate to an heteroatom-stabilized cation (formation of **3**), thus making it more attractive to nucleophilic attack. Similar catalysis can also be found with metallic ions (e.g., Ag^+) which act here as Lewis acids.[11] We have mentioned before (p. 242) that ions of type **3** are comparatively stable carbocations because the positive charge is spread by resonance.

[10]For a discussion of acid and base catalysis in these reactions, see Jencks, W.P.; Gilbert, H.F. *Pure Appl. Chem.* ***1977***, *49*, 1021.
[11]Toromanoff, E. *Bull. Soc. Chim. Fr.* ***1962***, 1190.

Reactivity factors in additions to carbon–heteroatom multiple bonds are similar to those for the tetrahedral mechanism of nucleophilic substitution.[12] If A and/or B are electron-donating groups, rates are decreased. Electron-attracting substituents increase rates. This means that aldehydes are more reactive than ketones. Aryl groups are somewhat deactivating compared to alkyl, because of resonance that stabilizes the substrate molecule, but is lost on going to the intermediate:



Double bonds in conjugation with the carbon–heteroatom multiple bond also lower addition rates, for similar reasons but, more important, may provide competition from 1,4-addition (p. 1008). Steric factors are also quite important and contribute to the decreased reactivity of ketones compared with aldehydes. Highly hindered ketones like hexamethylacetone and dineopentyl ketone either do not undergo many of these reactions or require extreme conditions.

Nucleophilic Substitution at an Aliphatic Trigonal Carbon: The Tetrahedral Mechanism

All the mechanisms so far discussed take place at a saturated carbon atom. Nucleophilic substitution is also important at trigonal carbons, especially when the carbon is double bonded to an oxygen, a sulfur, or a nitrogen. Substitution at a carbonyl group (or the corresponding nitrogen and sulfur analogs) most often proceeds by a second-order mechanism, which in this book is called the *tetrahedral*[13] *mechanism*.[14] The IUPAC designation is $A_N + D_N$. The S_N1 mechanisms, involving carbocations, are sometimes found with these substrates, especially with essentially ionic substrates such as $RCO^+ BF_4^-$; there is evidence that in certain cases simple S_N2 mechanisms can take place, especially with a very good leaving group such as Cl^-;[15]

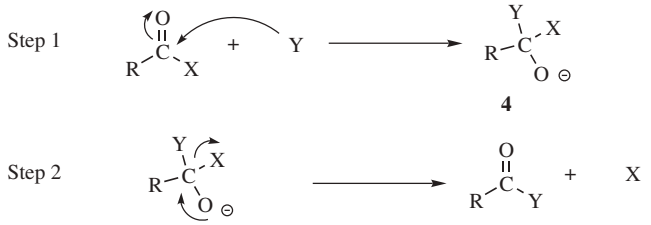
[12]For a review of the reactivity of nitriles, see Schaefer, F.C., in Rappoport, Z. *The Chemistry of the Cyano Group*, Wiley, NY, ***1970***, pp. 239–305.

[13]This mechanism has also been called the "additionelimination mechanism," but in this book we limit this term to the type of mechanism shown on p. $$$.

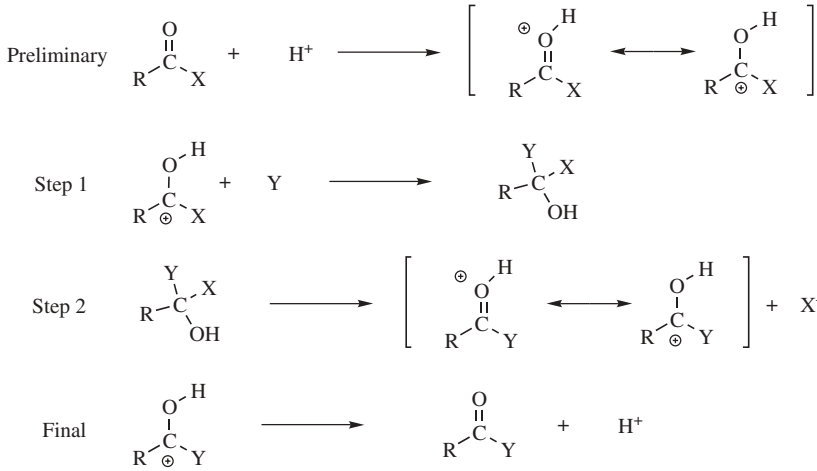
[14]For reviews of this mechanism, see Talbot, R.J.E., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 10, Elsevier, NY, ***1972***, pp. 209–223; Jencks, W.P. *Catalysis in Chemistry and Enzymology*, McGraw-Hill, NY, ***1969***, pp. 463–554; Satchell, D.P.N.; Satchell, R.S., in Patai, S. *The Chemistry of Carboxylic Acids and Esters*, Wiley, NY, ***1969***, pp. 375–452; Johnson, S.L. *Adv. Phys. Org. Chem.* ***1967***, *5*, 237.

[15]For a review, see Williams, A. *Acc. Chem. Res.* ***1989***, *22*, 387. For examples, see Kevill, D.N.; Foss, F.D. *J. Am. Chem. Soc.* ***1969***, *91*, 5054; Haberfield, P.; Trattner, R.B. *Chem. Commun.* ***1971***, 1481; De Tar, D.F. *J. Am. Chem. Soc.* ***1982***, *104*, 7205; Shpan'ko, I.V.; Goncharov, A.N. *J. Org. Chem. USSR* ***1987***, *23*, 2287; Guthrie, J.P.; Pike, D.C. *Can. J. Chem.* ***1987***, *65*, 1951; Kevill, D.N.; Kim, C. *Bull. Soc. Chim. Fr.* ***1988***, 383, *J. Chem. Soc. Perkin Trans. 2* ***1988***, 1353; Bentley, T.W.; Koo, I.S. *J. Chem. Soc. Perkin Trans. 2* ***1989***, 1385. See, however, Buncel, E.; Um, I.H.; Hoz, S. *J. Am. Chem. Soc.* ***1989***, *111*, 971.

and an SET mechanism has also been reported.[16] However, the tetrahedral mechanism is by far the most prevalent. Although this mechanism displays second-order kinetics, it is not the same as the S_N2 mechanism previously discussed. In the tetrahedral mechanism, first Y attacks to give an intermediate containing both X and Y (**4**), and then X leaves. This sequence, impossible at a saturated carbon, is possible at an unsaturated one because the central carbon can release a pair of electrons to the oxygen and so preserve its octet:



When reactions are carried out in acid solution, there may also be a preliminary and a final step:



The hydrogen ion is a catalyst. The reaction rate is increased because it is easier for the nucleophile to attack the carbon when the electron density of the latter has been decreased.[17]

Evidence for the existence of the tetrahedral mechanism is as follows:[18]

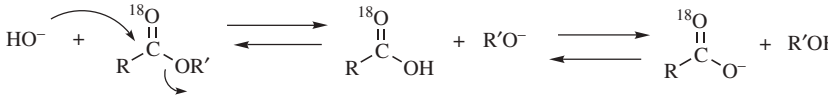
1. The kinetics are first order each in the substrate and in the nucleophile, as predicted by the mechanism.

[16]Bacaloglu, R.; Blaskó, A.; Bunton, C.A.; Ortega, F. *J. Am. Chem. Soc.* ***1990***, *112*, 9336.

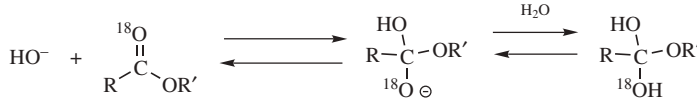
[17]For discussions of general acid and base catalysis of reactions at a carbonyl group, see Jencks, W.P. *Acc. Chem. Res.* ***1976***, *9*, 425; *Chem. Rev.* ***1972***, *72*, 705.

[18]For additional evidence, see Guthrie, J.P. *J. Am. Chem. Soc.* ***1978***, *100*, 5892; Kluger, R.; Chin, J. *J. Am. Chem. Soc.* ***1978***, *100*, 7382; O'Leary, M.H.; Marlier, J.F. *J. Am. Chem. Soc.* ***1979***, *101*, 3300.

2. There is other kinetic evidence in accord with a tetrahedral intermediate. For example, the rate "constant" for the reaction between acetamide and hydroxylamine is not constant, but decreases with increasing hydroxylamine concentration.[19] This is not a smooth decrease; there is a break in the curve. A straight line is followed at low hydroxylamine concentration and another straight line at high concentration. This means that the identity of the rate-determining step is changing. Obviously, this cannot happen if there is only one step: there must be two steps, and hence an intermediate. Similar kinetic behavior has been found in other cases as well,[20] in particular, plots of rate against pH are often bell shaped.
3. Basic hydrolysis has been carried out on carboxylic esters labeled with ^{18}O in the carbonyl group.[21] If this reaction proceeded by the normal S_N2 mechanism, all the ^{18}O would remain in the carbonyl group, even if, in an equilibrium process, some of the carboxylic acid formed went back to the starting material:

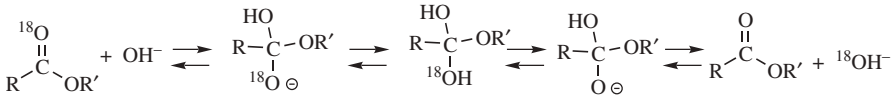


On the other hand, if the tetrahedral mechanism operates



5

then the intermediate **5**, by gaining a proton, becomes converted to the symmetrical intermediate **6**. In this intermediate the OH groups are equivalent, and (except for the small $^{18}O/^{16}O$ isotope effect) either one can lose a proton with equal facility:



5 **6** **7**

The intermediates **5** and **7** can now lose OR′ to give the acid (not shown in the equations given), or they can lose OH to regenerate the carboxylic ester. If **5** goes back to ester, the ester will still be labeled, but if **7** reverts to ester, the

[19]Jencks, W.P.; Gilchrist, M. *J. Am. Chem. Soc.* ***1964***, *86*, 5616.
[20]Hand, E.S.; Jencks, W.P. *J. Am. Chem. Soc.* ***1962***, *84*, 3505; Johnson, S.L. *J. Am. Chem. Soc.* ***1964***, *86*, 3819; Fedor, L.R.; Bruice, T.C. *J. Am. Chem. Soc.* ***1964***, *86*, 5697; ***1965***, *87*, 4138; Kevill, D.N.; Johnson, S.L. *J. Am. Chem. Soc.* ***1965***, *87*, 928; Leinhard, G.E.; Jencks, W.P. *J. Am. Chem. Soc.* ***1965***, *87*, 3855; Schowen, R.L.; Jayaraman, H.; Kershner, L.D. *J. Am. Chem. Soc.* ***1966***, *88*, 3373.
[21]Bender, M.L. *J. Am. Chem. Soc.* ***1951***, *73*, 1626; Bender, M.L.; Thomas, R.J. *J. Am. Chem. Soc.* ***1961***, *83*, 4183, 4189.

^{18}O will be lost. A test of the two possible mechanisms is to stop the reaction before completion and to analyze the recovered ester for ^{18}O. This is just what was done by Bender, who found that in alkaline hydrolysis of methyl, ethyl, and isopropyl benzoates, the esters had lost ^{18}O. A similar experiment carried out for acid-catalyzed hydrolysis of ethyl benzoate showed that here too the ester lost ^{18}O. However, alkaline hydrolysis of substituted benzyl benzoates showed *no* ^{18}O loss.[22] This result does not necessarily mean that no tetrahedral intermediate is involved in this case. If **5** and **7** do not revert to ester, but go entirely to acid, no ^{18}O loss will be found even with a tetrahedral intermediate. In the case of benzyl benzoates, this may very well be happening, because formation of the acid relieves steric strain. Another possibility is that **5** loses OR′ before it can become protonated to **6**.[23] Even the experiments that *do* show ^{18}O loss do not *prove* the existence of the tetrahedral intermediate, since it is possible that ^{18}O is lost by some independent process not leading to ester hydrolysis. To deal with this possibility, Bender and Heck[24] measured the rate of ^{18}O loss in the hydrolysis of ethyl trifluorothioloacetate-^{18}O:

This reaction had previously been shown[25] to involve an intermediate by the kinetic methods mentioned on p. 1256. Bender and Heck showed that the rate of ^{18}O loss and the value of the partitioning ratio k_2/k_3 as determined by the oxygen exchange technique were exactly in accord with these values as previously determined by kinetic methods. Thus the original ^{18}O-exchange measurements showed that there is a tetrahedral species present, though not necessarily on the reaction path, while the kinetic experiments showed that there is some intermediate present, though not necessarily tetrahedral. Bender and Heck's results demonstrate that there is a tetrahedral intermediate and that it lies on the reaction pathway.

4. In some cases, tetrahedral intermediates have been isolated[26] or detected spectrally.[27]

[22]Bender, M.L.; Matsui, H.; Thomas, R.J.; Tobey, S.W. *J. Am. Chem. Soc.* ***1961***, *83*, 4193. See also, Shain, S.A.; Kirsch, J.F. *J. Am. Chem. Soc.* ***1968***, *90*, 5848.

[23]For evidence for this possibility, see McClelland, R.A. *J. Am. Chem. Soc.* ***1984***, *106*, 7579.

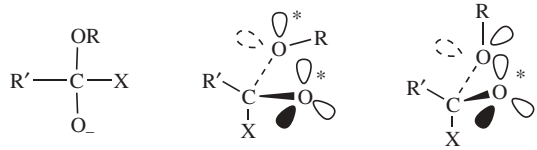
[24]Bender, M.L.; Heck, H. d'A. *J. Am. Chem. Soc.* ***1967***, *89*, 1211.

[25]Fedor, L.R.; Bruice, T.C. *J. Am. Chem. Soc.* ***1965***, *87*, 4138.

[26]Rogers, G.A.; Bruice, T.C. *J. Am. Chem. Soc.* ***1974***, *96*, 2481; Khouri, F.F.; Kaloustian, M.K. *J. Am. Chem. Soc.* ***1986***, *108*, 6683.

[27]For reviews, see Capon, B.; Dosunmu, M.I.; Sanchez, M. de N de M. *Adv. Phys. Org. Chem.* ***1985***, *21*, 37; McClelland, R.A.; Santry, L.J. *Acc. Chem. Res.* ***1983***, *16*, 394; Capon, B.; Ghosh, A.K.; Grieve, D.M.A. *Acc. Chem. Res.* ***1981***, *14*, 306. See also, Lobo, A.M.; Marques, M.M.; Prabhakar, S.; Rzepa, H.S. *J. Chem. Soc., Chem. Commun.* ***1985***, 1113; van der Wel, H.; Nibbering, N.M.M. *Recl. Trav. Chim. Pays-Bas* ***1988***, *107*, 479, 491.

Several studies have been made of the directionality of approach by the nucleophile.[28] Menger has proposed for reactions in general, and specifically for those that proceed by the tetrahedral mechanism, that there is no single definable preferred transition state, but rather a "cone" of trajectories. All approaches within this cone lead to reaction at comparable rates; it is only when the approach comes outside of the cone that the rate falls.



8 **A** **B**

Directionality has also been studied for the second step. Once the tetrahedral intermediate (**4**) is formed, it loses Y (giving the product) or X (reverting to the starting compound). Deslongchamps has proposed that one of the factors affecting this choice is the conformation of the intermediate; more specifically, the positions of the lone pairs. In this view, a leaving group X or Y can depart only if the other two atoms on the carbon both have an orbital antiperiplanar to the C—X or C—Y bond. For example, consider an intermediate **8** formed by attack of $^{-}$OR on a substrate R′COX. Cleavage of the C—X bond with loss of X can take place from conformation **A**, because the two lone-pair orbitals marked * are antiperiplanar to the C—X bond, but not from **B** because only the O^{-} has such an orbital. If the intermediate is in conformation **B**, the OR may leave (if X has a lone-pair orbital in the proper position) rather than X. This factor is called *stereoelectronic control*.[29] Of course, there is free rotation in acyclic intermediates, and many conformations are possible, but some are preferred, and cleavage reactions may take place faster than rotation, so stereoelectronic control can be a factor in some situations. Much evidence has been presented for this concept.[30] More generally, the term *stereoelectronic effects* refers to any case in which orbital

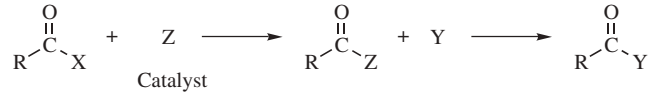
[28]For discussions, see Menger, F.M. *Tetrahedron* ***1983***, *39*, 1013; Liotta, C.L.; Burgess, E.M.; Eberhardt, W.H. *J. Am. Chem. Soc.* ***1984***, *106*, 4849.

[29]It has also been called the "antiperiplanar lone pair hypothesis (ALPH)." For a reinterpretation of this factor in terms of the principle of least nuclear motion (see **15-10**), see Hosie, L.; Marshall, P.J.; Sinnott, M.L. *J. Chem. Soc. Perkin Trans. 2* ***1984***, 1121; Sinnott, M.L. *Adv. Phys. Org. Chem.* ***1988***, *24*, 113.

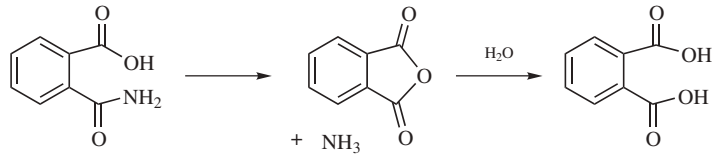
[30]For monographs, see Kirby, A.J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*, Springer, NY, ***1983***; Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*, Pergamon, NY, ***1983***. For lengthy treatments, see Sinnott, M.L. *Adv. Phys. Org. Chem.* ***1988***, *24*, 113; Gorenstein, D.G. *Chem. Rev.* ***1987***, *87*, 1047; Deslongchamps, P. *Heterocycles* ***1977***, *7*, 1271; *Tetrahedron* ***1975***, *31*, 2463. For additional evidence, see Perrin, C.L.; Arrhenius, G.M.L. *J. Am. Chem. Soc.* ***1982***, *104*, 2839; Briggs, A.J.; Evans, C.M.; Glenn, R.; Kirby, A.J. *J. Chem. Soc. Perkin Trans. 2* ***1983***, 1637; Ndibwami, A.; Deslongchamps, P.*Can. J. Chem.* ***1986***, *64*, 1788; Hegarty, A.F.; Mullane, M. *J. Chem. Soc. Perkin Trans. 2* ***1986***, 995. For evidence against the theory, see Perrin, C.L.; Nuñez, O. *J. Am. Chem. Soc.* ***1986***, *108*, 5997; ***1987***, *109*, 522.

position requirements affect the course of a reaction. The backside attack in the S_N2 mechanism is an example of a stereoelectronic effect.

Some nucleophilic substitutions at a carbonyl carbon are *catalyzed* by nucleophiles.[31] There occur, in effect, two tetrahedral mechanisms:



(For an example, see **16-58**). When this happens internally, we have an example of a neighboring-group mechanism at a carbonyl carbon.[32] For example, the hydrolysis of phthalamic acid (**9**) takes place as follows:



9

Evidence comes from comparative rate studies.[33] Thus **9** was hydrolyzed $\sim 10^5$ times faster than benzamide ($PhCONH_2$) at about the same concentration of hydrogen ions. That this enhancement of rate was not caused by the resonance or field effects of COOH (an electron-withdrawing group) was shown by the fact both *o*-nitrobenzamide and terephthalamic acid (the para isomer of **9**) were hydrolyzed more slowly than benzamide. Many other examples of neighboring-group participation at a carbonyl carbon have been reported.[34] It is likely that nucleophilic catalysis is involved in enzyme catalysis of ester hydrolysis.

The attack of a nucleophile on a carbonyl group can result in substitution or addition, though the first step of each mechanism is the same. The main factor that determines the product is the identity of the group X in RCOX. When X is alkyl or hydrogen, addition usually takes place. When X is halogen, OH, OCOR, NH_2, and so on, the usual reaction is substitution.

In both the S_N1 and S_N2 mechanisms, the leaving group departs during the rate-determining step and so directly affects the rate. In the tetrahedral mechanism at a carbonyl carbon, the bond between the substrate and leaving group is still intact during the slow step. Nevertheless, the nature of the leaving group still affects the reactivity in two ways: (*1*) By altering the

[31]For reviews of nucleophilic catalysis, see Bender, M.L. *Mechanisms of Homogeneous Catalysis from Protons to Proteins*, Wiley, NY, ***1971***, pp. 147–179; Jencks, W.P. *Catalysis in Chemistry and Enzymology*, McGraw-Hill, NY, ***1969***, pp. 67–77; Johnson, S.L. *Adv. Phys. Org. Chem.* ***1967***, *5*, p. 271. For a review where Z = a tertiary amine (the most common case), see Cherkasova, E.M.; Bogatkov, S.V.; Golovina, Z.P. *Russ. Chem. Rev.* ***1977***, *46*, 246.

[32]For reviews, see Kirby, A.J.; Fersht, A.R. *Prog. Bioorg. Chem.* ***1971***, *1*, 1; Capon, B. *Essays Chem.* ***1972***, *3*, 127.

[33]Bender, M.L.; Chow, Y.; Chloupek, F.J. *J. Am. Chem. Soc.* ***1958***, *80*, 5380.

[34]For examples, see Bruice, T.C.; Pandit, U.K. *J. Am. Chem. Soc.* ***1960***, *82*, 5858; Kluger, R.; Lam, C. *J. Am. Chem. Soc.* ***1978***, *100*, 2191; Page, M.I.; Render, D.; Bernáth, G. *J. Chem. Soc. Perkin Trans. 2* ***1986***, 867.

TABLE 16.1. The More Important Synthetic Reactions that Take Place by the Tetrahedral Mechanism[a]

Reaction Number	Reaction
16-57	$RCOX + H_2O \longrightarrow RCOOH$
16-58	$RCOOCOR' + H_2O \longrightarrow RCOOH + R'COOH$
16-59	$RCO_2R' + H_2O \longrightarrow RCOOH + R'OH$
16-59	$RCONR'_2 + H_2O \longrightarrow RCOOH + R_2NH$ ($R' = H$, alkyl, aryl)
16-61	$RCOX + R'OH \longrightarrow RCO_2R'$
16-62	$RCOOCOR + R'OH \longrightarrow RCO_2R'$
16-63	$RCOOH + R'OH \longrightarrow RCO_2R'$
16-64	$RCO_2R' + R''OH \longrightarrow RCO_2R'' + R'OH$
16-66	$RCOX + R'COO^- \longrightarrow RCOOCOR'$
10-21	$RCOX + H_2O_2 \longrightarrow RCO_3H$
16-69	$RCOX + R'SH \longrightarrow RCOSR'$
16-72	$RCOX + NHR'_2 \longrightarrow RCONR'_2$ ($R' = H$, alkyl, aryl)
16-73	$RCOOCOR + NHR'_2 \longrightarrow RCONR'_2$ ($R' = H$, alkyl, aryl)
16-74	$RCOOH + NHR'_2 \xrightarrow{\text{coupling agent}} RCONR'_2$ ($R' = H$, alkyl, aryl)
16-75	$RCO_2R' + NHR^2 \longrightarrow RCONR^2$ ($R^2 = H$, alkyl, aryl)
16-79	$RCOOH + SOCl_2 \longrightarrow RCOCl$
19-39	$RCOX + LiAlH(O\text{–}t\text{-}Bu)_3 \longrightarrow RCHO$
19-41	$RCONR'_2 + LiAlH_4 \longrightarrow RCHO$
16-81	$RCOX + R_{2'}CuLi \longrightarrow RCOR'$
16-85	$2RCH_2CO_2R' \longrightarrow RCH_2COCHRCO_2R'$

[a]Catalysts are not shown.

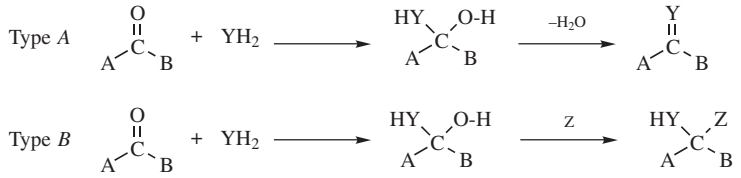
electron density at the carbonyl carbon, the rate of the reaction is affected. The greater the electron-withdrawing character of X, the greater the partial positive charge on C and the more rapid the attack by a nucleophile. (*2*) The nature of the leaving group affects the *position of equilibrium*. In the intermediate **4** (p. 1255), there is competition between X and Y as to which group leaves. If X is a poorer leaving group than Y, then Y will preferentially leave and **4** will revert to the starting compounds. Thus there is a partitioning factor between **4** going on to product (loss of X) or back to starting compound (loss of Y). The sum of these two factors causes the sequence of reactivity to be $RCOCl > RCOOCOR' > RCOOAr > RCOOR' > RCONH_2 > RCONR'_2 > RCOO^-$.[35] Note that this order is approximately the order of decreasing stability of the leaving-group anion. If the leaving group is bulky, it may exert a steric effect and retard the rate for this reason.

For a list of some of the more important reactions that operate by the tetrahedral mechanism, see Table 16.1, which shows the main reactions that proceed by the tetrahedral mechanism.

[35]RCOOH would belong in this sequence just after RCOOAr, but it fails to undergo many reactions for a special reason. Many nucleophiles, instead of attacking the C=O group, are basic enough to take a proton from the acid, converting it to the unreactive $RCOO^-$.

REACTIONS

Many of the reactions in this chapter are simple additions to carbon–hetero multiple bonds, with the reaction ending when the two groups have been added. But in many other cases subsequent reactions take place. We will meet a number of such reactions, but most are of two types:



In type *A*, the initially formed adduct loses water (or, in the case of addition to C=NH, ammonia, etc.), and the net result of the reaction is the substitution of C=Y for C=O (or C=NH, etc.). In type *B*, there is a rapid substitution, and the OH (or NH_2, etc.) is replaced by another group Z, which is often another YH moiety. This substitution is in most cases nucleophilic, since Y usually has an unshared pair and S_N1 reactions occur very well on this type of compound (see p. 482), even when the leaving group is as poor as OH or NH_2. In this chapter, we will classify reactions according to what is initially adding to the carbon–hetero multiple bond, even if subsequent reactions take place so rapidly that it is not possible to isolate the initial adduct.

Most of the reactions considered in this chapter can be reversed. In many cases, we will consider the reverse reactions with the forward ones, in the same section. The reverse of some of the other reactions are considered in other chapters. In still other cases, one of the reactions in this chapter is the reverse of another (e.g., **16-2** and **16-13**). For reactions that are reversible, the principle of microscopic reversibility (p. 309) applies.

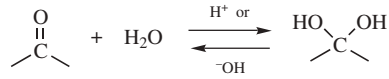
First, we will discuss reactions in which hydrogen or a metallic ion (or in one case phosphorus or sulfur) adds to the heteroatom and second reactions in which carbon adds to the heteroatom. Within each group, the reactions are classified by the nature of the nucleophile. Additions to isocyanides, which are different in character, follow. Acyl substitution reactions that proceed by the tetrahedral mechanism, which mostly involve derivatives of carboxylic acids, are treated at the end.

REACTIONS IN WHICH HYDROGEN OR A METALLIC ION ADDS TO THE HETEROATOM

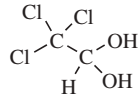
A. Attack by OH (Addition of H_2O)

16-1 The Addition of Water to Aldehydes and Ketones: Formation of Hydrates

O-Hydro-*C*-hydroxy-addition



The adduct formed upon addition of water to an aldehyde or ketone is called a hydrate or *gem*-diol.[36] These compounds are usually stable only in water solution and decompose on distillation; that is, the equilibrium shifts back toward the carbonyl compound. The position of the equilibrium is greatly dependent on the structure of the hydrate. Thus, formaldehyde in water at 20°C exists 99.99% in the hydrated form, while for acetaldehyde this figure is 58%, and for acetone the hydrate concentration is negligible.[37] It has been found, by exchange with ^{18}O, that the reaction with acetone is quite rapid when catalyzed by acid or base, but the equilibrium lies on the side of acetone and water.[38] Since methyl, a *+I* group, inhibits hydrate formation, it may be expected that electron-attracting groups would have the opposite effect, and this is indeed the case. The hydrate of chloral (trichloroacetaldehyde)[39] is a stable crystalline substance. In order for it to revert to chloral, ^{-}OH or H_2O must leave; this is made difficult by the electron-withdrawing character of the Cl_3C group. Some other[40] polychlorinated and polyfluorinated



Chloral hydrate

Hydrate of cyclopropanone

aldehydes and ketones[41] and α-keto aldehydes also form stable hydrates, as do cyclopropanones.[42] In the last case,[43] formation of the hydrate relieves some of the *I* strain (p. 399) of the parent ketone.

[36]For reviews, see Bell, R.P. *The Proton in Chemistry*, 2nd ed., Cornell University Press, Ithaca, NY, ***1973***, pp. 183–187; *Adv. Phys. Org. Chem.* ***1966***, *4*, 1; Le Hénaff, P. *Bull. Soc. Chim. Fr.* ***1968***, 4687.

[37]Bell, R.P.; Clunie, J.C. *Trans. Faraday Soc.* ***1952***, *48*, 439. See also, Bell, R.P.; McDougall, A.O. *Trans. Faraday Soc.* ***1960***, *56*, 1281.

[38]Cohn, M.; Urey, H.C. *J. Am. Chem. Soc.* ***1938***, *60*, 679.

[39]For a review of chloral, see Luknitskii, F.I. *Chem. Rev.* ***1975***, *75*, 259.

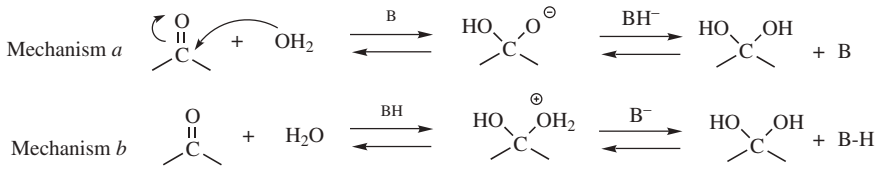
[40]For a discussion, see Schulman, E.M.; Bonner, O.D.; Schulman, D.R.; Laskovics, F.M. *J. Am. Chem. Soc.* ***1976***, *98*, 3793.

[41]For a review of addition to fluorinated ketones, see Gambaryan, N.P.; Rokhlin, E.M.; Zeifman, Yu.V.; Ching-Yun, C.; Knunyants, I.L. *Angew. Chem. Int. Ed.* ***1966***, *5*, 947.

[42]For other examples, see Krois, D.; Lehner, H. *Monatsh. Chem.* ***1982***, *113*, 1019.

[43]Turro, N.J.; Hammond, W.B. *J. Am. Chem. Soc.* ***1967***, *89*, 1028; Schaafsma, S.E.; Steinberg, H.; de Boer, T.J. *Recl. Trav. Chim. Pays-Bas* ***1967***, *86*, 651. For a review of cyclopropanone chemistry, see Wasserman, H.H.; Clark, G.M.; Turley, P.C. *Top. Curr. Chem.* ***1974***, *47*, 73.

The reaction is subject to both general-acid and general-base catalysis; the following mechanisms can be written for basic (B) and acidic (BH) catalysis, respectively:[44]



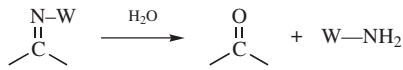
In mechanism *a*, as the H_2O attacks, the base pulls off a proton, and the net result is addition of ^-OH. This can happen because the base is already hydrogen bonded to the H_2O molecule before the attack. In mechanism *b*, because HB is already hydrogen bonded to the oxygen of the carbonyl group, it gives up a proton to the oxygen as the water attacks. In this way, B and HB accelerate the reaction even beyond the extent that they form ^-OH or H_3O^+ by reaction with water. Reactions in which the catalyst donates a proton to the electrophilic reagent (in this case the aldehyde or ketone) in one direction and removes it in the other are called class e reactions. Reactions in which the catalyst does the same to the nucleophilic reagent are called class n reactions.[45] Thus the acid-catalyzed process here is a class e reaction, while the base catalyzed process is a class n reaction.

For the reaction between ketones and H_2O_2, see **17-37**.

There are no OS references, but see OS **VIII**, 597, for the reverse reaction.

16-2 Hydrolysis of the Carbon-Nitrogen Double Bond[46]

Oxo-de-alkylimino-bisubstitution, and so on



Compounds containing carbon–nitrogen double bonds can be hydrolyzed to the corresponding aldehydes or ketones.[47] For imines (W = R or H) the hydrolysis is easy and can be carried out with water. When W = H, the imine is seldom stable enough for isolation, and in aqueous media hydrolysis usually occurs *in situ*, without isolation. The hydrolysis of Schiff bases (W = Ar) is more difficult and requires

[44]Bell, R.P.; Rand, M.H.; Wynne-Jones, K.M.A. *Trans. Faraday Soc.* ***1956***, *52*, 1093; Pocker, Y. *Proc. Chem. Soc.* ***1960***, 17; Sørensen, P.E.; Jencks, W.P. *J. Am. Chem. Soc.* ***1987***, *109*, 4675. For a comprehensive treatment, see Lowry, T.H.; Richardson, K.S. *Mechanism and Theory in Organic Chemistry*, 3rd ed., Harper and Row, NY, ***1987***, pp. 662–680. For a theoretical treatment see Wolfe, S.; Kim, C.-K.; Yang, K.; Weinberg, N.; Shi, Z. *J. Am. Chem. Soc.* ***1995***, *117*, 4240.

[45]Jencks, W.P. *Acc. Chem. Res.* ***1976***, *9*, 425.

[46]For a review, see Khoee, S.; Ruoho, A.E. *Org. Prep. Proceed. Int.* ***2003***, *35*, 527.

[47]The proton affinities of imines have been determined, see Hammerum, S.; Sølling, T.I. *J. Am. Chem. Soc.* ***1999***, *121*, 6002.

acid or base catalysis. Oximes (W = OH), arylhydrazones (W = NHAr), and, most easily, semicarbazones (W = $NHCONH_2$) can also be hydrolyzed. Often a reactive aldehyde (e.g., formaldehyde) is added to combine with the liberated amine.

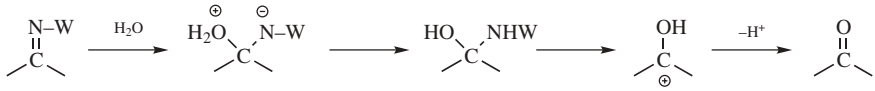
A number of other reagents[48] have been used to cleave C=N bonds, especially those not easily hydrolyzable with acidic or basic catalysts or that contain other functional groups that are attacked under these conditions. Oximes have been converted to the corresponding aldehyde or ketone[49] by treatment with, among other reagents, NBS in water,[50] glyoxylic acid (HCOCOOH),[51] Chloramine-T[52] Caro's acid on SiO_2,[53] HCOOH on SiO_2 with microwave irradiation,[54] bromosulfonamides,[55] $SiBr_4$ on wet silica,[56] and $KMnO_4$ on Al_2O_3[57] or on zeolite.[58] Chromate oxidizing agents can be quite effective, including tetraethylammonium permanganate,[59] tetraalkylammonium dichromate with microwave irradiation,[60] pyridinium fluorochromate,[61] quinolinium fluorochromate[62] or dichromate.[63] Alkaline H_2O_2,[64] iodine in acetonitrile,[65] singlet oxygen with NaOMe/MeOH[66] and with an ionic liquids on SiO_2[67] have also been used. Transition-metal compounds have been used, including $SbCl_5$,[68] $Co_2(CO)_8$[69] $Hg(NO_3)_2/SiO_2$,[70] or $BiBr_3$—$Bi(OTf)_3$ in aqueous media,[71] $Bi(NO_3)_3/SiO_2$,[72] a nickel(II) complex

[48]For a list of reagents, with references, see Ranu, B.C.; Sarkar, D.C. *J. Org. Chem.* ***1988***, *53*, 878.
[49]For a review, see Corsaro, A.; Chiacchio, U.; Pistarià, V. *Synthesis* ***2001***, 1903.
[50]Bandgar, B.P.; Makone, S.S. *Org. Prep. Proceed. Int.* ***2000***, *32*, 391.
[51]Chavan, S.P.; Soni, P. *Tetrahedron Lett.* ***2004***, *45*, 3161.
[52]Padmavathi, V.; Reddy, K.V.; Padmaja, A.; Venugopalan, P. *J. Org. Chem.* **2003**, *68*, 1567.
[53]Movassagh, B.; Lakouraj, M.M.; Ghodrati, K. *Synth. Commun.* ***2000***, *30*, 4501.
[54]A solvent-free reaction. See Zhou, J.-F.; Tu, S.-J.; Feng, J.-C. *Synth.Commun.* ***2002***, *32*, 959.
[55]Khazaei, A.; Vaghei, R.G.; Tajbakhsh, M. *Tetrahedron Lett.* ***2001***, *42*, 5099.
[56]De, S.K. *Tetrahedron Lett.* ***2003***, *44*, 9055.
[57]Chrisman, W.; Blankinship, M.J.; Taylor, B.; Harris, C.E. *Tetrahedron Lett.* ***2003***, *33*, 4775; Imanzadeh, G.H.; Hajipour, A.R.; Mallakpour, S.E. *Synth. Commun.* ***2003***, *33*, 735.
[58]Jadhav, V.K.; Wadgaonkar, P.P.; Joshi, P.L.; Salunkhe, M.M. *Synth. Commun.* ***1999***, *29*, 1989.
[59]Bigdeli, M.A.; Nikje, M.M.A.; Heravi, M.M. *J. Chem. Res. (S)* ***2001***, 496.
[60]Hajipour, A.R.; Mallakpour, S.E.; Khoee, E. *Synth. Commun.* ***2002***, *32*, 9.
[61]Ganguly, N.C.; De, P.; Sukai, A.K.; De, S. *Synth. Commun.* ***2002***, *32*, 1.
[62]Bose, D.S.; Narasaiah, A.V. *Synth. Commun.* ***2000***, *30*, 1153. See also, Ganguly, N.C.; Sukai, A.K.; De, S.; De, P. *Synth. Commun.* ***2001***, *31*, 1607.
[63]Sadeghi, M.M.; Mohammadpoor-Baltork, I.; Azarm, M.; Mazidi, M.R. *Synth. Commun.* ***2001***, *31*, 435. See also, Hajipour, A.R.; Mallakpour, S.E.; Mohammadpoor-Baltork, I.; Khoee, S. *Synth. Commun.* ***2001***, *31*, 1187; Tajbakhsh, M.; Heravi, M.M.; Mohanazadeh, F.; Sarabi, S.; Ghassemzadeh, M. *Monat. Chem.* ***2001***, *132*, 1229; Zhang, G.-S.; Yang, D.-H.; Chen. M.-F. *Org. Prep. Proceed. Int.* ***1998***, *30*, 713.
[64]Ho, T. *Synth. Commun.* ***1980***, *10*, 465.
[65]Yadav, J.S.; Sasmal, P.K.; Chand, P.K. *Synth. Commun.* ***1999***, *29*, 3667.
[66]Öcal, N.; Erden, I. *Tetrahedron Lett.* ***2001***, *42*, 4765.
[67]BAcIm BF_4, 3-butyl-1-(CH_2COOH)imidazolium tetrafluoroborate: Li, D.; Shi, F.; Guo, S.; Deng, Y. *Tetrahedron Lett.* ***2004***, *45*, 265. In Dmim BF_4, 1-decyl-3-methyl imidazolium tetrafluoroborate: Li, D.; Shi, F.; Deng, Y. *Tetrahedron Lett.* ***2004***, *45*, 6791.
[68]Narsaiah, A.V.; Nagaiah, K. *Synthesis* ***2003***, 1881.
[69]Mukai, C.; Nomura, I.; Kataoka, O.; Hanaoka, M. *Synthesis* ***1999***, 1872.
[70]De, S.K. *Synth. Commun.* 2004, *34*, 2289.
[71]Arnold, J.N.; Hayes, P.D.; Kohaus, R.L.; Mohan, R.S. *Tetrahedron Lett.* ***2003***, *44*, 9173.
[72]Samajdar, S.; Basu, M.K.; Becker, F.F.; Banik, B.K. *Synth. Commun.* ***2002***, *32*, 1917.

with trimethylacetaldehyde,[73] CuCl on Kieselguhr with oxygen,[74] $Bi(NO_3)_3$/$Cu(OAc)_2$ on Montmorillonite K10,[75] CrO_3-SiO_2,[76] and In addition, peroxomonosulfate-SiO_2,[77] $Cu(NO_3)_2$—SiO_2,[78] $Zn(NO_3)_2$-SiO_2,[79] and clay (Clayan)[80] have all been used with microwave irradiation. Phenylhydrazones can be converted to a ketone using Oxone® and $KHCO_3$,[81] polymer-bound iodonium salts,[82] or $KMnO_4$ on wet SiO_2.[83] Dimethylhydrazones have been converted to ketones by heating with potassium carbonate in dimethyl sulfate,[84] with $MeReO_3/H_2O_2$ in acetic acid-acetonitrile,[85] with $Pd(OAc)_2/SnCl_2$ in aq. DMF,[86] $FeSO_4 \cdot 7\,H_2O$ in chloroform,[87] Me_3SiCl/NaI in acetonitrile with 1% water,[88] $[Ni(en)_3]_2S_2O_3$, where en = ethylenediamine, in chloroform,[89] or $CeCl_3 \cdot 7\,H_2O$—SiO_2 with microwave irradiation.[90]

Hydrazones, such as RAMP or SAMP (see p. 633) can be hydrolyzed with aq. $CuCl_2$.[91] Tosylhydrazones can be hydrolyzed to the corresponding ketones with aq. acetone and BF_3–etherate,[92] as well as with other reagents.[93] Semicarbazones have been cleaved with ammonium chlorochromates on alumina[94] $(Bu_4N)_2S_2O_8$,[95] $Mg(HSO_4)_2$ on wet silica,[96] or by $SbCl_3$ with microwave irradiation.[97]

The hydrolysis of carbon–nitrogen double bonds involves initial addition of water and elimination of a nitrogen moiety:

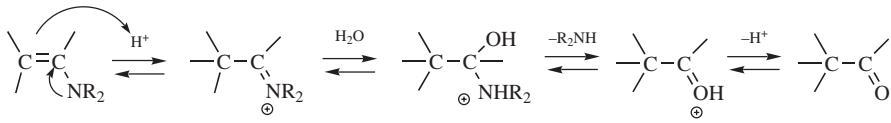


[73]Blay, G.; Benach, E.; Fernández, I.; Galletero, S.; Pedro, J.R.; Ruiz, R. *Synthesis* ***2000***, 403.
[74]Hashemi, M.M.; Beni, Y.A. *Synth. Commun.* ***2001***, *31*, 295.
[75]Nattier, B.A.; Eash, K.J.; Mohan, R.S. *Synthesis* ***2001***, 1010.
[76]Bendale, P.M.; Khadilkar, B.M. *Synth. Commun.* ***2000***, *30*, 665.
[77]Bose, D.S.; Narsaiah, A.V.; Lakshminarayana, V. *Synth. Commun.* ***2000***, *30*, 3121.
[78]Ghiaci, M.; Asghari, J. *Synth. Commun.* ***2000***, *30*, 3865.
[79]Tamami, B.; Kiasat, A.R. *Synth. Commun.* ***2000***, *30*, 4129.
[80]Meshram, H.M.; Srinivas, D.; Reddy, G.S.; Yadav, J.S. *Synth. Commun.* ***1998***, *28*, 4401; 2593.
[81]Hajipour, A.R.; Mahboubghah, N. *Org. Prep Proceed. Int.* ***1999***, *31*, 112.
[82]Chen, D.-J.; Cheng, D.-P.; Chen, Z.-C. *Synth. Commun.* ***2001***, *31*, 3847.
[83]Hajipour, A.R.; Adibi, H.; Ruoho, A.E. *J. Org. Chem.* ***2003***, *68*, 4553.
[84]Kamal, A.; Arifuddin, M.; Rao, N.V. *Synth. Commun.* ***1998***, *28*, 3927.
[85]Stanković, S.; Espenson, J.H. *J. Org. Chem.* ***2000***, *65*, 2218.
[86]Mino, C.; Hirota, T.; Fujita, N.; Yamashita, M. *Synthesis* ***1999***, 2024.
[87]Nasreen, A.; Adapa, S.R. *Org. Prep. Proceed. Int.* ***1999***, *31*, 573.
[88]Kamal, A.; Ramana, K.V.; Arifuddin, M. *Chem. Lett.* ***1999***, 827.
[89]Kamal, A.; Arifuddin, M.; Rao, M.V. *Synlett* ***2000***, 1482.
[90]Yadav, J.S.; Subba Reddy, B.V.; Reddy, M.S.K.; Sabitha, G. *Synlett* ***2001***, 1134.
[91]Enders, D.; Hundertmark, T.; Lazny, R. *Synth. Commun.* ***1999***, *29*, 27.
[92]Sacks, C.E.; Fuchs, P.L. *Synthesis* ***1976***, 456.
[93]DDQ with dichloromethane/water: Chandrasekhar, S.; Reddy, Ch.R.; Reddy, M.V. *Chem. Lett.* ***2000***, 430. For references, see Jiricny, J.; Orere, D.M.; Reese, C.B. *Synthesis* ***1970***, 919.
[94]Zhang, G.-S.; Gong, H.; Yang, D.-H.; Chen, M.-F. *Synth. Commun.* ***1999***, *29*, 1165; Gong, H.; Zhang, G.-S. *Synth. Commun.* ***1999***, *29*, 2591.
[95]Chen, F.-E.; Liu, J.-P.; Fu, H.; Peng, Z.-Z.; Shao, L.-Y. *Synth. Commun.* ***2000***, *30*, 2295.
[96]Shirini, F.; Zolfigol, M.A.; Mallakpour, B.; Mallakpour, S.E.; Hajipour, A.R.; Baltork, I.M. *Tetrahedron Lett.* ***2002***, *43*, 1555.
[97]Mitra, A.K.; De, A.; Karchaudhuri, N. *Synth. Commun.* ***2000***, *30*, 1651.

It is thus an example of reaction type *A* (p. 1261). The sequence shown is generalized.[98] In specific cases, there are variations in the sequence of the steps, depending on acid or basic catalysis or other conditions.[99] Which step is rate determining also depends on acidity and on the nature of W and of the groups connected to the carbonyl.[100]

10

Iminium ions (**10**)[101] would be expected to undergo hydrolysis quite readily, since there is a contributing form with a positive charge on the carbon. Indeed, they react with water at room temperature.[102] Acid-catalyzed hydrolysis of enamines (the last step of the Stork reaction, **10-69** involves conversion to iminium ions:[103]



The mechanism of enamine hydrolysis is thus similar to that of vinyl ether hydrolysis (**10-6**).

OS **I**, 217, 298, 318, 381; **II**, 49, 223, 234, 284, 310, 333, 395, 519, 522; **III**, 20, 172, 626, 818; **IV**, 120; **V**, 139, 277, 736, 758; **VI**, 1, 358, 640, 751, 901, 932; **VII**, 8; **65**, 108, 183; **67**, 33; **76**, 23.

Related to this process is the hydrolysis of isocyanates or isothiocyanates[104] where addition of water to the carbon–nitrogen double bond would give an *N*-substituted carbamic acid (**11**). Such compounds are unstable and break down to

[98]For reviews of the mechanism, see Bruylants, A.; Feytmants-de Medicis, E., in Patai, S. *The Chemistry of the Carbon–Nitrogen Double Bond*, Wiley, NY, ***1970***, pp. 465–504; Salomaa, P., in Patai, S. *The Chemistry of the Carbonyl Group* pt. 1, Wiley, NY, ***1966***, pp. 199–205.

[99]For example, see Reeves, R.L. *J. Am. Chem. Soc.* ***1962***, *82*, 3332; Sayer, J.M.; Conlon, E.H. *J. Am. Chem. Soc.* ***1980***, *102*, 3592.

[100]Cordes, E.H.; Jencks, W.P. *J. Am. Chem. Soc.* ***1963***, *85*, 2843.‘

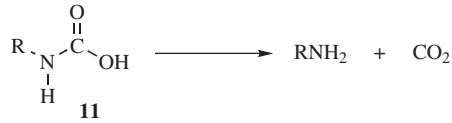
[101]For a review of iminium ions, see Böhme, H.; Haake, M. *Adv. Org. Chem.* ***1976***, *9*, pt. 1, 107.

[102]Hauser, C.R.; Lednicer, D. *J. Org. Chem.* ***1959***, *24*, 46. For a study of the mechanism, see Gopalakrishnan, G.; Hogg, J.L. *J. Org. Chem.* ***1989***, *54*, 768.

[103]Maas, W.; Janssen, M.J.; Stamhuis, E.J.; Wynberg, H. *J. Org. Chem.* ***1967***, *32*, 1111; Sollenberger, P.Y.; Martin, R.B. *J. Am. Chem. Soc.* ***1970***, *92*, 4261. For a review of enamine hydrolysis, see Stamhuis, E.J.; Cook, A.G., in Cook *Enamines*, 2nd ed.; Marcel Dekker, NY, ***1988***, pp. 165–180.

[104]For a study of the mechanism, see Castro, E.A.; Moodie, R.B.; Sansom, P.J. *J. Chem. Soc. Perkin Trans. 2* ***1985***, 737. For a review of the mechanisms of reactions of isocyanates with various nucleophiles, see Satchell, D.P.N.; Satchell, R.S. *Chem. Soc. Rev.* ***1975***, *4*, 231.

carbon dioxide (or COS in the case of isothiocyanates) and the amine:

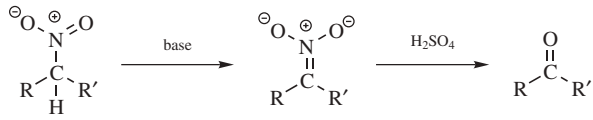


11

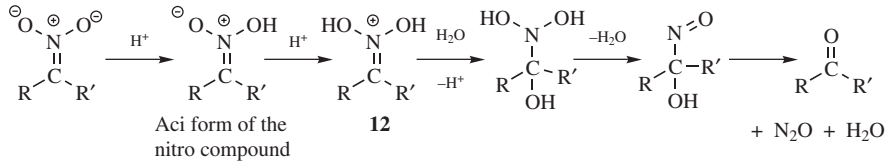
OS **II**, 24; **IV**, 819; **V**, 273; **VI**, 910.

16-3 Hydrolysis of Aliphatic Nitro Compounds

Oxo-de-hydro,nitro-bisubstitution



Primary or secondary aliphatic nitro compounds can be hydrolyzed, respectively, to aldehydes or ketones, by treatment of their conjugate bases with sulfuric acid. This is called the *Nef reaction*.[105] Tertiary aliphatic nitro compounds do not give the reaction because they cannot be converted to their conjugate bases. Like **16-2**, this reaction involves hydrolysis of a C=N double bond. A possible mechanism is[106]



Aci form of the nitro compound

12

Intermediates of type **12** have been isolated in some cases.[107]

The conversion of nitro compounds to aldehydes or ketones has been carried out with better yields and fewer side reactions by several alternative methods.[108] Among these are treatment of the nitro compound with tin complexes and $NaHSO_3$,[109] activated dry silica gel,[110] or 30% H_2O_2–K_2CO_3,[111] *t*-BuOOH and a catalyst,[112]

[105]For reviews, see Pinnick, H.W. *Org. React.* ***1990***, *38*, 655; Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Academic Press, NY, ***1988***, pp. 220–231, 416–419.

[106]Hawthorne, M.F. *J. Am. Chem. Soc.* ***1957***, *79*, 2510. A similar mechanism, but with some slight differences, was suggested earlier by van Tamelen, E.E.; Thiede, R.J. *J. Am. Chem. Soc.* ***1952***, *74*, 2615. See also, Sun, S.F.; Folliard, J.T. *Tetrahedron* ***1971***, *27*, 323.

[107]Feuer, H.; Spinicelli, L.F. *J. Org. Chem.* ***1977***, *42*, 2091.

[108]For a review, see Ballini, R.; Petrini, M. *Tetrhaedron* ***2004***, *60*, 1017.

[109]Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* ***1990***, *31*, 7499.

[110]Keinan, E.; Mazur, Y. *J. Am. Chem. Soc.* ***1977***, *99*, 3861.

[111]Olah, G.A.; Arvanaghi, M.; Vankar, Y.D.; Prakash, G.K.S. *Synthesis* ***1980***, 662.

[112]Bartlett, P.A.; Green III, F.R.; Webb, T.R. *Tetrahedron Lett.* ***1977***, 331.

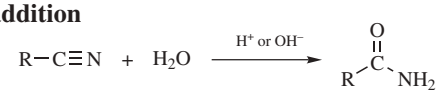
DBU in acetonitrile,[113] NaH and $Me_3SiOOSiMe_3$,[114] $NaNO_2$ in aq. DMSO,[115] or ceric ammonium nitrate (CAN).[116] The reaction of Al—$NiCl_2$•6 H_2O in THF converted α,β-unsaturated nitro compounds to the corresponding aldehyde, $PhCH{=}CHNO_2 \rightarrow PhCH_2CHO$.[117]

When *primary* nitro compounds are treated with sulfuric acid without previous conversion to the conjugate bases, they give carboxylic acids. Hydroxamic acids are intermediates and can be isolated, so that this is also a method for preparing them.[118] Both the Nef reaction and the hydroxamic acid process involve the aci form; the difference in products arises from higher acidity, for example, a difference in sulfuric acid concentration from 2 to 15.5 *M* changes the product from the aldehyde to the hydroxamic acid.[119] The mechanism of the hydroxamic acid reaction is not known with certainty, but if higher acidity is required, it may be that the protonated aci form of the nitro compound is further protonated.

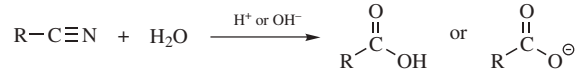
OS **VI**, 648; **VII**, 414. See also OS **IV**, 573.

16-4 Hydrolysis of Nitriles

***NN*-Dihydro-*C*-*oxo*-biaddition**



Hydroxy,oxo-de-nitrilo-tersubstitution



Nitriles can be hydrolyzed to give either amides or carboxylic acids.[120] The amide is formed initially, but since amides are also hydrolyzed with acid or basic treatment, the carboxylic acid is readily formed. When the acid is desired,[121] the reagent of choice is aq. NaOH containing ~6–12% H_2O_2, though acid-catalyzed hydrolysis is also frequently carried out. A ''dry'' hydrolysis of nitriles has been reported.[122] The hydrolysis of nitriles to carboxylic acids is one of the best methods for the preparation of these compounds. Nearly all nitriles give the reaction, with either acidic or basic catalysts. Hydrolysis of cyanohydrins, RCH(OH)CN, is usually carried out under acidic conditions, because basic solutions cause competing

[113]Ballini, R.; Bosica, G.; Fiorini, D.; Petrini, M. *Tetahedron Lett.* ***2002***, *43*, 5233.
[114]Shahi, S.P.; Vankar, Y.D. *Synth. Commun.* ***1999***, *29*, 4321.
[115]Gissot, A.; N'Gouela, S.; Matt, C.; Wagner, A.; Mioskowski, C. *J. Org. Chem.* ***2004***, *69*, 8997.
[116]Olah, G.A.; Gupta, B.G.B. *Synthesis* ***1980***, 44.
[117]Bezbarua, M.S.; Bez, G.; Barua, N.C. *Chem. Lett.* ***1999***, 325.
[118]Hydroxamic acids can also be prepared from primary nitro compounds with SeO_2 and Et3N: Sosnovsky, G.; Krogh, J.A. *Synthesis* ***1980***, 654.
[119]Kornblum, N.; Brown, R.A. *J. Am. Chem. Soc.* ***1965***, *87*, 1742. See also, Cundall, R.B.; Locke, A.W. *J. Chem. Soc. B* ***1968***, 98; Edward, J.T.; Tremaine, P.H. *Can J. Chem.* ***1971***, *49*, 3483, 3489, 3493.
[120]For reviews, see Zil'berman, E.N. *Russ. Chem. Rev.* ***1984***, *53*, 900; Compagnon, P.L.; Miocque, M. *Ann. Chim. (Paris)* ***1970***, *[14] 5*, 11, 23.
[121]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1986–1987.
[122]Chemat, F.; Poux, M.; Berlan, J. *J. Chem. Soc. Perkin Trans. 2* ***1996***, 1781; ***1994***, 2597.

reversion of the cyanohydrin to the aldehyde and CN^-. However, cyanohydrins have been hydrolyzed under basic conditions with borax or alkaline borates.[123] Enzymatic hydrolysis with *Rhodococcus* sp AJ270 has also been reported.[124] In methanol with BF_3•OEt_2, benzonitrile is converted to methyl benzoate.[125]

There are a number of procedures for stopping at the amide stage,[126] among them the use of concentrated H_2SO_4; 2 equivalents of chlorotrimethylsilane followed by H_2O,[127] aq. NaOH with PEG-400 and microwave irradiation,[128] $NaBO_3$ with 4 equivalents of water and microwave irradiation,[129] heating on neutral alumina,[130] Oxone®,[131] and dry HCl followed by H_2O. The same result can also be obtained by use of water and certain metal ions or complexes;[132] a ruthenium catalyst on alumina with water,[133] MnO_2/SiO_2 with microwave irradiation,[134] $Hg(OAc)_2$ in HOAc;[135] or 2-mercaptoethanol in a phosphate buffer.[136] Nitriles can be hydrolyzed to the carboxylic acids without disturbing carboxylic ester functions also present, by the use of tetrachloro- or tetrafluorophthalic acid.[137] Nitriles are converted to thioamides $ArC(=S)NH_2$ with ammonium sulfide $(NH_4)_2S$ in methanol, with microwave irradiation.[138]

Thiocyanates are converted to thiocarbamates in a similar reaction:[139] $R{-}S{-}C{\equiv}N + H_2O \rightarrow R{-}S{-}C{-}O\ NH_2$. Hydrolysis of cyanamides gives amines, produced by the breakdown of the unstable carbamic acid intermediates: $R_2NCN \rightarrow [R_2NCOOH] \rightarrow R_2NH$.

OS **I**, 21, 131, 201, 289, 298, 321, 336, 406, 436, 451; **II**, 29, 44, 292, 376, 512, 586 (see, however, **V**, 1054), 588; III; 34, 66, 84, 88, 114, 221, 557, 560, 615, 851; **IV**, 58, 93, 496, 506, 664, 760, 790; **V**, 239; **VI**, 932; **76**, 169. Also see, OS **III**, 609; **IV**, 359, 502; **66**, 142.

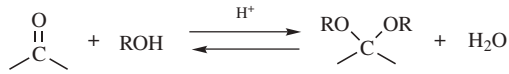
[123]Jammot, J.; Pascal, R.; Commeyras, A. *Tetrahedron Lett.* ***1989***, *30*, 563.
[124]Wang, M.-X.; Lin, S.-J. *J. Org. Chem.* ***2002***, *67*, 6542.
[125]Jayachitra, G.; Yasmeen, N..; Rao, K.S.; Ralte, S.L.; Srinivasan, R.; Singh, A.K. *Synth. Commun.* ***2003***, *33*, 3461.
[126]For a discussion, see Beckwith, A.L.J., in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 119–125. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1988–1990.
[127]Basu, M.K.; Luo, F.-T. *Tetrahedron Lett.* ***1998***, *39*, 3005.
[128]Bendale, P.M.; Khadilkar, B.M. *Synth. Commun.* ***2000***, *30*, 1713.
[129]Sharifi, A.; Mohsenzadeh, F.; Mohtihedi, M.M.; Saidi, M.R.; Balalaie, S. *Synth. Commun.* ***2001***, *31*, 431.
[130]Wligus, C.P.; Downing, S.; Molitor, E.; Bains, S.; Pagni, R.M.; Kabalka, G.W. *Tetrahedron Lett.* ***1995***, *36*, 3469.
[131]Bose, D.S.; Baquer, S.M. *Synth. Commun.* ***1997***, *27*, 3119.
[132]For example, see Bennett, M.A.; Yoshida, T. *J. Am. Chem. Soc.* ***1973***, *95*, 3030; Paraskewas, S. *Synthesis* ***1974***, 574; McKenzie, C.J.; Robson, R. *J. Chem. Soc., Chem. Commun.* ***1988***, 112.
[133]Yamaguchi, K.; Matsushita, M.; Mizuno, N. *Angew. Chem. Int. Ed.* ***2004***, *43*, 1576.
[134]A solvent-free reaction. See Khadilkar, B.M.; Madyar, V.R. *Synth. Commun.* ***2002***, *32*, 1731.
[135]Plummer, B.F.; Menendez, M.; Songster, M. *J. Org. Chem.* ***1989***, *54*, 718.
[136]Lee, Y.B.; Goo, Y.M.; Lee,Y.Y.; Lee, J.K. *Tetrahedron Lett.* ***1989***, *30*, 7439.
[137]Rounds, W.D.; Eaton, J.T.; Urbanowicz, J.H.; Gribble, G.W. *Tetrahedron Lett.* ***1988***, *29*, 6557.
[138]Bagley, M.C.; Chapaneri, K.; Glover, C.; Merritt, E.A. *Synlett* ***2004*** 2615.
[139]Zil'berman, E.N.; Lazaris, A.Ya. *J. Gen. Chem. USSR* ***1963***, *33*, 1012.

B. Attack by OR or SR (Addition of ROH; RSH)

16-5 The Addition of Alcohols to Aldehydes and Ketones

Dialkoxy-de-oxo-bisubstitution

Dithioalkyl-de-oxo-bisubstitution



Acetals and ketals are formed by treatment of aldehydes and ketones, respectively, with alcohols in the presence of acid catalysts.[140] Lewis acids such as $TiCl_4$[141] $RuCl_3$,[142] or $CoCl_2$[143] can be used in conjunction with alcohols. Dioxolanes have been prepared in ethylene glycol using microwave irradiation and *p*-toluenesulfonic acid as a catalyst.[144] This reaction is reversible, and acetals and ketals can be hydrolyzed by treatment with acid.[145] With small unbranched aldehydes the equilibrium lies to the right. If ketals or acetals of larger molecules must be prepared the equilibrium must be shifted, usually by removal of water. This can be done by azeotropic distillation, ordinary distillation, or the use of a drying agent such as Al_2O_3 or a molecular sieve.[146] The reaction is not catalyzed in either direction by bases, so most acetals and ketals are quite stable to bases, though they are easily hydrolyzed by acids. This reaction is therefore a useful method of protection of aldehyde or ketone functions from attack by bases. The reaction is of wide scope. Most aldehydes are easily converted to acetals.[147] With ketones the process is more difficult, presumably for steric reasons, and the reaction often fails, though many ketals, especially from cyclic ketones, have been made in this manner.[148] Many functional groups may be present without being affected. 1,2-Glycols and 1,3-glycols form cyclic acetals and ketals (1,3-dioxolanes[149]

[140]For reviews, see Meskens, F.A.J. *Synthesis* ***1981***, 501; Schmitz, E.; Eichhorn, I., in Patai, S. *The Chemistry of the Ether Linkage*, Wiley, NY, ***1967***, pp. 309–351.

[141]Clerici, A.; Pastori, N.; Porta, O. *Tetrahedron* ***2001***, *57*, 217.

[142]De, S.K.; Gibbs, R.A. *Tetrahedron Lett.* ***2004***, *45*, 8141.

[143]Velusamy, S.; Punniyamurthy, T. *Tetrahedron Lett.* ***2004***, *45*, 4917.

[144]Pério, B.; Dozias, M.-J.; Jacquault, P.; Hamelin, J. *Tetrahdron Lett.* ***1997***, *38*, 7867; Moghaddam, F.M.; Sharifi, A. *Synth. Commun.* ***1995***, *25*, 2457.

[145]See Heravi, M.M.; Tajbakhsh, M.; Habibzadeh, S.; Ghassemzadeh, M. *Monat. Chem.* ***2001***, *132*, 985.

[146]For many examples of each of these methods, see Meskens, F.A.J. *Synthesis* ***1981***, 501, pp. 502–505.

[147]For other methods, see Caputo, R.; Ferreri, C.; Palumbo, G. *Synthesis* ***1987***, 386; Ott, J.; Tombo, G.M.R.; Schmid, B.; Venanzi, L.M.; Wang, G.; Ward, T.R. *Tetrahedron Lett.* ***1989***, *30*, 6151, Liao, Y.; Huang, Y.; Zhu, F. *J. Chem. Soc., Chem. Commun.* ***1990***, 493; Chan, T.H.; Brook, M.A.; Chaly, T. *Synthesis* ***1983***, 203.

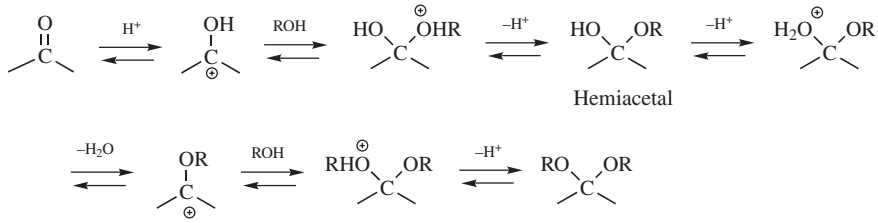
[148]High pressure has been used to improve the results with ketones: Dauben, W.G.; Gerdes, J.M.; Look, G.C. *J. Org. Chem.* ***1986***, *51*, 4964. For other methods, see Otera, J.; Mizutani, T.; Nozaki, H. *Organometallics*, ***1989***, *8*, 2063; Thurkauf, A.; Jacobson, A.E.; Rice, K.C. *Synthesis* ***1988***, 233.

[149]See Yadav, J.S.; Reddy, B.V.S.; Srinivas, R.; Ramalingam, T. *Synlett* ***2000***, 701; Laskar, D.D.; Prajapati, D.; Sandhu, J.S. *Chem. Lett.* ***1999***, 1283; Curini, M.; Epifano, F.; Marcotullio, M.C.; Rosati, O. *Synlett* ***2001***, 1182; Kawabata, T.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Tetrahedron Lett.* ***2001***, *42*, 8329; Reddy, B.M.; Reddy, V.R.; Giridhar, D. *Synth. Commun.* ***2001***, *31*, 1819; Gopinath, R.; Haque, Sk.J.; Patel, B.K. *J. Org. Chem.* ***2002***, *67*, 5842.

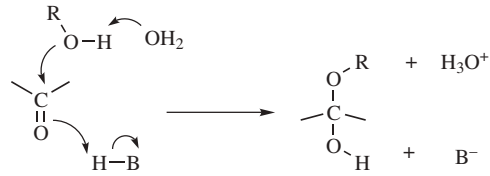
and 1,3-dioxanes,[150] respectively), and these are often used to protect aldehydes and ketones. Chiral dioxolanes have been prepared from chiral diols.[151] Dioxolanes have been prepared from ketones in ionic liquids.[152] Ketones are converted with dimethyl ketals by electrolysis with NaBr in methanol.[153]

Intramolecular reactions are possible in which a keto diol or an aldehyde diol generates a bicyclic ketal or acetal. Fused ring [2.2.0] ketals have been prepared in this manner.[154]

The mechanism, which involves initial formation of a *hemiacetal*,[155] is the reverse of that given for acetal hydrolysis:



In a study of the acid-catalyzed formation of the hemiacetal, Grunwald showed[156] that the data best fit a mechanism in which the three steps shown here are actually all concerted; that is, the reaction is simultaneously catalyzed by acid and base, with water acting as the base:[157]



If the original aldehyde or ketone has an α hydrogen, it is possible for water to split out in that way and enol ethers can be prepared in this manner:

[150]Wu, H.-H.; Yang, F.; Cui, P.; Tang, J.; He, M.-Y. *Tetrahedron Lett.* ***2004***, *45*, 4963; Ishihara, K.; Hasegawa, A.; Yamamoto, H. *Synlett* ***2002***, 1296.

[151]Kurihara, M.; Hakamata, W. *J. Org. Chem.* ***2003***, *68*, 3413.

[152]In AmBIm Cl,: Li, D.; Shi, F.; Peng, J.; Guo, S.; Deng, Y. *J. Org. Chem.* ***2004***, *69*, 3582.

[153]Elinson, M.N.; Feducovich, S.K.; Dmitriev, D.E.; Dorofeev, A.S.; Vereshchagin, A.N.; Nikishin, G.I. *Tetrahedron Lett.* ***2001***, *42*, 5557.

[154]Wang, G.; Wang, Y.; Arcari, A.R.; Rheingold, A.L.; Concolino, T. *Tetrahedron Lett.* ***1999***, *40*, 7051.

[155]For a review of hemiacetals, see Hurd, C.D. *J. Chem. Educ.* ***1966***, *43*, 527.

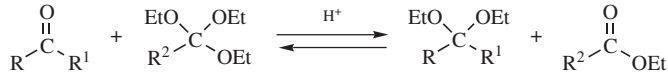
[156]Grunwald, E. *J. Am. Chem. Soc.* ***1985***, *107*, 4715.

[157]Grunwald also studied the mechanism of the base-catalyzed formation of the hemiacetal, and found it to be the same as that of base-catalyzed hydration (**16-1**, mechanism *a*): Grunwald, E. *J. Am. Chem. Soc.* ***1985***, *107*, 4710. See also, Sørensen, P.E.; Pedersen, K.J.; Pedersen, P.R.; Kanagasabapathy, V.M.; McClelland, R.A. *J. Am. Chem. Soc.* ***1988***, *110*, 5118; Leussing, D.L. *J. Org. Chem.* ***1990***, *55*, 666.

Similarly, treatment with an anhydride and a catalyst can give an enol ester (see **16-6**).[158]

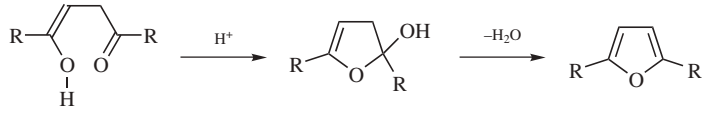
Hemiacetals themselves are no more stable than the corresponding hydrates (**16-1**). As with hydrates, hemiacetals of cyclopropanones[159] and of polychloro and polyfluoro aldehydes and ketones may be quite stable.

When acetals or ketals are treated with an alcohol of higher molecular weight than the one already there, it is possible to get a transacetalation (see **10-13**). In another type of transacetalation, aldehydes or ketones can be converted to acetals or ketals by treatment with another acetal or ketal or with an ortho ester,[160] in the presence of an acid catalyst (shown for an ortho ester):



This method is especially useful for the conversion of ketones to ketals, since the direct reaction of a ketone with an alcohol often gives poor results. In another method, the substrate is treated with an alkoxysilane $ROSiMe_3$ in the presence of trimethylsilyl trifluoromethanesulfonate.[161]

1,4-Diketones give furans when treated with acids. This is actually an example of an intramolecular addition of an alcohol to a ketone, since it is the enol form that adds:



Similarly, 1,5-diketones give pyrans. Conjugated 1,4-diketones, such as 1,4-diphenylbut-2-en-1,4-dione is converted to 2,5-diphenylfuran with formic acid, 5% Pd/C, PEG-200, and a sulfuric acid catalyst with microwave irradiation.[162] Formic acid reacts with alcohols to give orthoformates. Note that alkynyl ketones are converted to furans with palladium (II) acetate.[163]

[158]For a list of catalysts, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1484–1485.

[159]For a review, see Salaun, J. *Chem. Rev.* ***1983***, *83*, 619.

[160]For a review with respect to ortho esters, see DeWolfe, R.H. *Carboxylic Ortho Ester Derivatives*; Academic Press, NY, ***1970***, pp. 154–164. See Karimi, B.; Ebrahimian, G.R.; Seradj, H. *Org. Lett.* ***1999***, *1*, 1737; Karimi, B.; Ashtiani, A.M. *Chem. Lett.* ***1999***, 1199; Firouzabadi, H.; Iranpoor, N.; Karimi, B. *Synlett* ***1999***, 321; Firouzabadi, H.; Iranpoor, N,; Karimi, B. *Synth. Commun.* ***1999***, *29*, 2255; Leonard, N.M.; Oswald, M.C.; Freiberg, D.A.; Nattier, B.A.; Smith, R.C.; Mohan, R.S. *J. Org. Chem.* ***2002***, *67*, 5202.

[161]Tsunoda, T.; Suzuki, M.; Noyori, R.*Tetrahedron Lett.* ***1980***, *21*, 1357; Kato, J.; Iwasawa, N.; Mukaiyama, T. *Chem. Lett.* ***1985***, 743. See also, Torii, S.; Takagishi, S.; Inokuchi, T.; Okumoto, H. *Bull. Chem. Soc. Jpn.* ***1987***, *60*, 775.

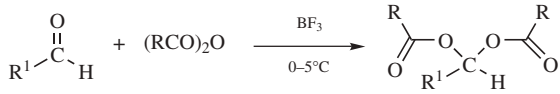
[162]Rao, H.S.P.; Jothilingam, S. *J. Org. Chem.* ***2003***, *68*, 5392.

[163]Jeevanandam, A.; Narkunan, K.; Ling, Y.-C. *J. Org. Chem.* ***2001***, *66*, 6014. See Arcadi, A.; Cerichelli, G.; Chiarini, M.; Di Giuseppe, S. Marinelli, F. *Tetrahedron Lett.* ***2000***, *41*, 9195.

OS **I**, 1, 298, 364, 381; **II**, 137; **III**, 123, 387, 502, 536, 644, 731, 800; **IV**, 21, 479, 679; **V**, 5, 292, 303, 450, 539; **VI**, 567, 666, 954; **VII**, 59, 149, 168, 177, 241, 271, 297; **VIII**, 357. Also see OS **IV**, 558, 588; **V**, 25; **VIII**, 415.

16-6 Acylation of Aldehydes and Ketones

O-Acyl-*C*-acyloxy-addition

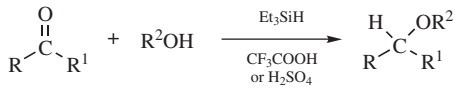


Aldehydes can be converted to *acylals* by treatment with an anhydride in the presence of BF_3, proton acids,[164] PCl_3,[165] NBS,[166] $LiBF_4$,[167] $FeCl_3$,[168] $InCl_3$,[169] $InBr_3$,[170] $Cu(OTf)_2$,[171] $Bi(OTf)_3$,[172] $BiCl_3$,[173] $Bi(NO_3)_3$,[174] WCl_6,[175] $ZrCl_4$,[176] ceric ammonium nitrate,[177] With Envirocat EPZ10 and microwave irradiation, acetic anhydride react with aldehydes to give the acylal.[178] Conjugated aldehydes are converted to the corresponding acylal by reaction with acetic anhydride and a $FeCl_3$ catalyst.[179] The reaction cannot normally be applied to ketones, though an exception has been reported when the reagent is trichloroacetic anhydride, which gives acylals with ketones without a catalyst.[180]

OS **IV**, 489.

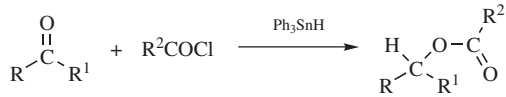
16-7 Reductive Alkylation of Alcohols

C-Hydro-*O*-alkyl-addition



[164]For example, see Olah, G.A.; Mehrotra, A.K. *Synthesis* ***1982***, 962.
[165]See Michie, J.K.; Miller, J.A. *Synthesis* ***1981***, 824.
[166]Karimi, B.; Seradj, H.; Ebrahimian, G.R. *Synlett* ***2000***, 623
[167]Sumida, N.; Nishioka, K.; Sato, T. *Synlett* ***2001***, 1921; Yadav, J.S.; Reddy, B.V.S.; Venugapal, C.; Ramalingam, V.T. *Synlett* ***2002***, 604.
[168]Li, Y.-Q. *Synth. Commun.* ***2000***, *30*, 3913; Trost, B.M.; Lee, C.B. *J. Am. Chem. Soc.* ***2001***, *123*, 3671; Wang, C.; Li, M. *Synth. Commun.* ***2002***, *32*, 3469.
[169]Yadav, J.S.; Reddy, B.V.S.; Srinivas, Ch. *Synth. Commun.* ***2002***, *32*, 1175, 2169.
[170]Yin, L.; Zhang, Z.H.; Wang, Y.-M. ; Pang, M.-L. *Synlett* ***2004***, 1727.
[171]Chandra, K.L.; Saravanan, P.; Singh, V.K. *Synlett* ***2000***, 359.
[172]Carrigan, M.D.; Eash, K.J.; Oswald, M.C.; Mohan, R.S. *Tetrahedron Lett.* ***2001***, *42*, 8133.
[173]Mohammadpoor-Baltork, I.; Aliyan, H. *Synth. Commun.* ***1999***, *29*, 2741.
[174]Aggen, D.H.; Arnold, J.N.; Hayes, P.D.; Smoter, N.J.; Mohan, R.S. *Tetrahedron* ***2004***, *60*, 3675.
[175]A solvent-free reaction. See Karimi, B.; Ebrahimian, G.-R.; Seradj, H. *Synth. Commun.* ***2002***, *32*, 669.
[176]Smitha, G.; Reddy, Ch.S. *Tetrahedron* ***2003***, *59*, 9571.
[177]Roy, S.C.; Banerjee, B. *Synlett* ***2002***, 1677.
[178]Bandgar, B.P.; Makone, S.S.; Kulkarni, S.R. *Monat. Chem.* ***2000***, *131*, 417.
[179]Trost, B.M.; Lee, C.B. *J. Am. Chem. Soc.* ***2001***, *123*, 3671.
[180]Libman, J.; Sprecher, M.; Mazur, Y. *Tetrahedron* ***1969***, *25*, 1679.

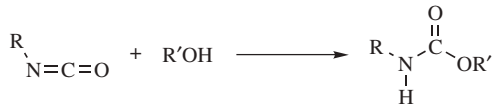
Aldehydes and ketones can be converted to ethers by treatment with an alcohol and triethylsilane in the presence of a strong acid[181] or by hydrogenation in alcoholic acid in the presence of platinum oxide.[182] The process can formally be regarded as addition of ROH to give a hemiacetal, $RR'C(OH)OR^2$, followed by reduction of the OH. In this respect, it is similar to **16-17**. The reaction of an aldehyde with $BuOSiHMe_2$ and a Me_3SiI catalyst gives the corresponding butyl alkyl ether.[183] In a similar reaction, ketones can be converted to carboxylic esters (reductive acylation of ketones) by treatment with an acyl chloride and triphenyltin hydride.[184]



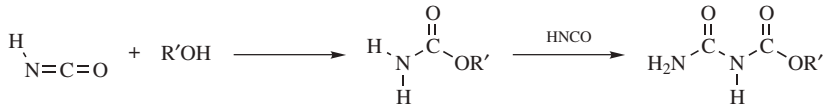
Ethers have also been prepared by the reductive dimerization of two molecules of an aldehyde or ketone (e.g., cyclohexanone → dicyclohexyl ether). This was accomplished by treatment of the substrate with a trialkylsilane and a catalyst.[185]

16-8 The Addition of Alcohols to Isocyanates

N-Hydro-*C*-alkoxy-addition



Carbamates (substituted urethanes) are prepared when isocyanates are treated with alcohols. This is an excellent reaction, of wide scope, and gives good yields. Isocyanic acid HNCO gives unsubstituted carbamates. Addition of a second equivalent of HNCO gives *allophanates*.



Allophanate

The isocyanate can be generated *in situ* by the reaction of an amine and oxalyl chloride, and subsequent reaction with HCl and then an alcohol gives the carbamate.[186] Polyurethanes are made by combining compounds with two NCO groups with

[181]Doyle, M.P.; DeBruyn, D.J.; Kooistra, D.A. *J. Am. Chem. Soc.* ***1972***, *94*, 3659.
[182]Verzele, M.; Acke, M.; Anteunis, M. *J. Chem. Soc.* ***1963***, 5598. For still another method, see Loim, L.M.; Parnes, Z.N.; Vasil'eva, S.P.; Kursanov, D.N. *J. Org. Chem. USSR* ***1972***, *8*, 902.
[183]Miura, K.; Ootsuka, K.; Suda, S.; Nishikori, H.; Hosomi, A. *Synlett* ***2002***, 313.
[184]Kaplan, L. *J. Am. Chem. Soc.* ***1966***, *88*, 4970.
[185]Sassaman, M.B.; Kotian, K.D.; Prakash, G.K.S.; Olah, G.A. *J. Org. Chem.* ***1987***, *52*, 4314. See also, Kikugawa, Y. *Chem. Lett.* ***1979***, 415.
[186]Oh, L.M.; Spoors, P.G.; Goodman, R.M. *Tetrahedron Lett.* ***2004***, *45*, 4769.

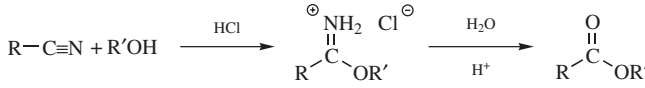
compounds containing two OH groups. Cyclic carbamates, such as 1,3-oxazine-2-ones, are generated by the reaction of an isocyanate with an oxetane, in the presence of a palladium catalyst.[187] Isothiocyanates similarly give thiocarbamates[188] RNHCSOR′, though they react slower than the corresponding isocyanates. Isocyanates react with LiAlHSeH and then iodomethane to give the corresponding selenocarbonate (RNHCOSeMe).[189]

The details of the mechanism are poorly understood,[190] though the oxygen of the alcohol is certainly attacking the carbon of the isocyanate. Hydrogen bonding complicates the kinetic picture.[191] The addition of ROH to isocyanates can also be catalyzed by metallic compounds,[192] by light,[193] or, for tertiary ROH, by lithium alkoxides[194] or *n*-butyllithium.[195]

OS **I**, 140; **V**, 162; **VI**, 95, 226, 788, 795.

16-9 Alcoholysis of Nitriles

Alkoxy,oxo-de-nitrilo-tersubstitution



The addition of dry HCl to a mixture of a nitrile and an alcohol in the absence of water leads to the hydrochloride salt of an imino ester (imino esters are also called imidates and imino ethers). This reaction is called the *Pinner synthesis*.[196] The salt can be converted to the free imino ester by treatment with a weak base such as sodium bicarbonate, or it can be hydrolyzed with water and an acid catalyst to the corresponding carboxylic ester. If the latter is desired, water may be present from the beginning, in which case aq. HCl can be used and the need for gaseous HCl is eliminated. Imino esters can also be prepared from nitriles with basic catalysts.[197]

[187]Larksarp, C.; Alper, H. *J. Org. Chem.* ***1999***, *64*, 4152.

[188]For a review of thiocarbamates, see Walter, W.; Bode, K. *Angew. Chem. Int. Ed.* ***1967***, *6*, 281. See also, Wynne, J.H.; Jensen, S.D.; Snow, A.W. *J. Org. Chem.* ***2003***, *68*, 3733.

[189]Koketsu, M.; Ishida, M.; Takakura, N.; Ishihara, H. *J. Org. Chem.* ***2002***, *67*, 486.

[190]For reviews, see Satchell, D.P.N.; Satchell, R.S.*Chem. Soc. Rev.* ***1975***, *4*, 231; Entelis, S.G.; Nesterov, O.V. *Russ. Chem. Rev.* ***1966***, *35*, 917.

[191]See for example, Robertson, W.G.P.; Stutchbury, J.E. *J. Chem. Soc.* ***1964***, 4000; Donohoe, G.; Satchell, D.P.N.; Satchell, R.S. *J. Chem. Soc. Perkin Trans. 2* ***1990***, 1671 and references cited therein. See also, Sivakamasundari, S.; Ganesan, R. *J. Org. Chem.* ***1984***, *49*, 720.

[192]For example, see Kim, Y.H.; Park, H.S. *Synlett* ***1998***, 261; Hazzard, G.; Lammiman, S.A.; Poon, N.L.; Satchell, D.P.N.; Satchell, R.S. *J. Chem. Soc. Perkin Trans. 2* ***1985***, 1029; Duggan, M.E.; Imagire, J.S. *Synthesis* ***1989***, 131.

[193]McManus, S.P.; Bruner, H.S.; Coble, H.D.; Ortiz, M. *J. Org. Chem.* ***1977***, *42*, 1428.

[194]Bailey, W.J.; Griffith, J.R. *J. Org. Chem.* ***1978***, *43*, 2690.

[195]Nikoforov, A.; Jirovetz, L.; Buchbauer, G. *Liebigs Ann. Chem.* ***1989***, 489.

[196]For a review, see Compagnon, P.L.; Miocque, M. *Ann. Chim. (Paris)* ***1970***, *[14] 5*, 23, see pp. 24–26. For a review of imino esters, see Neilson, D.G., in Patai, S. *The Chemistry of Amidines and Imidates*, Wiley, NY, ***1975***, pp. 385–489.

[197]Schaefer, F.C.; Peters, G.A. *J. Org. Chem.* ***1961***, *26*, 412.

This reaction is of broad scope and is good for aliphatic, aromatic, and heterocyclic R and for nitriles with oxygen-containing functional groups. The application of the reaction to nitriles containing a carboxyl group constitutes a good method for the synthesis of mono esters of dicarboxylic acids with the desired group esterified and with no diester or diacid present.

Cyanogen chloride reacts with alcohols in the presence of an acid catalyst, such as dry HCl or $AlCl_3$, to give carbamates:[198]

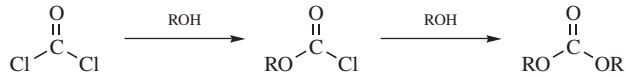
$$ClCN + 2\,ROH \xrightarrow[\text{or } AlCl_3]{HCl} ROCONH_2 + RCl$$

ROH can also be added to nitriles in another manner (**16-91**).

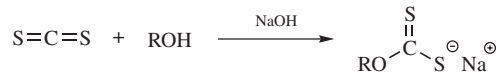
OS **I**, 5, 270; **II**, 284, 310; **IV**, 645; **VI**, 507; **VIII**, 415.

16-10 The Formation of Carbonates and Xanthates

Di-*C*-alkoxy-addition; *S*-Metallo-*C*-alkoxy-addition



The reaction of phosgene with an alcohol generates a haloformic esters, and reaction with a second equivalent of alcohol gives a carbonate. This reaction is related to the acyl addition reactions of acyl chlorides in Reaction **16-98**. An important example is the preparation of carbobenzoxy chloride ($PhCH_2OCOCl$) from phosgene and benzyl alcohol. This compound is widely used for protection of amino groups during peptide synthesis. When an alcohol reacts with certain alkyl halides (e.g., benzyl chloride) and carbon dioxide, in the presence of Cs_2CO_3 and tetrabutylammonium iodide, a mixed carbonate is formed.[199]



The addition of alcohols to carbon disulfide in the presence of a base produces xanthates.[200] The base is often HO^-, but in some cases better results can be obtained by using methylsulfinyl carbanion $MeSOCH_2^-$.[201] If an alkyl halide RX is present, the xanthate ester ROCSSR′ can be produced directly. In a similar manner, alkoxide ions add to CO_2 to give carbonate ester salts ($ROCOO^-$).

OS **V**, 439; **VI**, 207, 418; **VII**, 139.

[198]Bodrikov, I.V.; Danova, B.V. *J. Org. Chem. USSR* ***1968***, *4*, 1611; ***1969***, *5*, 1558; Fuks, R.; Hartemink, M.A. *Bull. Soc. Chim. Belg.* ***1973***, *82*, 23.

[199]Kim, S.i.; Chu, F.; Dueno, E.E.; Jung, K.W. *J. Org. Chem.* ***1999***, *64*, 4578.

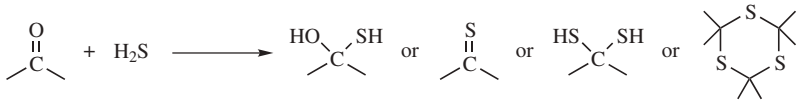
[200]For a review of the formation and reactions of xanthates, see Dunn, A.D.; Rudorf, W. *Carbon Disulphide in Organic Chemistry*; Ellis Horwood: Chichester, ***1989***, pp. 316–367.

[201]Meurling, P.; Sjöberg, B.; Sjöberg, K. *Acta Chem. Scand.* ***1972***, *26*, 279.

C. Sulfur Nucleophiles

16-11 The Addition of H_2S and Thiols to Carbonyl Compounds

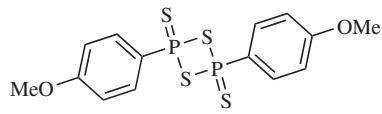
***O*-Hydro-*C*-mercapto-addition**[202]



13 **14** **15** **16**

The addition of H_2S to an aldehyde or ketone can result in a variety of products. The most usual product is the trithiane **16**.[203] *gem*-Dithiols (**15**) are much more stable than the corresponding hydrates or α-hydroxy thiols.[204] They have been prepared by the treatment of ketones with H_2S under pressure[205] and under mild conditions with HCl as a catalyst.[206] Thiols add to aldehydes and ketones to give hemimercaptals, CH(OH)SR and dithioacetals, $CH(SR)_2$ (**16-5**). α-Hydroxy thiols (**13**) can be prepared from polychloro and polyfluoro aldehydes and ketones.[207] Apparently **13** are stable only when prepared from these compounds, and not even for all of them.

Thioketones[2] (**14**) can be prepared from certain ketones, such as diaryl ketones, by treatment with H_2S and an acid catalyst, usually HCl. They are often unstable and usually trimerize (to **16**) or react with air. Thioaldehydes[208] are even less stable and simple ones[209] apparently have never been isolated, though *t*-BuCHS has been prepared in



17

[202]This name applies to formation of **13**. Names for formation of **14**–**16**, are, respectively, thioxo-de-oxo-bisubstitution, dimercapto-de-oxo-bisubstitution, and carbonyl–trithiane transformation.

[203]Campaigne, E.; Edwards, B.E. *J. Org. Chem.* ***1962***, *27*, 3760.

[204]For a review of the preparation of *gem*-dithiols, see Mayer, R.; Hiller, G.; Nitzschke, M.; Jentzsch, J. *Angew. Chem. Int. Ed.* ***1963***, *2*, 370.

[205]Cairns, T.L.; Evans, G.L.; Larchar, A.W.; McKusick, B.C. *J. Am. Chem. Soc.* ***1952***, *74*, 3982.

[206]Campaigne, E.; Edwards, B.E. *J. Org. Chem.* ***1962***, *27*, 3760; Demuynck, M.; Vialle, J. *Bull. Soc. Chim. Fr.* ***1967***, 1213.

[207]Harris Jr., J.F. *J. Org. Chem.* ***1960***, *25*, 2259.

[208]For a review of thioaldehydes, see Usov, V.A.; Timokhina, L.V.; Voronkov, M.G. *Russ. Chem. Rev.* ***1990***, *59*, 378.

[209]For the preparation and reactions of certain substituted thioaldehydes, see Hofstra, G.; Kamphuis, J.; Bos, H.J.T. *Tetrahedron Lett.* ***1984***, *25*, 873; Okazaki, R.; Ishii, A.; Inamoto, N. *J. Am. Chem. Soc.* ***1987***, *109*, 279; Adelaere, B.; Guemas, J.; Quiniou, H. *Bull. Soc. Chim. Fr.* ***1987***, 517; Muraoka, M.; Yamamoto, T.; Enomoto, K.; Takeshima, T. *J. Chem. Soc. Perkin Trans. 1* ***1989***, 1241, and references cited in these papers.

solution, where it exists for several hours at 20°C.[210] A high-yield synthesis of thioketones involves treatment of acyclic[211] ketones with 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide **9**[212] (known as *Lawesson's reagent*)[213]. Thioketones can also be prepared by treatment of ketones with P_4S_{10},[214] P_4S_{10} and hexamethyldisiloxane,[215] P_4S_{10} on alumina,[216] or $CF_3SO_3SiMe_3/S(SiMe_3)_2$,[217] and from oximes or various types of hydrazone (overall conversion $C{=}N^- \rightarrow C{=}S$).[218] Reagent **17** converts the C=O groups of amides and carboxylic esters[219] to C=S groups.[220] Similarly, $POCl_3$ followed by $S(TMS)_2$ converts lactams to thiolactams[221] and treatment with triflic anhydride, and then H_2S converts amides to thioamides.[222] The reaction of an amide with triflic anhydride, and then aq. $S(NH_4)_2$ gives the corresponding thioamide.[223] The $H_2S{-}Me_3SiCl$-$(i\text{Pr})_2NLi$ complex converts carboxylic esters to thiono esters.[224] Lactones react with **9** in the presence of hexamethyldisiloxane an microwave irradiation to give the thiolactone.[225] Carboxylic acids (RCOOH) can be converted directly to dithiocarboxylic esters ($RCSSR'$)[226] in moderate yield, with P_4S_{10} and a primary alcohol ($R'OH$).[227]

Thiols add to aldehydes and ketones to give hemimercaptals and dithioacetals. Hemimercaptals are ordinarily unstable,[228] though they are more stable than the corresponding hemiacetals and can be isolated in certain cases.[229] Dithioacetals,

[210]Vedejs, E.; Perry, D.A. *J. Am. Chem. Soc.* ***1983***, *105*, 1683. See also, Baldwin, J.E.; Lopez, R.C.G. *J. Chem. Soc., Chem. Commun.* ***1982***, 1029.

[211]Cyclopentanone and cyclohexanone gave different products: Scheibye, S.; Shabana, R.; Lawesson, S.; Rømming, C. *Tetrahedron* ***1982***, *38*, 993.

[212]See Thomsen, I.; Clausen, K.; Scheibye, S.; Lawesson, S. *Org. Synth.* ***VII***, 372.

[213]For reviews of this and related reagents, see Cava, M.P.; Levinson, M.I.*Tetrahedron* ***1985***, *41*, 5061; Cherkasov, R.A.; Kutyrev, G.A.; Pudovik, A.N. *Tetrahedron* ***1985***, *41*, 2567; Jesberger, M.; Davis, T.P.; Barner, L. *Synthesis* ***2003***, 1929. For a study of the mechanism, see Rauchfuss, T.B.; Zank, G.A. *Tetrahedron Lett.* ***1986***, *27*, 3445.

[214]See, for example, Scheeren, J.W.; Ooms, P.H.J.; Nivard, R.J.F. *Synthesis* ***1973***, 149.

[215]Curphey, T.J. *J. Org. Chem.* ***2002***, *67*, 6461.

[216]Polshettiwar, V.; Kaushik, M.P. *Tetrahedron Lett.* ***2004***, *45*, 6255.

[217]Degl'Innocenti, A.; Capperucci, A.; Mordini, A.; Reginato, G.; Ricci, A.; Cerreta, F. *Tetrahedron Lett.* ***1993***, *34*, 873.

[218]See for example, Kimura, K.; Niwa, H.; Motoki, S. *Bull. Chem. Soc. Jpn.* ***1977***, *50*, 2751; de Mayo, P.; Petrainas, G.L.R.; Weedon, A.C. *Tetrahedron Lett.* ***1978***, 4621; Okazaki, R.; Inoue, K.; Inamoto, N. *Tetrahedron Lett.* ***1979***, 3673.

[219]For a review of thiono esters $RC(=S)OR'$, see Jones, B.A.; Bradshaw, J.S. *Chem. Rev.* ***1984***, *84*, 17.

[220]Ghattas, A.A.G.; El-Khrisy, E.A.M.; Lawesson, S. *Sulfur Lett.* ***1982***, *1*, 69; Yde, B.; Yousif, N.M.; Pedersen, U.S.; Thomsen, I.; Lawesson, S.-O. *Tetrahedron* ***1984***, *40*, 2047; Thomsen, I.; Clausen, K.; Scheibye, S.; Lawesson, S. *Org. Synth.* ***VII***, 372.

[221]Smith, D.C.; Lee, S.W.; Fuchs, P.L. *J. Org. Chem.* ***1994***, *59*, 348.

[222]Charette, A.B.; Chua, P. *Tetrahedron Lett.* ***1998***, *39*, 245.

[223]Charette, A.B.; Grenon, M. *J. Org. Chem.* ***2003***, *68*, 5792.

[224]Corey, E.J.; Wright, S.W. *Tetrahedron Lett.* ***1984***, *25*, 2639.

[225]Filippi, J.-J.; Fernandez, X.; Lizzani-Cuvelier, L.; Loiseau, A.-M. *Tetrahedron Lett.* ***2003***, *44*, 6647.

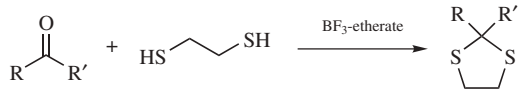
[226]For a review of dithiocarboxylic esters, see Kato, S.; Ishida, M. *Sulfur Rep.*, ***1988***, *8*, 155.

[227]Davy, H.; Metzner, P. *Chem. Ind. (London)* ***1985***, 824.

[228]See, for example, Fournier, L.; Lamaty, G.; Nata, A.; Roque, J.P. *Tetrahedron* ***1975***, *31*, 809.

[229]For example, see Field, L.; Sweetman, B.J. *J. Org. Chem.* ***1969***, *34*, 1799.

like acetals, are stable in the presence of bases, except that a strong base can remove the aldehyde proton, if there is one[230] (see **10-71**).



18

The reaction of aldehydes or ketones with thiols, usually with a Lewis acid catalyst, leads to dithioacetals[231] or dithioketals. The most common catalyst used is probably boron trifluoride etherate (BF_3•OEt_2).[232] Similarly reactions that use 1,2-ethanedithiol or 1,3-propanedithiol lead to 1,3-dithiolanes, such as **18**[233] or 1,3-dithianes.[234] Dithioacetals can also be prepared from aldehydes or ketones by treatment with thiols in the presence of $TiCl_4$,[235] $SiCl_4$,[236] $LiBF_4$,[237] $Al(OTf)_3$,[238] with a disulfide RSSR (R = alkyl or aryl),[239] or with methylthiotrimethylsilane ($MeSSiMe_3$).[240]

Dithioacetals and dithioketals are used as protecting groups for aldehydes and ketones, and after subsequent reactions involving the R or R′ group, the protecting group can then be removed.[241] There are a variety of reagents that convert these compounds back to the carbonyl.[242] Simple hydrolysis is the most common method for converting thiocarbonyls to carbonyls. Stirring thioketones with 4-nitrobenzaldehyde and a catalytic amount of TMSOTf gives the ketone.[243] The reaction of a thioketone and Clayfen with microwave irradiation give the ketone.[244] Thioamides

[230]Truce, W.E.; Roberts, F.E. *J. Org. Chem.* ***1963***, *28*, 961.

[231]See Samajdar, S.; Basu, M.K.; Becker, F.F.; Banik, N.K. *Tetrahedron Lett.* ***2001***, *42*, 4425.

[232]Fujita, E.; Nagao, Y.; Kaneko, K. *Chem. Pharm. Bull.* 1978, *26*, 3743; Corey, E.J.; Bock, M.G. *Tetrahedron Lett.* ***1975***, 2643.

[233]See Anand, R.V.; Saravanan, P.; Singh, V.K. *Synlett* ***1999***, 415; Ceschi, M.A.; Felix, L.de A.; Peppe, C. *Tetrahedron Lett.* ***2000***, *41*, 9695; Muthusamy, S.; Babu, S.A.; Gunanathan, C. *Tetrahedron Lett.* ***2001***, *42*, 359; Yadav, J.S.; Reddy, B.V.S.; Pandey, S.K. *Synlett* ***2001***, 238; Ballini, R.; Barboni, L.; Maggi, R.; Sartori, G. *Synth. Commun.* ***1999***, *29*, 767; Jin, T.-S.; Sun, X.; Ma, Y.-R.; Li, T.-S. *Synth. Commun.* ***2001***, *31*, 1669; Deka, N.; Sarma, J.C. *Chem. Lett.* ***2001***, 794; Kamal, A.; Chouhan, G. *Synlett* ***2002***, 474. For a review, see Olsen, R.K.; Currie, Jr., J.O., in Patai, S. *The Chemistry of the Thiol Group*, pt. 2, Wiley, NY, ***1974***, pp. 521–532.

[234]See Firouzabadi, H.; Karimi, B.; Eslami, S. *Tetrahedron Lett.* ***1999***, *40*, 4055; Firouzabadi, H.; Iranpoor, N.; Karimi, B. *Synthesis* ***1999***, 58; Tietze, L.F.; Weigand, B.; Wulff, C. *Synthesis* ***2000***, 69; Graham, A.E. *Synth. Commun.* ***1999***, *29*, 697; Firouzabadi, H.; Eslami, S.; Karimi, B. *Bull. Chem. Soc. Jpn.* ***2001***, *74*, 2401; Laskar, D.D.; Prajapati, D.; Sandhu, J.S. *J. Chem. Res. (S)* ***2001***, 313; De, S.K. *Tetrahedron Lett.* ***2004***, *45*, 1035, 2339.

[235]Kumar, V.; Dev, S. *Tetrahedron Lett.* ***1983***, *24*, 1289.

[236]Ku, B.; Oh, D.Y. *Synth. Commun.* ***1989***, 433.

[237]This reaction is done neat, see Kazaraya, K.; Tsuji, S.; Sato, T. *Synlett* ***2004***, 1640.

[238]This is a solvent-free reaction. See Firouzabadi, H.; Iranpoor, N.; Kohmarch, G. *Synth. Commun.* ***2003***, *33*, 167.

[239]Tazaki, M.; Takagi, M. *Chem. Lett.* ***1979***, 767.

[240]Evans, D.A.; Grimm, K.G.; Truesdale, L.K. *J. Am. Chem. Soc.* ***1975***, *97*, 3229.

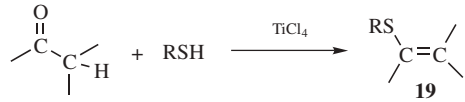
[241]For example, see Ganguly, N.C.; Datta, M. *Synlett* ***2004***, 659.

[242]Corsaro, A.; Pistarà, V. *Tetrahedron* ***1998***, *54*, 15027.

[243]Ravindrananthan, T.; Chavan, S.P.; Awachat, M.M.; Kelkar, S.V. *Tetrahedron Lett.* ***1995***, *36*, 2277.

[244]Varma, R.S.; Kumar, D. *Synth. Commun.* ***1999***, *29*, 1333.

are converted to amides with Caro's acid on SiO_2.[245] Lewis acids, such as aluminum chloride ($AlCl_3$) and mercuric salts, are common reagents and their use is referred to as the Corey–Seebach procedure.[246] Other reagents include $BF_3 \bullet OEt_2$ in aq. THF containing mercuric oxide (HgO),[247] NBS,[248] iodine in DMSO,[249] ceric ammonium nitrate, $Ce(NH_4)_2(NO_3)_6$,[250] iodomethane in aqueous media,[251] Clayfen with microwave irradiation,[252] $PhI(OAc)_2$ in aqueous acetone,[253] and NCS with silver nitrate in aqueous acetonitrile.[254] When aldehydes and ketones react with mercapto-alcohols, mixed acetals or ketals are formed. The use of 2-mercaptoethanol ($HSCH_2CH_2OH$), for example, leads to an oxathiolane[255] and 3-mercaptopropanol ($HSCH_2CH_2CH_2OH$) leads to an oxathiane. Alternatively, the dithioketal can be desulfurized with Raney nickel (**14-27**), giving the overall conversion $C{=}O \rightarrow CH_2$.



19

If an aldehyde or ketone possesses an α hydrogen, it can be converted to the corresponding enol thioether (**19**) by treatment with a thiol in the presence of $TiCl_4$.[256] Aldehydes and ketones have been converted to sulfides by treatment with thiols and pyridine–borane, $RCOR' + R^2SH \rightarrow RR'CHSR^2$,[257] in a reductive alkylation reaction, analogous to **16-7**.

OS **II**, 610; **IV**, 927; **VI**, 109; **VII**, 124, 372. Also see OS **III**, 332; **IV**, 967; **V**, 780; **VI**, 556; **VIII**, 302.

16-12 Formation of Bisulfite Addition Products

***O*-Hydro-*C*-sulfonato-addition**

[245]Movassagh, B.; Lakouraj, M.M.; Ghodrati, K. *Synth. Commun.* ***2000***, *30*, 2353.
[246]Seebach, D.; Corey, E.J. J. *Org. Chem.* ***1975***, *40*, 231; Seebach, D. *Synthesis* ***1969***, 17; Vedejs, E.; Fuchs, P.L. *J. Org. Chem.* ***1971***, *36*, 366.
[247]Vedejs, E.; Fuchs, P.L. *J. Org. Chem.* ***1971***, *36*, 366.
[248]Cain, E.N.; Welling, L.L. *Tetrahedron Lett.* ***1975***, 1353; Corey, E.J.; Erickson, B.W. *J. Org. Chem.* ***1971***, *36*, 3553.
[249]Chattopadhyaya, J.B.; Rama Rao, A.V. *Tetrahedron Lett.* ***1973***, 3735.
[250]Ho, T.-L.; Ho, H.C.; Wong, C.M. *J. Chem. Soc., Chem. Commun.* ***1972***, 791a.
[251]Fétizon, M.; Jurion, M. *J. Chem. Soc., Chem. Commun.* ***1972***, 382; Takano, S.; Hatakeyama, S.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* ***1977***, 68.
[252]Meshram, H.M.; Reddy, G.S.; Sumitra, G.; Yadav, J.S. *Synth. Commun.* ***1999***, *29*, 1113.
[253]Shi, X.-X.; Wu, Q.-Q. *Synth. Commun.* ***2000***, *30*, 4081.
[254]Corey, E.J.; Erickson, B.W. *J. Org. Chem.* ***1971***, *36*, 3553.
[255]See Karimi, B.; Seradj, H. *Synlett* ***2000***, 805; Ballini, R.; Bosica, G.; Maggi, R. ; Mazzacani, A.; Righi, P.; Sartori, G. *Synthesis* ***2001***,1826; Mondal, E.; Sahu, P.R.; Khan, A.T. *Synlett* ***2002***, 463.
[256]Mukaiyama, T.; Saigo, K. *Chem. Lett.* ***1973***, 479.
[257]Kikugawa, Y. *Chem. Lett.* ***1981***, 1157.

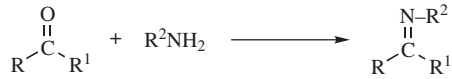
Bisulfite addition products are formed from aldehydes, methyl ketones, cyclic ketones (generally seven-membered and smaller rings), α-keto esters, and isocyanates, upon treatment with sodium bisulfite. Most other ketones do not undergo the reaction, probably for steric reasons. The reaction is reversible (by treatment of the addition product with either acid or base[258])[259] and is useful for the purification of the starting compounds, since the addition products are soluble in water and many of the impurities are not.[260]

OS **I**, 241, 336; **III**, 438; **IV**, 903; **V**, 437.

D. Attack by NH_2, NHR, or NR_2 (Addition of NH_3, RNH_2, R_2NH)

16-13 The Addition of Amines to Aldehydes and Ketones

Alkylimino-de-oxo-bisubstitution



The addition of ammonia[261] to aldehydes or ketones does not generally give useful products. According to the pattern followed by analogous nucleophiles, the initial products would be expected to be *hemiaminals*,[262] but these compounds are generally unstable. Most imines with a hydrogen on the nitrogen spontaneously polymerize.[263] In the presence of an oxidizing agent, such a MnO_2 (see **19-3**), primary alcohols can be converted to imines.[264]

In contrast to ammonia, primary, secondary, and tertiary amines can add to aldehydes[265] and ketones to give different kinds of products. Primary amines give imines[266] and secondary amines gives enamines (**10-69**). This section will focus on imines. Reduction of ω-azido ketones leads to the amino-ketones, which cyclizes to form a 2-substituted pyrroline.[267] Reduction of nitro-ketones in the presence

[258]For cleavage with ion-exchange resins, see Khusid, A.Kh.; Chizhova, N.V. *J. Org. Chem. USSR* ***1985***, *21*, 37.

[259]For a discussion of the mechanism, see Young, P.R.; Jencks, W.P. *J. Am. Chem. Soc.* ***1978***, *100*, 1228.

[260]The reaction has also been used to protect an aldehyde group in the presence of a keto group: Chihara, T.; Wakabayashi, T.; Taya, K. *Chem. Lett.* ***1981***, 1657.

[261]For a review of this reagent in organic synthesis, see Jeyaraman, R., in Pizey, J.S. *Synthetic Reagents*, Vol. 5, Wiley, NY, ***1983***, pp. 9–83.

[262]These compounds have been detected by ^{13}C NMR: Chudek, J.A.; Foster, R.; Young, D. *J. Chem. Soc. Perkin Trans. 2* ***1985***, 1285.

[263]Methanimine CH_2=NH is stable in solution for several hours at −95°C, but rapidly decomposes at −80°C: Braillon, B.; Lasne, M.C.; Ripoll, J.L.; Denis, J.M. *Nouv. J. Chim.*, ***1982***, *6*, 121. See also, Bock, H.; Dammel, R. *Chem. Ber.* ***1987***, *120*, 1961.

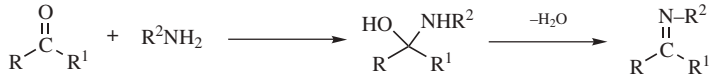
[264]Kanno, H.; Taylor, R.J.K. *Synlett* ***2002***, 1287.

[265]For a review of the reactions between amines and formaldehyde, see Farrar, W.V. *Rec. Chem. Prog.*, ***1968***, *29*, 85.

[266]For reviews of reactions of carbonyl compounds leading to the formation of C=N bonds, see Dayagi, S.; Degani, Y. in Patai, S. *The Chemistry of the Carbon–Nitrogen Double Bond*, Wiley, NY, ***1970***, pp. 64–83; Reeves, R.L., in Patai, S. *The Chemistry of the Carbonyl Group*, pt. 1, Wiley, NY, ***1966***, pp. 600–614.

[267]Prabhu, K.P.; Sivanand, P.S.; Chandrasekaran, S. *Synlett* ***1998***, 47.

of ruthenium compounds and CO also leads to 1-substituted pyrrolines.[268] In contrast to imines in which the nitrogen is attached to a hydrogen, these imines are stable enough for isolation. However, in some cases, especially with simple R groups, they rapidly decompose or polymerize unless there is at least one aryl group on the nitrogen or the carbon. When there is an aryl group, the compounds are quite stable. They are usually called *Schiff bases*, and this reaction is the best way to prepare them.[269] The reaction is straightforward and proceeds in high yields. Even sterically hindered imines can be prepared.[270] Both imines and enamines (see below) have been prepared on clay with microwave irradiation.[271] The initial *N*-substituted hemiaminals[272] lose water to give the stable Schiff bases:



In general, ketones react more slowly than aldehydes, and higher temperatures and longer reaction times are often required.[273] In addition, the equilibrium must often be shifted, usually by removal of the water, either azeotropically by distillation, or with a drying agent, such as $TiCl_4$,[274] or with a molecular sieve.[275] Imines have been formed from aldehydes and amines in an ionic liquid.[276]

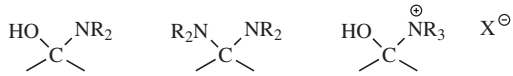
The reaction is often used to effect ring closure.[277] The *Friedländer quinoline synthesis*[278] is an example where ortho alkenyl aniline derivatives give the quinoline, **20**.[279] The alkene derivative can be prepared *in situ* from an aldehyde and a suitably functionalized ylid.[280]

20

[268]Watanabe, Y.; Yamamoto, J.; Akazome, M.; Kondo, T.; Mitsudo, T. *J. Org. Chem.* ***1995***, *60*, 8328.
[269]See Lai, J.T. *Tetrahedron Lett.* ***2002***, *43*, 1965.
[270]Love, B.E.; Ren, J. *J. Org. Chem.* ***1993***, *58*, 5556.
[271]Varma, R.S.; Dahiya, R.; Kumar, S. *Tetrahedron Lett.* ***1997***, *38*, 2039.
[272]Some of these have been observed spectrally; see Forlani, L.; Marianucci, E.; Todesco, P.E. *J. Chem. Res. (S)* ***1984***, 126.
[273]For improved methods, see Morimoto, T.; Sekiya, M. *Chem. Lett.* ***1985***, 1371; Eisch, J.J.; Sanchez, R. *J. Org. Chem.* ***1986***, *51*, 1848.
[274]Weingarten, H.; Chupp, J.P.; White, W.A. *J. Org. Chem.* ***1967***, *32*, 3246.
[275]Bonnett, R.; Emerson, T.R. *J. Chem. Soc.* ***1965***, 4508; Roelofsen, D.P.; van Bekkum, H. *Recl. Trav. Chim. Pays-Bas* ***1972***, *91*, 605.
[276]Andrade, C.K.Z.; Takada, S.C.S.; Alves, L.M.; Rodrigues, J.P.; Suarez, P.A.Z.; Brand, R.F.; Soares, V.C.D. *Synlett* ***2004***, 2135.
[277]For a review of such ring closures, see Katritzky, A.R.; Ostercamp, D.L.; Yousaf, T.I. *Tetrahedron* ***1987***, *43*, 5171.
[278]For a review, see Cheng, C.; Yan, S. *Org. React.* ***1982***, *28*, 37.
[279]See Arcadi, A.; Chiarini, M.; Di Giuseppe, S.; Marinelli, F. *Synlett* ***2003***, 203; Yadav, J.S.; Reddy, B.V.S.; Premalatha, K. *Synlett* ***2004***, 963.
[280]Hsiao, Y.; Rivera, N.R.; Yasuda, N.; Hughes, D.L.; Reider, P.J. *Org. Lett.* ***2001***, *3*, 1101.

Pyrylium ions react with ammonia or primary amines to give pyridinium ions[281] (see p. 498). Primary amines react with 1,4-diketones, with microwave irradiation, to give *N*-substituted pyrroles.[282] Similar reactions in the presence of Montmorillonite KSF[283] or by simply heating the components with tosic acid[284] have been reported.

As mentioned, the reaction of secondary amines with ketones leads to enamines (**10-69**). When secondary amines are added to aldehydes or ketones, the initially formed *N,N*-disubstituted hemiaminals (**21**) cannot lose water in the same way, and in some cases it is possible to isolate them.[285] However, they are generally unstable, and under the reaction conditions usually react further. If no α hydrogen is present, **10** is converted to

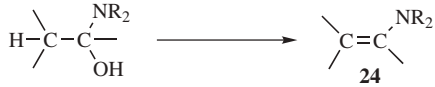


21 **22** (aminal) **23**

the more stable *aminal* (**22**).[286] However, if an α hydrogen is present, water (from **21**) or RNH_2 (from **22**) can be lost in that direction to give an enamine, **24**.[287] This is the most common method[288] for the preparation of enamines and usually takes place when an aldehyde or ketone containing an α hydrogen is treated with a secondary amine. The water is usually removed azeotropically or with a drying agent,[289] but molecular sieves can also be used.[290] Silyl carbamates, such as $Me_2NCO_2SiMe_3$, have been used to convert ketones to enamines.[291] Stable primary enamines have also been prepared.[292] Enamino-ketones have been prepared from diketones and secondary amines using low molecular weight amines in water,[293] or using microwave irradiation on silica gel.[294] Secondary amine perchlorates react

[281]For a review, see Zvezdina, E.A.; Zhadonva, M.P.; Dorofeenko, G.N. *Russ. Chem. Rev.* ***1982***, *51*, 469.
[282]Danks, T.N. *Tetrahedron Lett.* ***1999***, *40*, 3957.
[283]Banik, B.K.; Samajdar, S.; Banik, I. *J. Org. Chem.* ***2004***, *69*, 213.
[284]Klappa, J.J.; Rich, A.E.; McNeill, K. *Org. Lett.* ***2002***, *4*, 435.
[285]For example, see Duhamel, P.; Cantacuzène, J. *Bull. Soc. Chim. Fr.* ***1962***, 1843.
[286]For a review of aminals, see Duhamel, P., in Patai, S. *The Chemistry of Functional Groups, Supplement F*, pt. 2, Wiley, NY, ***1982***, pp. 849–907.
[287]For reviews of the preparation of enamines, see Haynes, L.W.; Cook, A.G., in Cook, A.G. *Enamines*, 2nd. ed., Marcel Dekker, NY, ***1988***, pp. 103–163; Pitacco, G.; Valentin, E., in Patai, S. *The Chemistry of Functional Groups, Supplement F*, pt. 1, Wiley, NY, ***1982***, pp. 623–714.
[288]For another method, see Katritzky, A.R.; Long, Q.; Lue, P.; Jozwiak, A. *Tetrahedron* ***1990***, *46*, 8153.
[289]For example, $TiCl_4$: White, W.A.; Weingarten, H. *J. Org. Chem.* ***1967***, *32*, 213; Kuo, S.C.; Daly, W.H. *J. Org. Chem.* ***1970***, *35*, 1861; Nilsson, A.; Carlson, R. *Acta Chem. Scand. Ser. B* ***1984***, *38*, 523.
[290]Brannock, K.C.; Bell, A.; Burpitt, R.D.; Kelly, C.A. *J. Org. Chem.* ***1964***, *29*, 801; Taguchi, K.; Westheimer, F.H. *J. Org. Chem.* ***1971***, *36*, 1570; Roelofsen, D.P.; van Bekkum, H. *Recl. Trav. Chim. Pays-Bas* ***1972***, *91*, 605; Carlson, R.; Nilsson, A.; Strömqvist, M. *Acta Chem. Scand. Ser. B* ***1983***, *37*, 7.
[291]Kardon, F.; Mörtl, M.; Knausz, D. *Tetrahedron Lett.* ***2000***, *41*, 8937.
[292]Erker, G.; Riedel, M.; Koch, S.; Jödicke, T.; Würthwein, E.-U. *J. Org. Chem.* ***1995***, *60*, 5284.
[293]Stefani, H.A.; Costa, I.M.; Silva, D. de O. *Synthesis* ***2000***, 1526.
[294]Rechsteiner, B.; Texier-Boullet, F.; Hamelin, J. *Tetrahedron Lett.* ***1993***, *34*, 5071.

with aldehydes and ketones to give iminium salts (**10**, p. $$$).[295] Tertiary amines can only give salts (**23**). Enamines have been prepared by the reaction of an aldehyde, a secondary amine and a terminal alkyne in the presence of AgI at 100°C,[296] AgI in an ionic liquid,[297] CuI with microwave irradiation,[298] or a gold catalyst.[299]

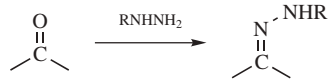


24

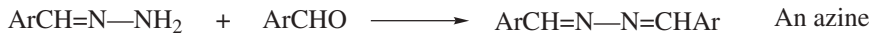
OS **I**, 80, 355, 381; **II**, 31, 49, 65, 202, 231, 422; **III**, 95, 328, 329, 332, 358, 374, 513, 753, 827; **IV**, 210, 605, 638, 824; **V**, 191, 277, 533, 567, 627, 703, 716, 736, 758, 808, 941, 1070; **VI**, 5, 448, 474, 496, 520, 526, 592, 601, 818, 901, 1014; **VII**, 8, 135, 144, 473; **VIII**, 31, 132, 403, 451, 456, 493, 586, 597. Also see OS **IV**, 283, 464; **VII**, 197; **VIII**, 104, 112, 241.

16-14 The Addition of Hydrazine Derivatives to Carbonyl Compounds

Hydrazono-de-oxo-bisubstitution



The product of condensation of a hydrazine and an aldehyde or ketone is called a *hydrazone*. Hydrazine itself gives hydrazones only with aryl ketones. With other aldehydes and ketones, either no useful product can be isolated, or the remaining NH_2 group condenses with a second equivalent of carbonyl compound to give an *azine*. This type of product is especially important for aromatic aldehydes:

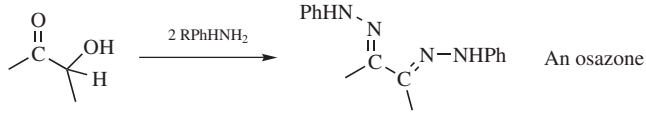


However, in some cases azines can be converted to hydrazones by treatment with excess hydrazine and NaOH.[300] Arylhydrazines, especially phenyl, *p*-nitrophenyl, and 2,4-dinitrophenyl,[301] are used much more often and give the corresponding hydrazones with most aldehydes and ketones.[302] Since these are usually solids, they make excellent derivatives and are commonly employed for this purpose. Cyclic hydrazones are also known,[303] as are conjugated hydrazones.[304] Azides react

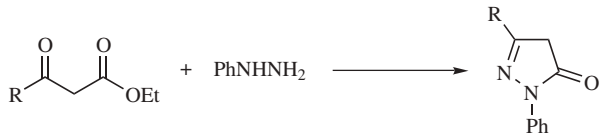
[295]Leonard, N.J.; Paukstelis, J.V. *J. Org. Chem.* ***1964***, *28*, 3021.
[296]Wei, C.; Li, Z.; Li, C.-J. *Org. Lett.* ***2003***, *5*, 4473.
[297]In bmim BF_4, 1-butyl-3-methylimidazolium tetrafluoroborate: Li, Z.; Wei, C.; Chen, L.; Varma, R.S.; Li, C.-J. *Tetrahedron Lett.* ***2004***, *45*, 2443.
[298]Shi, L.; Tu, Y.-Q.; Wang, M.; Zhang, F.-M.; Fan, C.-A. *Org. Lett.* ***2004***, *6*, 1001.
[299]Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* ***2003***, *125*, 9584.
[300]For example, see Day, A.C.; Whiting, M.C. *Org. Synth.* ***VI***, 10.
[301]For an improved procedure for the preparation of 2,4-dinitrophenylhydrazones, see Behforouz, M.; Bolan, J.L.; Flynt, M.S. *J. Org. Chem.* ***1985***, *50*, 1186.
[302]For a review of arylhydrazones, see Buckingham, J. *Q. Rev. Chem. Soc.* ***1969***, *23*, 37.
[303]Nakamura, E.; Sakata, G.; Kubota, K. *Tetrahedron Lett.* ***1998***, *39*, 2157.
[304]Palacios, F.; Aparicio, D.; de los Santos, J.M. *Tetrahedron Lett.* ***1993***, *34*, 3481.

with *N,N*-dimethylhydrazine and ferric chloride to give the *N,N*-dimethylhydrazone.[305] Alkenes react with CO/H_2, phenylhydrazine and a diphosphine catalyst to give a regioisomeric mixture of phenylhydrazones that favored "anti-Markovnikov" addition.[306] Oximes are converted to hydrazones with water and hydrazine in refluxing ethanol.[307]

α-Hydroxy aldehydes and ketones and α-dicarbonyl compounds give *osazones*, in which two adjacent carbons have carbon–nitrogen double bonds:



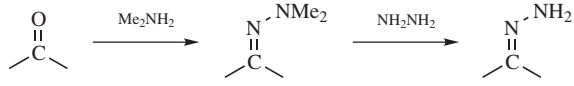
Osazones are particularly important in carbohydrate chemistry. In contrast to this behavior, β-diketones and β-keto esters give *pyrazoles* and *pyrazolones*, respectively (illustrated for β-keto esters):



Other hydrazine derivatives frequently used to prepare the corresponding hydrazone are semicarbazide $NH_2NHCONH_2$, in which case the hydrazone is called a semicarbazone, and *Girard's reagents T and P*, in which case the hydrazone is water soluble because of the ionic group. Girard's reagents are often used for purification of carbonyl compounds.[308]

Girard's reagent T Girard's reagent P

Simple *N*-unsubstituted hydrazones can be obtained by an exchange reaction. The *N,N*-dimethylhydrazone is prepared first, and then treated with hydrazine:[309]



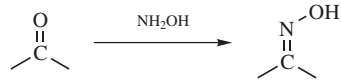
No azines are formed under these conditions.

[305]Barrett, I.C.; Langille, J.D.; Kerr, M.A. *J. Org. Chem.* ***2000***, *65*, 6268.
[306]Ahmed, M.; Jackstell, R.; Seayad, A.M.; Klein, H.; Beller, M. *Tetrahedron Lett.* ***2004***, *45*, 869.
[307]Pasha, M.A.; Nanjundaswamy, H.M. *Synth. Commun.* ***2004***, *34*, 3827.
[308]For a study of the mechanism with Girard's reagent T, see Stachissini, A.S.; do Amaral, L. *J. Org. Chem.* ***1991***, *56*, 1419.
[309]Newkome, G.R.; Fishel, D.L. *J. Org. Chem.* ***1966***, *31*, 677.

OS **II**, 395; **III**, 96, 351; **IV**, 351, 377, 536, 884; **V**, 27, 258, 747, 929; **VI**, 10, 12, 62, 242, 293, 679, 791; **VII**, 77, 438. Also see OS **III**, 708; **VI**, 161; **VIII**, 597.

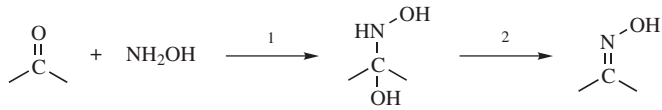
16-15 The Formation of Oximes

Hydroxyimino-de-oxo-bisubstitution



In a reaction very much like **16-14**, oximes can be prepared by the addition of hydroxylamine to aldehydes or ketones. Derivatives of hydroxylamine [e.g., H_2NOSO_3H and $HON(SO_3Na)_2$] have also been used. For hindered ketones, such as hexamethylacetone, high pressures (as high as 10,000 atm) may be necessary.[310] The reaction of hydroxylamine with unsymmetrical ketones or with aldehydes leads to a mixture of (*E*)- and (*Z*)-isomers. For aromatic aldehydes, heating with K_2CO_3 led to the (*E*)- isomer whereas heating with $CuSO_4$ gave the (*Z*)-hydroxylamine.[311] Hydroxylamines react with ketones in ionic liquids[312] and on silica gel.[313]

It has been shown[314] that the rate of formation of oximes is at a maximum at a pH that depends on the substrate but is usually ~4, and that the rate decreases as the pH is either raised or lowered from this point. We have previously seen (p. 1256) that bell-shaped curves like this are often caused by changes in the rate-determining step. In this case, at low pH values step 2 is rapid (because it is acid-catalyzed), and step 1

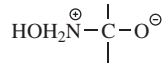


25

is slow (and rate-determining), because under these acidic conditions most of the NH_2OH molecules have been converted to the conjugate NH_3OH^+ ions, which cannot attack the substrate. As the pH is slowly increased, the fraction of free NH_2OH molecules increases and consequently so does the reaction rate, until the maximum rate is reached at ~pH 4. As the rising pH has been causing an increase in the rate of step 1, it has also been causing a *decrease* in the rate of the acid-catalyzed step 2, although this latter process has not affected the overall rate since step 2 was still faster than step 1. However, when the pH goes above ~4, step 2 becomes rate-determining, and although the rate of step 1 is still increasing (as it will until essentially all the NH_2OH is unprotonated), it is now

[310]Jones, W.H.; Tristram, E.W.; Benning, W.F. *J. Am. Chem. Soc.* ***1959***, *81*, 2151.
[311]Sharghi, H.; Sarvari, M.H. *Synlett* ***2001***, 99.
[312]In bmim PF_6, 1-butyl-3-methylimidazolium hexafluorophosphate: Ren, R.X.; Ou, W. *Tetrahedron Lett.* ***2001***, *42*, 8445.
[313]Hajipour, A.R.; Mohammadpoor-Baltork, I.; Nikbaghat, K.; Imanzadeh, G. *Synth. Commun.* ***1999***, *29*, 1697.
[314]Jencks, W.P. *J. Am. Chem. Soc.* ***1959***, *81*, 475; *Prog. Phys. Org. Chem.* ***1964***, *2*, 63.

step 2 that determines the rate, and this step is slowed by the decrease in acid concentration. Thus the overall rate decreases as the pH rises beyond ~4. It is likely that similar considerations apply to the reaction of aldehydes and ketones with amines, hydrazines, and other nitrogen nucleophiles.[315] There is evidence that when the nucleophile is 2-methylthiosemicarbazide, there is a second change in the rate-determining step: above pH ~10 *basic* catalysis of step 2 has increased the rate of this step to the point where step 1 is again rate determining.[316] Still a third change in the rate-determining step has been found at about pH 1, showing that at least in some cases step 1 actually consists of two steps: formation of a zwitterion, for example,



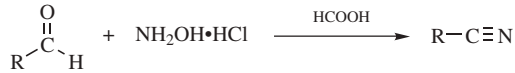
in the case shown above, and conversion of this to **25**.[317] The intermediate **25** has been detected by nmr in the reaction between NH_2OH and acetaldehyde.[318]

In another type of process, oximes can be obtained by passing a mixture of ketone vapor, NH_3, and O_2 over a silica-gel catalyst.[319] Ketones can also be converted to oximes by treatment with other oximes, in a transoximation reaction.[320]

OS **I**, 318, 327; **II**, 70, 204, 313, 622; **III**, 690, **IV**, 229; **V**, 139, 1031; **VII**, 149. See also, OS **VI**, 670.

16-16 The Conversion of Aldehydes to Nitriles

Nitrilo-de-hydro,oxo-tersubstitution



Aldehydes can be converted to nitriles in one step by treatment with hydroxylamine hydrochloride and either formic acid,[321] $NaHSO_4$•SiO_2 with microwave irradiation,[322] or $(Bu_4N)_2S_2O_8$ with $Cu(HCO_2)$•$Ni(COOH)_2$ and aq. KOH.[323] Heating in NMP is also effective with aryl aldehydes[324] and heating on dry alumina with

[315]For reviews of the mechanism of such reactions, see Cockerill, A.F.; Harrison, R.G., in Patai, S. *The Chemistry of Functional Groups: Supplement A*, pt. 1, Wiley, NY, ***1977***, pp. 288–299; Sollenberger, P.Y.; Martin, R.B., in Patai, S. *The Chemistry of the Amino Group*, Wiley, NY, ***1968***, pp. 367–392. For isotope effect studies, see Rossi, M.H.; Stachissini, A.S.; do Amaral, L. *J. Org. Chem.* ***1990***, *55*, 1300.

[316]Sayer, J.M.; Jencks, W.P. *J. Am. Chem. Soc.* ***1972***, *94*, 3262.

[317]Sayer, J.M.; Edman, C. *J. Am. Chem. Soc.* ***1979***, *101*, 3010.

[318]Cocivera, M.; Fyfe, C.A.; Effio, A.; Vaish, S.P.; Chen, H.E. *J. Am. Chem. Soc.* ***1976***, *98*, 1573; Cocivera, M.; Effio, A. *J. Am. Chem. Soc.* ***1976***, *98*, 7371.

[319]Armor, J.N. *J. Am. Chem. Soc.* ***1980***, *102*, 1453.

[320]For example, see Block Jr., P.; Newman, M.S. *Org. Synth.* ***V***, 1031.

[321]Olah, G.A.; Keumi, T. *Synthesis* ***1979***, 112.

[322]Das, B.; Ramesh, C.; Madhusudhan, P. *Synlett* ***2000***, 1599.

[323]Chen, F.-E.; Fu, H.; Meng, G.; Cheng, Y.; Lü, Y.-X. *Synthesis* ***2000***, 1519.

[324]Kumar, H.M.S.; Reddy, B.V.S.; Reddy, P.T.; Yadav, J.S. *Synthesis* ***1999***, 586; Chakraborti, A.K.; Kaur, G. *Tetrahedron* ***1999***, *55*, 13265.

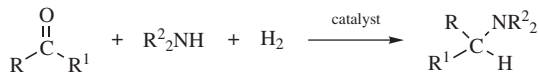
aliphatic aldehyde.[325] The reaction is a combination of **16-15** and **17-29**. Direct nitrile formation has also been accomplished with certain derivatives of NH_2OH, notably, NH_2OSO_2OH.[326] Treatment with hydroxylamine and NaI[327] or certain carbonates[328] also converts aldehydes to the nitrile. Another method involves treatment with hydrazoic acid, though the Schmidt reaction (**18-16**) may compete.[329] Aromatic aldehydes have been converted to nitriles in good yield with NH_2OH/HCOOH on silica gel.[330] Microwave irradiation has been used with NH_2OH•HCl and another reagent, which includes phthalic anhydride,[331] Bu_2SnO•Al_2O_3,[332] or H—Y zeolite.[333] Other reagents include *N*-phenylurea with tosic acid,[334] MnO_2 and ammonia,[335] I_2 with aqueous ammonia,[336] dimethylhydrazine followed by dimethyl sulfoxide,[337] trimethylsilyl azide,[338] and with hydroxylamine hydrochloride, $MgSO_4$, and TsOH.[339] The reaction of a conjugated aldehyde with ammonia, CuCl and 50% H_2O_2 gave the conjugated nitrile.[340] Benzylic alcohols can be oxidized in the presence of ammonia to give the nitrile.[341] Trichloroisocyanuric acid with a catalytic amount of TEMPO (p. 274) converts aldehydes to nitriles at 0°C in dichloromethane.[342]

On treatment with 2 equivalents of dimethylaluminum amide Me_2AlNH_2, carboxylic esters can be converted to nitriles: RCOOR′ → RCN.[343] This is very likely a combination of **16-75** and **17-30**. See also, **19-5**.

OS **V**, 656.

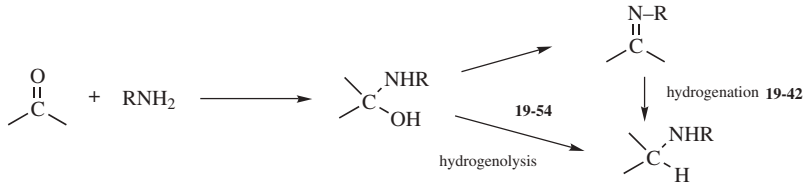
16-17 Reductive Alkylation of Ammonia or Amines

Hydro,dialkylamino-de-oxo-bisubstitution



[325]Sharghi, H.; Sarvari, M.H. *Tetrahedron* ***2002***, *58*, 10323. With wet alumina followed by $MeSO_2Cl$ the product is an amide.
[326]Streith, J.; Fizet, C.; Fritz, H. *Helv. Chim. Acta* ***1976***, *59*, 2786.
[327]Ballini, R.; Fiorini, D.; Palmieri, A. *Synlett* ***2003***, 1841.
[328]Bose, D.S.; Goud, P.R. *Synth. Commun.* ***2002***, *32*, 3621.
[329]For additional methods, see Gelas-Mialhe, Y.; Vessière, R. *Synthesis* ***1980***, 1005; Arques, A.; Molina, P.; Soler, A. *Synthesis* ***1980***, 702; Sato, R.; Itoh, K.; Itoh, K.; Nishina, H.; Goto, T.; Saito, M. *Chem. Lett.* ***1984***, 1913; Reddy, P.S.N.; Reddy, P.P. *Synth. Commun.* ***1988***, *18*, 2179; Neunhoeffer, H.; Diehl, W.; Karafiat, U. *Liebigs Ann. Chem.* ***1989***, 105.
[330]Kabalka, G.W.; Yang, K. *Synth. Commun.* ***1998***, *28*, 3807.
[331]Veverková, E.; Toma, Š. *Synth. Commun.* ***2000***, *30*, 3109.
[332]Yadav, J.S.; Reddy, B.V.S.; Madan, Ch. *J. Chem. Res. (S)* ***2001***, 190.
[333]Srinivas, K.V.N.S.; Reddy, E.B.; Das, B. *Synlett* ***2002***, 625.
[334]Cokun, N.; Arikan, N. *Tetrahedron* ***1999***, *55*, 11943.
[335]Lai, G.; Bhamare, N.K.; Anderson, W.K. *Synlett* ***2001***, 230.
[336]Talukdar, S.; Hsu, J.-L.; Chou, T.-C.; Fang, J.-M. *Tetrahedron Lett.* ***2001***, *42*, 1103.
[337]Kamal, A.; Arifuddin, M.; Rao, N.V. *Synth. Commun.* ***1998***, *28*, 4507.
[338]Nishiyama, K.; Oba, M.; Watanabe, A. *Tetrahedron* ***1987***, *43*, 693.
[339]Ganboa, I.; Palomo, C. *Synth. Commun.* ***1983***, *13*, 219.
[340]Erman, M.B.; Snow, J.W.; Williams, M.J. *Tetrahedron Lett.* ***2000***, *41*, 6749.
[341]See Baxendale, I.R.; Ley, S.V.; Sneddon, H.F. *Synlett* ***2002***, 775; McAllister, G.D.; Wilfred, C.D.; Taylor, R.J.K. *Synlett* ***2002***, 1291.
[342]Chen, F.-E.; Kuang, Y.-Y.; Dai, H.-F.; Lu, L.; Huo, M. *Synthesis* ***2003***, 2629.
[343]Wood, J.L.; Khatri, N.A.; Weinreb, S.M. *Tetrahedron Lett.* ***1979***, 4907.

When an aldehyde or a ketone is treated with ammonia or a primary or secondary amine in the presence of hydrogen and a hydrogenation catalyst (heterogeneous or homogeneous),[344] *reductive alkylation* of ammonia or the amine (or *reductive amination* of the carbonyl compound) takes place.[345] The reaction can formally be regarded as occurring in the following manner (shown for a primary amine), which probably does correspond to the actual sequence of steps:[346] In this regard, the reaction of an aldehyde with an amine to give an iminium salt (**16-31**) can be followed in a second chemical step of reduction of the C=N unit (**19-42**) using $NaBH_4$ or a variety of other reagents.[347]



Primary amines have been prepared from many aldehydes with at least five carbons and from many ketones by treatment with ammonia and a reducing agent. Smaller aldehydes are usually too reactive to permit isolation of the primary amine. Secondary amines have been prepared by both possible procedures: 2 equivalents of ammonia and 1 equivalent of aldehyde or ketone, and 1 equivalent of primary amine and 1 equivalent of carbonyl compound, the latter method being better for all but aromatic aldehydes. Tertiary amines can be prepared in three ways, but the method is seldom carried out with 3 equivalents of ammonia and 1 equivalent of carbonyl compound. Much more often they are prepared from primary or secondary amines.[348] When the reagent is ammonia, it is possible for the initial product to react again and for this product to react again, so that secondary and tertiary amines are usually obtained as side products. Similarly, primary amines give tertiary as well as secondary amines. In order to minimize this, the aldehyde or ketone is treated with an excess of ammonia or primary amine (unless of course the higher amine is desired).

For ammonia and primary amines there are two possible pathways, but when secondary amines are involved, only the hydrogenolysis pathway is possible. The reaction is compatible with amino acids, giving the *N*-alkylated amino acid.[349]

[344]**Rh**: Kadyrov, R.; Riermeier, T.H.; Dingerdissen, U.; Tararov, V.; Börner, A. *J. Org. Chem.* ***2003***, *68*, 4067; Gross, T.; Seayad, A.M.; Ahmad, M.; Beller, M. *Org. Lett.* ***2002***, *4*, 2055. **Ir**: Chi, Y.; Zhou, Y.-G.; Zhang, X. *J. Org. Chem.* ***2003***, *68*, 4120.

[345]For reviews, see Rylander, P.N. *Hydrogenation Methods*, Academic Press, NY, ***1985***, pp. 82–93; Klyuev, M.V.; Khidekel, M.L. *Russ. Chem. Rev.* ***1980***, *49*, 14; Rylander, P.N. *Catalytic Hydrogenation over Platinum Metals*, Academic Press, NY, ***1967***, pp. 291–303.

[346]See, for example, Le Bris, A.; Lefebvre, G.; Coussemant, F. *Bull. Soc. Chim. Fr.* ***1964***, 1366, 1374, 1584, 1594.

[347]For a simple example see, Bhattacharyya, S. *Synth. Commun.* ***2000***, *30*, 2001.

[348]For a review of the preparation of tertiary amines by reductive alkylation, see Spialter, L.; Pappalardo, J.A. *The Acyclic Aliphatic Tertiary Amines*, Macmillan, NY, ***1965***, pp. 44–52.

[349]Song, Y.; Sercel, A.D.; Johnson, D.R.; Colbry, N.L.; Sun, K.-L.; Roth, B.D. *Tetrahedron Lett.* ***2000***, *41*, 8225.

Other reducing agents[350] can be used instead of hydrogen and a catalyst, among them zinc and HCl, $B_{10}H_{14}$[351] or $B_{10}H_{14}$ with Pd/C,[352] a picolinyl borane complex in acetic acid–methanol,[353] $PhSiH_3$ with 2% Bu_2SnCl_2,[354] and polymethylhydrosiloxane.[355] Several hydride reducing agents can be used, including $NaBH_4$[356] sodium borohydride with $Ti(OiPr)_4$[357] or $NiCl_2$,[358] $NaBH_4/H_3BO_4$,[359] borohydride-exchange resin,[360] sodium cyanoborohydride ($NaBH_3CN$),[361] sodium triacetoxyborohydride,[362] or a polymer-bound triethylammonium acetoxyborohydride.[363] A Hantzsch dihydropyridine in conjunction with a scandium catalyst has been used.[364] An interesting variation uses a benzylic alcohol in a reaction with a primary amine, and a mixture of MnO_2 and $NaBH_4$, giving *in situ* oxidation to the aldehyde and reductive amination to give the amine as the final product.[365]

Formic acid is commonly used for reductive amination[366] in what is called the *Wallach reaction*. Secondary amines react with formaldehyde and NaH_2PO_3 to give the *N*-methylated tertiary amine[367] and microwave irradiation has also been used.[368] Conjugated aldehydes are converted to alkenyl-amines with the amine/silica gel followed by reduction with zinc borohydride.[369] In the particular case where primary or secondary amines are reductively methylated with formaldehyde and formic acid, the method is called the *Eschweiler–Clarke procedure*. Heating with paraformaldehyde and oxalyl chloride has been used to give the same result.[370] It is

[350]For a list of many of these, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 835–840.
[351]Bae, J.W.; Lee, S.H.; Cho, Y.J.; Yoon, C.M. *J. Chem. Soc., Perkin Trans. 1* ***2000***, 145.
[352]Jung, Y.J.; Bae, J.W.; Park, E.S.; Chang, Y.M.; Yoon, C.M. *Tetrahedron* ***2003***, *59*, 10331.
[353]Sato, S.; Sakamoto, T.; Miyazawa, E.; Kitugawa, Y. *Tetrahedron* ***2004***, *60*, 7899.
[354]Apodaca, R.; Xiao, W. *Org. Lett.* ***2001***, *3*, 1745.
[355]Chandrasekhar, S.; Reddy, Ch.R.; Ahmed, M. *Synlett* ***2000***, 1655.
[356]Sondengam, B.L.; Hentchoya Hémo, J.; Charles, G. *Tetrahedron Lett.* ***1973***, 261; Schellenberg, K.A. *J. Org. Chem.* ***1963***, *28*, 3259; Gribble, G.W.; Nutaitis, C.F. *Synthesis* ***1987***, 709.
[357]Neidigh, K.A.; Avery, M.A.; Williamson, J.S.; Bhattacharyya, S. *J. Chem. Soc. Perkin Trans. 1* ***1998***, 2527; Bhattacharyya, S. *J. Org. Chem.* ***1995***, *60*, 4928.
[358]Saxena, I.; Borah, R.; Sarma, J.C. *J. Chem. Soc., Perkin Trans. 1* ***2000***, 503.
[359]This is a solvent-free reaction. See Cho, B.T.; Kang, S.K. *Synlett* ***2004***, 1484.
[360]Yoon, N.M.; Kim, E.G.; Son, H.S.; Choi, J. *Synth. Commun.* ***1993***, *23*, 1595.
[361]Borch, R.F.; Bernstein, M.D.; Durst, H.D. *J. Am. Chem. Soc.* ***1971***, *93*, 2897; Mattson, R.J.; Pham, K.M.; Leuck, D.J.; Cowen, K.A. *J. Org. Chem.* ***1990***, *55*, 2552. See also, Barney, C.L.; Huber, E.W.; McCarthy, J.R. *Tetrahedron Lett.* ***1990***, *31*, 5547. For reviews of $NaBH_3CN$, see Hutchins, R.O.; Natale, N.R. *Org. Prep. Proced. Int.* ***1979***, *11*, 201; Lane, C.F. *Synthesis* ***1975***, 135.
[362]Abdel-Magid, A.F.; Maryanoff, C.A.; Carson, K.G. *Tetrahedron Lett.* ***1990***, *31*, 5595; Abdel-Magid, A.F.; Carson, K.G.; Harris, B.D.; Maryanoff, C.A.; Shah, R.D. *J. Org. Chem.* ***1996***, *61*, 3849.
[363]Bhattacharyya, S.; Rana, S.; Gooding, O.W.; Labadie, J. *Tetrahedron Lett.* ***2003***, *44*, 4957.
[364]Itoh, T.; Nagata, K.; Kurihara, A.; Miyazaki, M.; Ohsawa, A. *Tetrahedron lett.* ***2002***, *43*, 3105; Itoh, T.; Nagata, K.; Miyazaki, M.; Ishikawa, H.; Kurihara, A.; Ohsawa, A. *Tetrahedron* ***2004***, *60*, 6649.
[365]Kanno, H.; Taylor, R.J.K. *Tetrahedron Lett.* ***2002***, *43*, 7337.
[366]For a microwave induced reaction see Torchy, S.; Barbry, D. *J. Chem. Res. (S)* ***2001***, 292.
[367]Davis, B.A.; Durden, D.A. *Synth. Commun.* ***2000***, *30*, 3353.
[368]Barbry, D.; Torchy, S. *Synth. Commun.* ***1996***, *26*, 3919.
[369]Ranu, B.C.; Majee, A.; Sarkar, A. *J. Org. Chem.* ***1998***, *63*, 370.
[370]Rosenau, T.; Potthast, A.; Röhrling, J.; Hofinger, A.; Sixxa, H.; Kosma, P. *Synth. Commun.* ***2002***, *32*, 457.

possible to use ammonium (or amine) salts of formic acid,[371] or formamides, as a substitute for the Wallach conditions. This method is called the *Leuckart reaction*,[372] and in this case the products obtained are often the *N*-formyl derivatives of the amines instead of the free amines. A transition-metal catalyzed variation has been reported.[373] Primary and secondary amines can be *N*-ethylated (e.g., ArNHR → ArNREt) by treatment with $NaBH_4$ in acetic acid.[374] Aldehydes react with aniline in the presence of Montmorillonite K10 clay and microwaves to give the amine.[375] Tributyltin hydride is used with an ammonium salt,[376] or Bu_2SnClH•HMPA with an aromatic amine,[377] in the presence of a ketone to give the corresponding amine. Allylic silanes react with aldehydes and carbamates, in the presence of bismuth catalysts,[378] or BF_3•OEt_2[379] to give the corresponding allylic *N*-carbamoyl derivative, and trityl perchlorate has been used for the same purpose when *N*-trimethylsilyl carbamates are employed.[380] The reaction can be done with aromatic amines in the presence of vinyl ethers and a copper complex to give β-amino ketones.[381] Reductive amination of an aryl amine and an aryl aldehyde that contains a ortho conjugated ketone substituents gives the amine, which adds 1,4- (**15-AA**) to the α,β-unsaturated ketone unit to give a bicyclic amine.[382] Alternative methods of reductive alkylation have been developed. Alkylation of an imine formed *in situ* is also possible.[383]

Reductive alkylation has also been carried out on nitro, nitroso, azo, and other compounds that are reduced *in situ* to primary or secondary amines. Azo compounds react with aldehydes, in the presence of proline, and subsequent reduction with $NaBH_4$ gives the chiral hydrazine derivative.[384]

[371]For a review of ammonium formate in organic synthesis, see Ram, S.; Ehrenkaufer, R.E. *Synthesis* ***1988***, 91.

[372]For a review, see Moore, M.L. *Org. React.* ***1949***, *5*, 301. For discussions of the mechanism, see Awachie, P.I.; Agwada, V.C. *Tetrahedron* ***1990***, *46*, 1899, and references cited therein. For a microwave-induced variation, see Loupy, A.; Monteux, D.; Petit, A.; Aizpurua, J.M.; Domínguez, E.; Palomo, C. *Tetrahedron Lett.* ***1996***, *37*, 8177. For the effects of added formamide, see Lejon, T.; Helland, I. *Acta Chem. Scand.* ***1999***, *53*, 76.

[373]Using a rhodium catalyst, see Kitamura, M.; Lee, D.; Hayashi, S.; Tanaka, S.; Yoshimura, M. *J. Org. Chem.* ***2002***, *67*, 8685. For a review of this reaction, see Riermeier, T.H.; Dingerdissen, U.; Börner, A. *Org. Prep. Proceed. Int.* ***2004***, *36*, 99.

[374]For a review, see Gribble, G.W.; Nutaitis, C.F. *Org. Prep. Proced. Int.* ***1985***, *17*, 317, pp. 336–350.

[375]Varma, R.S.; Dahiya, R. *Tetrahedron* ***1998***, *54*, 6293.

[376]Suwa, T.; Sugiyama, E.; Shibata, I.; Baba, A. *Synlett* ***2000***, 556.

[377]Suwa, T.; Sugiyama, E.; Shibata, I.; Baba, A. *Synthesis* ***2000***, 556.

[378]Ollevier, T.; Ba, T. *Tetrahedron Lett.* ***2003***, *44*, 9003.

[379]Billet, M.; Klotz, P.; Mann, A. *Tetrahedron lett.* ***2001***, *42*, 631.

[380]Niimi, L.; Serita, K.-i.; Hiraoka, S.; Yokozawa, T. *Tetrahedron Lett.* ***2000***, *41*, 7075.

[381]Kobayashi, S.; Ueno, M.; Suzuki, R.; Ishitani, H.; Kim, H.-S.; Wataya, Y. *J. Org. Chem.* ***1999***, *64*, 6833.

[382]Suwa, T.; Shibata, I.; Nishino, K.; Baba, A. *Org. Lett.* ***1999***, *1*, 1579.

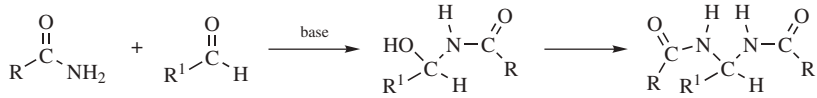
[383]See Choudary, B.M.; Jyothi, K.; Madhi, S.; Kantam, M.L. *Synlett* ***2004***, 231. For an example in the ionic liquid bmim BF_4, 1-butyl-3-methylimidazolium tetrafluoroborate, see Yadav, J.S.; Reddy, B.V.S.; Raju, A.K. *Synthesis* ***2003***, 883.

[384]List, B. *J. Am. Chem. Soc.* ***2002***, *124*, 5656; Kumaragurubaran, N.; Juhl, K.; Zhuang, W.; Bøgevig, A.; Jørgensen, K.A. *J. Am. Chem. Soc.* ***2002***, *124*, 6254.

OS **I**, 347, 528, 531; **II**, 503; **III**, 328, 501, 717, 723; **IV**, 603; **V**, 552; **VI**, 499; **VII**, 27.

16-18 Addition of Amides to Aldehydes

Alkylamido-de-oxo-bisubstitution

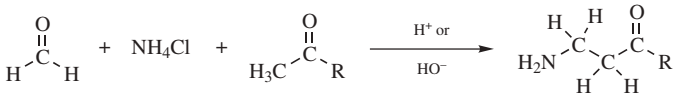


Amides can add to aldehydes in the presence of bases (so the nucleophile is actually $RCONH^-$) or acids to give acylated amino alcohols, which often react further to give alkylidene or arylidene bisamides.[385] If the R′ group contains an α hydrogen, water may split out.

Sulfonamides add to aldehydes to give the *N*-sulfonyl imine. Benzaldehyde reacts with $TsNH_2$, for example, at 160°C in the presence of $Si(OEt)_4$,[386] with trifluoroacetic anhydride (TFAA) in refluxing dichloromethane,[387] or with $TiCl_4$ in refluxing dichloroethane,[388] to give the *N*-tosylimine, Ts—N=CHPh. In a similar manner, the reaction of $TolSO_2Na + PhSO_2Na$ with an aldehyde in aqueous formic acid gives the *N*-phenylsulfonyl imine.[389] The reaction of an aldehyde with $Ph_3P{=}NTs$ and a ruthenium catalyst gives the *N*-tosyl imine.[390] Reaction of aldehydes with $LiAl(NHBn)_4$ also give the corresponding *N*-benzylimine.[391]

16-19 The Mannich Reaction

Acyl,**amino-de-oxo-bisubstitution**, and so on



In the *Mannich reaction*, formaldehyde (or sometimes another aldehyde) is condensed with ammonia, in the form of its salt, and a compound containing an active hydrogen.[392] This can formally be considered as an addition of ammonia to give

[385]For reviews, see Challis, B.C.; Challis, J.A. in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 754–759; Zaugg, H.E.; Martin, W.B. *Org. React.* ***1965***, *14*, 52, 91–95, 104–112. For a discussion, see Gilbert, E.E. *Synthesis* ***1972***, 30.

[386]Love, B.E.; Raje, P.S.; Williams II, T.C. *Synlett* ***1994***, 493.

[387]Lee, K.Y.; Lee, C.G.; Kim, J.N. *Tetrahedron Lett.* ***2003***, *44*, 1231.

[388]Ram, R.N.; Khan, A.A. *Synth. Commun.* ***2001***, *31*, 841.

[389]Chemla, F.; Hebbe, V.; Normant, J.-F. *Synthesis* ***2000***, 75.

[390]Jain, S.L.; Sharma, V.B.; Sain, B. *Tetrahedron Lett.* ***2004***, *45*, 4341.

[391]Solladié-Cavallo, A.; Benchegroun, M.; Bonne, F. *Synth. Commun.* ***1993***, *23*, 1683.

[392]For reviews, see Tramontini, M.; Angiolini, L. *Tetrahedron* ***1990***, *46*, 1791; Gevorgyan, G.A.; Agababyan, A.G.; Mndzhoyan, O.L. *Russ. Chem. Rev.* ***1984***, *53*, 561; Tramontini, M. *Synthesis* ***1973***, 703; House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 654–660. For reviews on the reactions of Mannich Bases, see Tramontini, M.; Angeloni, L. cited above; Gevorgyan, G.A.; Agababyan, A.G.; Mndzhoyan, O.L. *Russ. Chem. Rev.* ***1985***, *54*, 495.

H_2NCH_2OH, followed by a nucleophilic substitution. Instead of ammonia, the reaction can be carried out with salts of primary or secondary amines,[393] or with amides,[394] in which cases the product is substituted on the nitrogen with R, R_2, and RCO, respectively. The imine can be generated *in situ*, and the reaction of a ketone, formaldehyde, and diethylamine with microwave irradiation gave the Mannich product, a β-amino ketone.[395] Arylamines do not normally give the reaction. Hydrazines can be used.[396] The product is referred to as a *Mannich base*. Many active hydrogen compounds give the reaction, including ketones and aldehydes, esters, nitroalkanes,[397] and nitriles as well as ortho-carbons of phenols, the carbon of terminal alkynes, the oxygen of alcohols and the sulfur of thiols.[398] Vinylogous Mannich reactions are known.[399]

The Mannich base can react further in three ways. If it is a primary or secondary amine, it may condense with one or two additional molecules of aldehyde and active compound, for example,

$$H_2NCH_2CH_2COR \xrightarrow[CH_3COR]{HCHO} HN(CH_2CH_2COR)_2 \xrightarrow[CH_3COR]{HCHO} N(CH_2CH_2COR)_3$$

If the active hydrogen compound has two or three active hydrogens, the Mannich base may condense with one or two additional molecules of aldehyde and ammonia or amine, for example,

$$H_2NCH_2CH_2COR \xrightarrow[NH_3]{HCHO} (H_2NCH_2)_2CHCOR \xrightarrow[NH_3]{HCHO} (H_2NCH_2)_3CHCOR$$

Another further reaction consists of condensation of the Mannich base with excess formaldehyde:

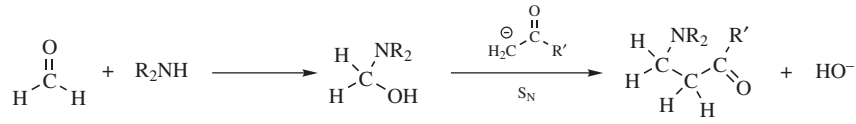
$$H_2NCH_2CH_2COR + HCHO \longrightarrow H_2C{=}NCH_2CH_2COR$$

Sometimes it is possible to obtain these products of further condensation as the main products of the reaction. At other times they are side products.

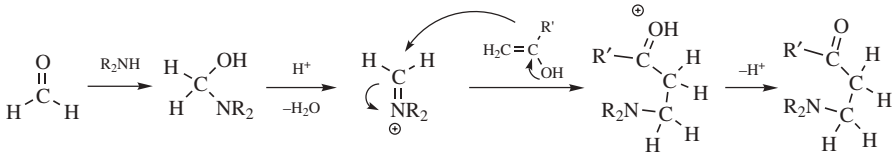
When the Mannich base contains an amino group β to a carbonyl (and it usually does), ammonia is easily eliminated. This is a route to α,β-unsaturated aldehydes, ketones, esters, and so on.

[393]For a review where the amine component is an amino acid, see Agababyan, A.G.; Gevorgyan, G.A.; Mndzhoyan, O.L. *Russ. Chem. Rev.* ***1982***, *51*, 387.
[394]Hellmann, H. *Angew. Chem.* ***1957***, *69*, 463; *Newer Methods Prep. Org. Chem.* ***1963***, *2*, 277.
[395]Gadhwal, S.; Baruah, M.; Prajapati, D.; Sandhu, J.S. *Synlett* ***2000***, 341.
[396]El Kaim, L.; Grimaud, L.; Perroux, Y.; Tirla, C. *J. Org. Chem.* ***2003***, *68*, 8733.
[397]Qian, C.; Gao, F.; Chen, R. *Tetrahedron Lett.* ***2001***, *42*, 4673. See Baer, H.H.; Urbas, L., in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, Wiley, NY, ***1970***, pp. 117–130.
[398]see Massy, D.J.R. *Synthesis* ***1987***, 589; Dronov, V.I.; Nikitin, Yu.E. *Russ. Chem. Rev.* ***1985***, *54*, 554
[399]Bur, S.; Martin, S.F. *Tetrahedron* ***2001***, *57*, 3221. For a review, see Martin, S.F. *Acc. Chem. Res.* ***2002***, *35*, 895.

Studies of the reaction kinetics have led to the following proposals for the mechanism of the Mannich reaction.[400]
The base-catalyzed reaction:



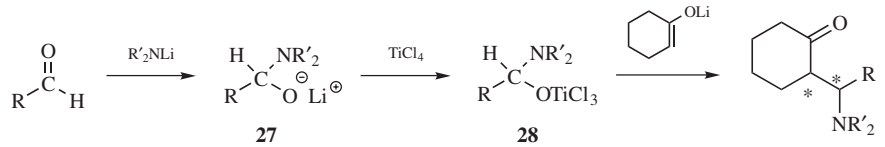
The acid-catalyzed reaction:



26

According to this mechanism, it is the free amine, not the salt that reacts, even in acid solution; and the active-hydrogen compound (in the acid-catalyzed process) reacts as the enol when that is possible. This latter step is similar to what happens in **12-4**. There is kinetic evidence for the intermediacy of the iminium ion (**26**).[401]

When an unsymmetrical ketone is used as the active-hydrogen component, two products are possible. Regioselectivity has been obtained by treatment of the ketone with pre-formed iminium ions:[402] the use of $Me_2N^+{=}CH_2$ $CF_3COO^\ominus$ in CF_3COOH gives substitution at the more highly substituted position, while with $(i\text{Pr})_2N{=}CH_2^+$ $ClO_4^\ominus$ the reaction takes place at the less highly substituted position.[403] The pre-formed iminium compound dimethyl(methylene)ammonium iodide $CH_2{=}N^+Me_2$ $I^\ominus$, called *Eschenmoser's salt*,[404] has also been used in Mannich reactions.[405] The analogous chloride salt has been condensed with an imine to give and a β,β′-dimethylamino ketone after acid hydrolysis.[406]



27 **28**

[400]Cummings, T.F.; Shelton, J.R. *J. Org. Chem.* ***1960***, *25*, 419.
[401]Benkovic, S.J.; Benkovic, P.A.; Comfort, D.R. *J. Am. Chem. Soc.* ***1969***, *91*, 1860.
[402]For earlier use of pre-formed iminium ions in the Mannich reaction, see Ahond, A.; Cavé, A.; Kan-Fan, C.; Potier, P. *Bull. Soc. Chim. Fr.* ***1970***, 2707; Schreiber, J.; Maag, H.; Hashimoto, N.; Eschenmoser, A. *Angew. Chem. Int. Ed.* ***1971***, *10*, 330.
[403]Jasor, Y.; Luche, M.; Gaudry, M.; Marquet, A. *J. Chem. Soc., Chem. Commun.* ***1974***, 253; Gaudry, M.; Jasor, Y.; Khac, T.B. *Org. Synth.* ***VI***, 474.
[404]Schreiber, J.; Maag, H.; Hashimoto, N.; Eschenmoser, A. *Angew. Chem. Int. Ed.* ***1971***, *10*, 330.
[405]See Holy, N.; Fowler, R.; Burnett, E.; Lorenz, R. *Tetrahedron* ***1979***, *35*, 613; Bryson, T.A.; Bonitz, G.H.; Reichel, C.J.; Dardis, R.E. *J. Org. Chem.* ***1980***, *45*, 524, and references cited therein.
[406]Arend, M.; Risch, N. *Tetrahedron Lett.* ***1999***, *40*, 6205.

Another type of pre-formed reagent (**28**) has been used to carry out diastereoselective Mannich reactions. The lithium salts **27** are treated with $TiCl_4$ to give **28**, which is then treated with the enolate of a ketone.[407] The palladium catalyzed Mannich reaction of enol ethers to imines is also known.[408] The reaction of silyl enol ethers and imines is catalyzed by HBF_4 in aqueous methanol.[409] Similarly, silyl enol ethers react with aldehydes and aniline in the presence of $InCl_3$ to give the β-amino ketone.[410] Imines react on Montmorillonite K10 clay and microwave irradiation gives β-amino esters.[411] Enol ethers react similarly in the presence of $Yb(OTf)_3$.[412]

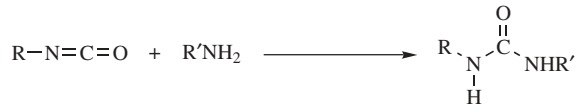
Enantioselective Mannich reactions are known.[413] The most common method uses a chiral catalyst, including proline,[414] proline derivatives or proline analogs.[415] Chiral diamine[416] or phosphine-imine[417] ligands have been used. Chiral auxiliaries on the carbonyl fragment can be used.[418] Chiral imines, in the form of chiral hydrazones have been used with silyl enol ethers and a scandium catalyst.[419] Chiral amine react with aldehydes, with silyl enol ethers and an $InCl_3$ catalyst in ionic liquids, to give the Mannich product with good enantioselectivity.[420]

Also see, **11-22**.

OS **III**, 305; **IV**, 281, 515, 816; **VI**, 474, 981, 987; **VII**, 34. See also, OS **VIII**, 358.

16-20 The Addition of Amines to Isocyanates

***N*-Hydro-*C*-alkylamino-addition**



[407]Seebach, D.; Schiess, M.; Schweizer, W.B. *Chimia* ***1985***, *39*, 272. See also, Heaney, H.; Papageorgiou, G.; Wilkins, R.F. *J. Chem. Soc., Chem. Commun.* ***1988***, 1161; Katritzky, A.R.; Harris, P.A. *Tetrahedron* ***1990***, *46*, 987.

[408]For a discussion of the mechanism, see Fujii, A.; Hagiwara, E.; Sodeoka, M. *J. Am. Chem. Soc.* ***1999***, *121*, 5450.

[409]Akiyama, T.; Takaya, J.; Kagoshima, H. *Synlett* ***1999***, 1045; Akiyama, T.; Takaya, J.; Kagoshima, H. *Tetrahedron Lett.* ***2001***, *42*, 4025.

[410]Loh, T.-P.; Wei, L.L. *Tetrahedron Lett.* ***1998***, *39*, 323.

[411]Texier-Boullet, F.; Latouche, R.; Hamelin, J. *Tetrahedron Lett.* ***1993***, *34*, 2123.

[412]Kobayashi, S.; Ishitani, H. *J. Chem. Soc., Chem. Commun.* ***1995***, 1379.

[413]For a review, see Córdova, A. *Acc. Chem. Res.* ***2004***, *37*, 102.

[414]List, B.; Pojarliev, P.; Biller, W.T.; Martin, H.J. *J. Am. Chem. Soc.* ***2004***, *124*, 827; Ibrahem, I.; Casas, J.; Córdova, A. *Angew. Chem. Int. Ed.* ***2004***, *43*, 6528.

[415]Notz, W.; Sakthivel, K.; Bui, T.; Zhong, G.; Barbas III, C.F. *Tetrahedron Lett.* ***2000***, *42*, 199.

[416]Kobayashi, S.; Hamada, T.; Manabe, K. *J. Am. Chem. Soc.* ***2002***, *124*, 5640; Trost, B.M.; Terrell, C.R. *J. Am. Chem. Soc.* ***2003***, *125*, 338.

[417]Josephsohn, N.S.; Snapper, M.L.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***2004***, *126*, 3734.

[418]Hata, S.; Iguchi, M.; Iwasawa, T.; Yamada, K.-i.; Tomioka, K. *Org. Lett.* ***2004***, *6*, 1721.

[419]Jacobsen, M.F.; Ionita, L.; Skrydstrup, T. *J. Org. Chem.* ***2004***, *69*, 4792.

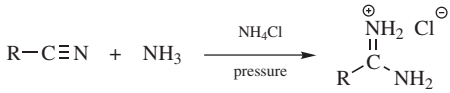
[420]In bmim BF_4, 1-butyl-3-methylimidazolium tetrafluoroborate: Sun, W.; Xia, C.-G.; Wang, H.-W. *Tetrahedron Lett.* ***2003***, *44*, 2409.

Ammonia and primary and secondary amines can be added to isocyanates[421] to give substituted ureas.[422] Isothiocyanates give thioureas.[423] This is an excellent method for the preparation of ureas and thioureas, and these compounds are often used as derivatives for primary and secondary amines. Isocyanic acid (HNCO) also gives the reaction; usually its salts (e.g., NaNCO) are used. Wöhler's famous synthesis of urea involved the addition of ammonia to a salt of this acid.[424]

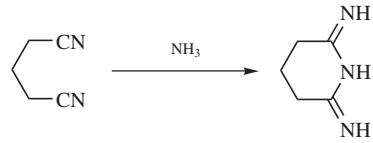
OS **II**, 79; **III**, 76, 617, 735; **IV**, 49, 180, 213, 515, 700; **V**, 555, 801, 802, 967; **VI**, 936, 951; **VIII**, 26.

16-21 The Addition of Ammonia or Amines to Nitriles

N-Hydro-*C*-amino-addition



Unsubstituted amidines (in the form of their salts) can be prepared by addition of ammonia to nitriles.[425] Many amidines have been made in this way. Dinitriles of suitable chain length can give imidines:[426]



Primary and secondary amines can be used instead of ammonia, to give substituted amidines, but only if the nitrile contains electron-withdrawing groups; for example, Cl_3CCN gives the reaction. Ordinary nitriles do not react, and, in fact, acetonitrile is often used as a solvent in this reaction.[427] Ordinary nitriles can be converted to amidines by treatment with an alkylchloroaluminum amide, $MeAl(Cl)NR_2$ (R = H or Me).[428] The addition of ammonia to cyanamide (NH_2CN) gives guanidine, $(NH_2)_2C{=}NH$. Guanidines can also be formed from amines.[429]

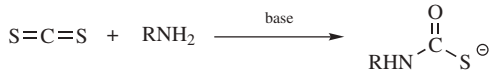
[421]For a review of the mechanism, see Satchell, D.P.N.; Satchell, R.S. *Chem. Soc. Rev.* ***1975***, *4*, 231.
[422]For a review of substituted ureas, see Vishnyakova, T.P.; Golubeva, I.A.; Glebova, E.V. *Russ. Chem. Rev.* ***1985***, *54*, 249.
[423]Herr, R.J.; Kuhler, J.L.; Meckler, H.; Opalka, C.J. *Synthesis* ***2000***, 1569.
[424]For a history of the investigation of the mechanism of the Wöhler synthesis, see Shorter, J. *Chem. Soc. Rev.* ***1978***, *7*, 1. See also, Williams, A.; Jencks, W.P. *J. Chem. Soc. Perkin Trans. 2* ***1974***, 1753, 1760; Hall, K.J.; Watts, D.W. *Aust. J. Chem.* ***1977***, *30*, 781, 903.
[425]For reviews of amidines, see Granik, V.G. *Russ. Chem. Rev.* ***1983***, *52*, 377; Gautier, J.; Miocque, M.; Farnoux, C.C., in Patai, S. *The Chemistry of Amidines and Imidates*, Wiley, NY, ***1975***, pp. 283–348.
[426]Elvidge, J.A.; Linstead, R.P.; Salaman, A.M. *J. Chem. Soc.* ***1959***, 208.
[427]Grivas, J.C.; Taurins, A. *Can. J. Chem.* ***1961***, *39*, 761.
[428]Garigipati, R.S. *Tetrahedron Lett.* ***1990***, *31*, 1969.
[429]Dräger, G.; Solodenko, W.; Messinger, J.; Schön, U.; Kirschning, A. *Tetrahedron Lett.* ***2002***, *43*, 1401.

If water is present, in the presence of a ruthenium catalyst[430] or a platinum catalyst,[431] the addition of a primary or secondary amine to a nitrile gives an amide: $RCN + R^1NHR^2 + H_2O \rightarrow RCONR^1R^2 + NH_3$ (R^2 may be H). When benzonitrile reacts with $H_2PO_3Se^-$ in aqueous methanol, a selenoamide, $PhC{=}Se)NH_2$, is formed after treatment with aq. potassium carbonate.[432]

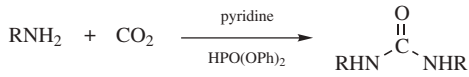
OS **I**, 302 [but also see OS **V**, 589]; **IV**, 245, 247, 515, 566, 769. See also, OS **V**, 39.

16-22 The Addition of Amines to Carbon Disulfide and Carbon Dioxide

S-Metallo-*C*-alkylamino-addition



Salts of dithiocarbamic acid can be prepared by the addition of primary or secondary amines to carbon disulfide.[433] This reaction is similar to **16-10**. Hydrogen sulfide can be eliminated from the product, directly or indirectly, to give isothiocyanates (RNCS). Isothiocyanates can be obtained directly by the reaction of primary amines and CS_2 in pyridine in the presence of dicyclohexylcarbodiimide.[434] Aniline derivatives react with CS_2 and NaOH, and then ethyl chloroformate to give the aryl isothiocyanate.[435] In the presence of diphenyl phosphite and pyridine, primary amines add to CO_2 and to CS_2 to give, respectively, symmetrically substituted ureas and thioureas:[436] Isoselenoureas, $R_2NC(=NR^1)SeR^2$, can also be formed.[437]



OS **I**, 447; **III**, 360, 394, 599, 763; **V**, 223.

[430]Murahashi, S.; Naota, T.; Saito, E. *J. Am. Chem. Soc.* ***1986***, *108*, 7846.

[431]Cobley, C.J.; van den Heuvel, M.; Abbadi, A.; de Vries, J.G. *Tetrahedron Lett.* ***2000***, *41*, 2467.

[432]Kamiński, R.; Glass, R.S.; Skowroñska, A. *Synthesis* ***2001***, 1308.

[433]For reviews, see Dunn, A.D.; Rudorf, W. *Carbon Disuphide in Organic Chemistry*, Ellis Horwood, Chichester, ***1989***, pp. 226–315; Katritzky, A.R.; Faid-Allah, H.; Marson, C.M. *Heterocycles* ***1987***, *26*, 1657; Yokoyama, M.; Imamoto, T. *Synthesis* ***1984***, 797, see pp. 804–812. For a review of the addition of heterocyclic amines to CO_2 to give, for example, salts of pyrrole-1-carboxylic acids, see Katritzky, A.R.; Marson, C.M.; Faid-Allah, H. *Heterocycles* ***1987***, *26*, 1333.

[434]Jochims, J.C. *Chem. Ber.* ***1968***, *101*, 1746. For other methods, see Sakai, S.; Fujinami, T.; Aizawa, T. *Bull. Chem. Soc. Jpn.* ***1975***, *48*, 2981; Gittos, M.W.; Davies, R.V.; Iddon, B.; Suschitzky, H. *J. Chem. Soc. Perkin Trans. 1* ***1976***, 141; Shibanuma, T.; Shiono, M.; Mukaiyama, T. *Chem. Lett.* ***1977***, 573; Molina, P.; Alajarin, M.; Arques, A. *Synthesis* ***1982***, 596.

[435]Li, Z.; Qian, X.; Liu, Z.; Li, Z.; Song, G. *Org. Prep. Proceed. Int.* ***2000***, *32*, 571.

[436]Yamazaki, N.; Higashi, F.; Iguchi, T. *Tetrahedron Lett.* ***1974***, 1191. For other methods for the conversion of amines and CO_2 to ureas, see Ogura, H.; Takeda, K.; Tokue, R.; Kobayashi, T. *Synthesis* ***1978***, 394; Fournier, J.; Bruneau, C.; Dixneuf, P.H.; Lécolier, S. *J. Org. Chem.* ***1991***, *56*, 4456. See Chiarotto, I.; Feroci, M. *J. Org. Chem.* ***2003***, *68*, 7137; Lemoucheux, L.; Rouden, J.; Ibazizene, M.; Sobrio, F.; Lasne, M.-C. *J. Org. Chem.* ***2003***, *68*, 7289.

[437]Asanuma, Y.; Fujiwara, S.-i.; Shi-ike, T.; Kambe, N. *J. Org. Chem.* ***2004***, *69*, 4845.

E. Halogen Nucleophiles

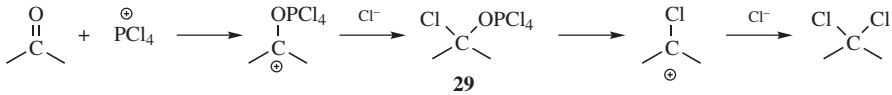
16-23 The Formation of *gem*-Dihalides from Aldehydes and Ketones

Dihalo-de-oxo-bisubstitution

Aliphatic aldehydes and ketones can be converted to *gem*-dichlorides[438] by treatment with PCl_5. The reaction fails for perhalo ketones.[439] If the aldehyde or ketone has an α hydrogen, elimination of HCl may follow and a vinylic chloride is a frequent side product:[440]

or even the main product.[441] The PBr_5 does not give good yields of *gem*-dibromides,[442] but these can be obtained from aldehydes, by the use of Br_2 and triphenyl phosphite.[443] *gem*-Dichlorides can be prepared by reacting an aldehyde with $BiCl_3$.[444]

The mechanism of *gem*-dichloride formation involves initial attack on PCl_4^+ (which is present in solid PCl_5) at the oxygen, followed by addition of Cl^- to the carbon:[445]



29

This chloride ion may come from PCl_6^- (which is also present in solid PCl_5). There follows a two-step S_N1 process. Alternatively, **29** can be converted to the product without going through the chlorocarbocation, by an S_Ni process.

This reaction has sometimes been performed on carboxylic esters, though these compounds very seldom undergo any addition to the C=O bond. An example is the conversion of $F_3CCOOPh$ to F_3CCCl_2OPh.[446] However, formates commonly give the reaction.

[438]For a list of reagents that convert aldehydes and ketones to *gem*-dihalides or vinylic halides, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 719–722.

[439]Farah, B.S.; Gilbert, E.E. *J. Org. Chem.* ***1965***, *30*, 1241.

[440]See, for example, Nikolenko, L.N.; Popov, S.I. *J. Gen. Chem. USSR* ***1962***, *32*, 29.

[441]See, for example, Newman, M.S.; Fraenkel, G.; Kirn, W.N. *J. Org. Chem.* ***1963***, *28*, 1851.

[442]For an indirect method of converting ketones to *gem*-dibromides, see Napolitano, E.; Fiaschi, R.; Mastrorilli, E. *Synthesis* ***1986***, 122.

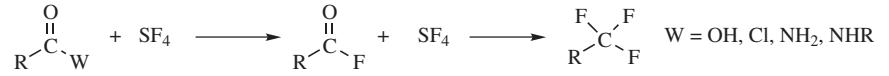
[443]Hoffmann, R.W.; Bovicelli, P. *Synthesis* ***1990***, 657. See also, Lansinger, J.M.; Ronald, R.C. *Synth. Commun.* ***1979***, *9*, 341.

[444]Kabalka, G.W.; Wu, Z. *Tetrahedron Lett.* ***2000***, *41*, 579.

[445]Newman, M.S. *J. Org. Chem.* ***1969***, *34*, 741.

[446]Kirsanov, A.V.; Molosnova, V.P. *J. Gen. Chem. USSR* ***1958***, *28*, 31; Clark, R.F.; Simons, J.H. *J. Org. Chem.* ***1961***, *26*, 5197.

Many aldehydes and ketones have been converted to *gem*-difluoro compounds with sulfur tetrafluoride SF_4,[447] including quinones, which give 1,1,4,4-tetrafluorocyclohexadiene derivatives. With ketones, yields can be raised and the reaction temperature lowered, by the addition of anhydrous HF.[448] Carboxylic acids, acyl chlorides, and amides react with SF_4 to give 1,1,1-trifluorides. In these cases the first product is the acyl fluoride, which then undergoes the *gem*-difluorination reaction:



The acyl fluoride can be isolated. Carboxylic esters also give trifluorides, but more vigorous conditions are required. In this case, the carbonyl group of the ester is attacked first, and RCF_2OR' can be isolated from $RCOOR'$[449] and then converted to the trifluoride. Anhydrides can react in either manner. Both types of intermediate are isolable under the right conditions and SF_4 even converts carbon dioxide to CF_4. A disadvantage of reactions with SF_4 is that they require a pressure vessel lined with stainless steel. Selenium tetrafluoride SeF_4 gives similar reactions, but atmospheric pressure and ordinary glassware can be used.[450] Another reagent that is often used to convert aldehydes and ketones to *gem*-difluorides is the commercially available diethylaminosulfur trifluoride (DAST, Et_2NSF_3), and CF_2Br_2 in the presence of zinc.[451] The mechanism with SF_4 is probably similar in general nature, if not in specific detail, to that with PCl_5.

Treatment with hydrazine to give the hydrazone, and then $CuBr_2$/*t*-BuOLi, generated the *gem*-dibromide.[452] Oximes gives *gem*-dichlorides upon treatment with chlorine and BF_3•OEt_2, and then HCl.[453] Some dithianes can be converted to *gem*-difluorides with a mixture of fluorine and iodine in acetonitrile.[454] Oximes give *gem*-difluorides with $NO^+BF_4^-$ and pyridinium polyhydrogen fluoride.[455]

In a related process, α-halo ethers can be prepared by treatment of aldehydes and ketones with an alcohol and HX. The reaction is applicable to aliphatic aldehydes and ketones and to primary and secondary alcohols. The addition of HX to an aldehyde or ketone gives α-halo alcohols, which are usually unstable, although exceptions are known, especially with perfluoro and perchloro species.[456]

[447]For reviews, see Wang, C.J. *Org. React.* ***1985***, *34*, 319; Boswell, Jr., G.A.; Ripka, W.C.; Scribner, R.M.; Tullock, C.W. *Org. React.* ***1974***, *21*, 1.

[448]Muratov, N.N.; Mohamed, N.M.; Kunshenko, B.V.; Burmakov, A.I.; Alekseeva, L.A.; Yagupol'skii, L.M. *J. Org. Chem. USSR* ***1985***, *21*, 1292.

[449]For methods of converting $RCOOR'$ to RCF_2OR', see Boguslavskaya, L.S.; Panteleeva, I.Yu.; Chuvatkin, N.N. *J. Org. Chem. USSR* ***1982***, *18*, 198; Bunnelle, W.H.; McKinnis, B.R.; Narayanan, B.A. *J. Org. Chem.* ***1990***, *55*, 768.

[450]Olah, G.A.; Nojima, M.; Kerekes, I. *J. Am. Chem. Soc.* ***1974***, *96*, 925.

[451]Hu, C.-M.; Qing, F.-L.; Shen, C.-X. *J. Chem. Soc. Perkin Trans. 1* ***1993***, 335.

[452]Takeda, T.; Sasaki, R.; Nakamura, A.; Yamauchi, S.; Fujiwara, T. *Synlett* ***1996***, 273.

[453]Tordeux, M.; Boumizane, K.; Wakselman, C. *J. Org. Chem.* ***1993***, *58*, 1939.

[454]Chambers, R.D.; Sandford, G.; Atherton, M. *J. Chem. Soc., Chem. Commun.* ***1995***, 177.

[455]York, C.; Prakash, G.K.S.; Wang, Q.; Olah, G.A. *Synlett* ***1994***, 425.

[456]For example, see Andreades, S.; England, D.C. *J. Am. Chem. Soc.* ***1961***, *83*, 4670; Clark, D.R.; Emsley, J.; Hibbert, F. *J. Chem. Soc. Perkin Trans. 2* ***1988***, 1107.

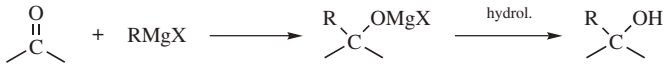
Aromatic aldehydes are converted to benzylic bromides with dibromoboranes, such as c-$C_6H_{11}BBr_2$.[457] Aldehydes are converted directly to benzylic chlorides with $HSiMe_2Cl$ and an $In(OH)_3$ catalyst.[458] The reaction of $BuBCl_2$ and oxygen gives alkylation (**16-25**) and chlorination.[459]

OS **II**, 549; **V**, 365, 396, 1082; **VI**, 505, 845; **VIII**, 247. Also see OS **I**, 506. For α-halo-ethers, see OS **I**, 377; **IV**, 101 (see, however, OS **V**, 218), 748; **VI**, 101.

F. Attack at Carbon by Organometallic Compounds[460]

16-24 The Addition of Grignard Reagents and Organolithium Reagents to Aldehydes and Ketones

***O*-Hydro-*C*-alkyl-addition**



Organomagnesium compounds, commonly known as Grignard reagents (RMgX), are formed by the reaction of alkyl, vinyl, or aryl halides with magnesium metal, usually in ether solvents such as diethyl ether or THF (**12-38**), although the reaction can be done in water[461] under certain conditions. Halogen–magnesium exchange generates a Grignard reagent by reaction of aryl halides with reactive aliphatic Grignard reagents.[462] The addition of Grignard reagents to aldehydes and ketones [463] is known as the *Grignard reaction.*[464] The initial product is a magnesium alkoxide, requiring a hydrolysis step to generate the final alcohol product. Formaldehyde gives primary alcohols; other aldehydes give secondary alcohols; and ketones give tertiary alcohols. The reaction is of very broad scope. In many cases, the hydrolysis step is carried out with dilute HCl or H_2SO_4, but this cannot be done for tertiary alcohols in which at least one R group is alkyl because such alcohols are easily dehydrated under acidic conditions (**17-1**). In such cases (and often for other alcohols as well), an aqueous solution of ammonium chloride is used instead of a strong acid. Grignard reagents have been used in solid phase synthesis.[465]

[457]Kabalka, G.W.; Wu, Z.; Ju, Y. *Tetrahedron Lett.* ***2000***, *41*, 5161.
[458]Onishi, Y.; Ogawa, D.; Yasuda, M.; Baba, A. *J. Am. Chem. Soc.* ***2002***, *124*, 13690.
[459]Kabalka, G.W.; Wu, Z.; Ju, Y. *Tetrahedron Lett.* ***2001***, *42*, 6239.
[460]Discussions of most of the reactions in this section are found, in Hartley, F.R.; Patai, S. *The Chemistry of the Metal-Carbon Bond*, Vols. 2–4, Wiley, NY, ***1985–1987***.
[461]Li, C.-J. *Tetrahedron* ***1996***, *52*, 5643.
[462]Song, J.J.; Yee, N.K.; Tan, Z.; Xu, J.; Kapadia, S.R.; Senanayake, C.H. *Org. Lett.* ***2004***, *6*, 4905.
[463]For a discussion of the effect of addends on aggregation and reactivity, see Leung, S.S.-W.; Streitwieser, A. *J. Org. Chem.* ***1999***, *64*, 3390.
[464]For reviews of the addition of organometallic compounds to carbonyl groups, see Eicher, T., in Patai, S. *The Chemistry of the Carbonyl Group*, pt. 1, Wiley, NY, ***1966***, pp. 621–693; Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall: Englewood Cliffs, NJ, ***1954***, pp. 138–528. For a review of reagents that extend carbon chains by three carbons, with some functionality at the new terminus, see Stowell, J.C. *Chem. Rev.* ***1984***, *84*, 409. For a computational study of this reaction, see Yamazaki, S.; Yamabe, S. *J. Org. Chem.* ***2002***, *67*, 9346.
[465]Franzén, R.G. *Tetrahedron* ***2000***, *56*, 685.

Alternative methods to generate the arylmagnesium compound are available, including the reaction of an aryl bromide with Bu_3MgLi in THF.[466] Subsequent addition of an aldehyde leads to addition of the aryl group to form an alcohol. An interesting method to form an alkylmagnesium halide used dibutylmagnesium (Bu_2Mg) and a chiral diamine, and subsequent reaction with an aldehyde led to the alcohol derived from acyl addition of a butyl group with good enantioselectivity.[467]

Organolithium reagents (RLi), prepared from alkyl halides and lithium metal or by exchange of an alkyl halide with a reactive organolithium (**12-38**) react with aldehydes and ketones by acyl addition to give the alcohol,[468] after hydrolysis. Organolithium reagents are more basic than the corresponding Grignard reagent, which leads to problems of deprotonation in some cases. Organolithium regents are generally more nucleophilic, and can add to hindered ketones with relative ease when compared to the analogous Grignard reagent.[469] These reagents tend to form aggregates, which influences the reactivity and selectivity of the addition reaction.[470] Alkyl, vinyl[471] and aryl organolithium reagents can be prepared and undergo this reaction. Structural variations are also possible. A lithio-epoxide was formed by treating an epoxide with *sec*-butyllithium in the presence of sparteine,[472] or with *n*-butyllithium/TMEDA,[473] and subsequent reaction with an aldehyde led to an epoxy alcohol. Treatment of an allenic silyl enol ether ($R_3SiOC{=}C{=}C$) with *tert*-butyllithium and then a ketone leads to acyl addition of a vinyllithium reagents to give a product with a conjugated ketone in which the C=C is allylic to the alcohol, $R_3SiC(=O)C(=CH_2)–C(OH)R_2$.[474] The dilithio compound $LiC{\equiv}CCH_2Li$ reacts with ketones via acyl addition, and an interesting workup with formaldehyde and then aqueous ammonium chloride gave the homopropargyl alcohol, $R_2C(OH)CH_2C{\equiv}CH$.[475] Aryl sulfonamides can be treated with 2 equivalents of *n*-butyllithium to give an ortho aryllithium which can then be added to an aldehyde to give the resulting diaryl carbinol.[476] A very interesting variation of the fundamental acyl addition reaction of organolithium reagents treated an aldehyde with an acyllithio amide, $LiC(=O)N(Me)CH_2Me$, to give an α-hydroxy amide derivative.[477]

The reaction of aldehydes or ketones with alkyl and aryl Grignard reagents has also been done without preliminary formation of RMgX, by mixing RX the carbonyl compound and magnesium metal in an ether solvent. This approach

[466]Inoue, A.; Kitagawa, K.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* ***2001***, *66*, 4333.
[467]Yong, K.H.; Taylor, N.J.; Chong, J.M. *Org. Lett.* ***2002***, *4*, 3553.
[468]For a study of Hammett ρ values for this reaction, see Maclin, K.M.; Richey Jr., H.G. *J. Org. Chem.* ***2002***, *67*, 4370.
[469]Lecomte, V.; Stéphan, E.; Le Bideau, F.; Jaouen, G. *Tetrahedron* ***2003***, *59*, 2169.
[470]See Fressigné, C.; Maddaluno, J.; Marquez, A.; Giessner-Prettre, C. *J. Org. Chem.* ***2000***, *65*, 8899; Granander, J.; Sott, R.; Hilmersson, G. *Tetrahedron* ***2002***, *58*, 4717.
[471]For a discussion of selectivity, see Spino, C.; Granger, M.-C.; Tremblay, M.-C. *Org. Lett.* ***2002***, *4*, 4735.
[472]Hodgson, D.M.; Reynolds, N.J.; Coote, S.J. *Org. Lett.* ***2004***, *6*, 4187.
[473]Florio, S.; Aggarwal, V.; Salomone, A. *Org. Lett.* ***2004***, *6*, 4191.
[474]Stergiades, I.A.; Tius, M.A. *J. Org. Chem.* ***1999***, *64*, 7547.
[475]Cabezas, J.A.; Pereira, A.R.; Amey, A. *Tetrahedron Lett.* ***2001***, *42*, 6819.
[476]Stanetty, P.; Emerschitz, T. *Synth. Commun.* ***2001***, *31*, 961.
[477]Cunico, R.F. *Tetrahedron Lett.* ***2002***, *43*, 355.

preceded Grignard's work, and is now known as the *Barbier reaction*.[478] The organolithium analog of this process is also known.[479] Yields were generally satisfactory. Carboxylic ester, nitrile, and imide groups in the R are not affected by the reaction conditions.[480] Modern versions of the Barbier reaction employ other metals and/or reaction conditions, and will be discussed in **16-25**. A retro-Barbier reaction has been reported in which a cyclic tertiary alcohol was treated to an excess of bromine and potassium carbonate to give 6-bromo-2-hexanone from 1-methylcyclopentanol.[481] This section will focus on variations of the Barbier reaction that employ Mg or Li derivatives. The reaction of allyl iodide, benzaldehyde and Mg/I_2, for example, gave the acyl addition product 1-phenylbut-3-en-1-ol.[482]

The reaction of RMgX or RLi with α,β-unsaturated aldehydes or ketones can proceed via 1,4-addition as well as normal 1,2-addition (see **15-25**).[483] In general, alkyllithium reagents give less 1,4-addition than the corresponding Grignard reagents.[484] Quinones add Grignard reagents on one or both sides or give 1,4-addition. In a compound containing both an aldehyde and a ketone it is possible to add RMgX chemoselectively to the aldehyde without significantly disturbing the carbonyl of the ketone group[485] (see also, p. 1306). In conjunction with $BeCl_2$, organolithium reagents add to conjugated ketones. In THF, 1,4- addition is observed, but in diethyl ether the 1,2-addition product is formed.[486] Organocerium reagents, generated from cerium chloride ($CeCl_3$ and a Grignard reagent or an organolithium reagent) gives an organometallic reagent that adds chemoselectively.[487] Grignard reagents with a catalytic amount of $InCl_3$ to give a mixture of 1,2- and 1,4-addition products with the 1,4-product predominating, but there was an increased 1,2-addition relative to the uncatalyzed reaction.[488]

As with the reduction of aldehydes and ketones (**19-36**), the addition of organometallic compounds to these substrates can be carried out enantioselectively and diastereoselectively.[489] Chiral secondary alcohols have been obtained with high

[478]Barbier, P. *Compt. Rend.*, ***1899***, *128*, 110. For a review, with Mg, Li, and other metals, see Blomberg, C.; Hartog, F.A. *Synthesis* ***1977***, 18. For a discussion of the mechanism, see Molle, G.; Bauer, P. *J. Am. Chem. Soc.* ***1982***, *104*, 3481. For a list of Barbier-type reactions, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1125–1134.

[479]Guijarro, A.; Yus, M. *Tetrahedron Lett.* ***1993***, *34*, 3487; de Souza-Barboza, J.D.; Pétrier, C.; Luche, J. *J. Org. Chem.* ***1988***, *53*, 1212.

[480]Yeh, M.C.P.; Knochel, P.; Santa, L.E. *Tetrahedron Lett.* ***1988***, *29*, 3887.

[481]Zhang, W.-C.; Li, C.-J. *J. Org.Chem.* ***2000***, *65*, 5831.

[482]Zhang, W.-C.; Li, C.-J. *J. Org. Chem.* ***1999***, *64*, 3230.

[483]For a discussion of the mechanism of this reaction, see Holm, T. *Acta Chem. Scand.* ***1992***, *46*, 985.

[484]An example was given on p. $$$.

[485]Vaskan, R.N.; Kovalev, B.G. *J. Org. Chem. USSR* ***1973***, *9*, 501.

[486]Krief, A.; de Vos, M.J.; De Lombart, S.; Bosret, J.; Couty, F. *Tetrahedron Lett.* ***1997***, *38*, 6295.

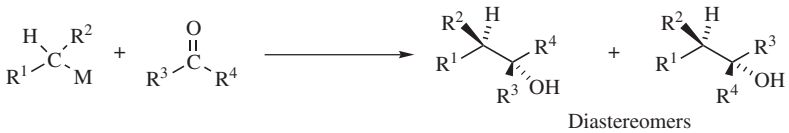
[487]Bartoli, G.; Marcantoni, E.; Petrini, M. *Angew. Chem. Int. Ed.* ***1993***, *32*, 1061; Dimitrov, V.; Bratovanov, S.; Simova, S.; Kostova, K. *Tetrahedron Lett.* ***1994***, *35*, 6713; Greeves, N.; Lyford, L. *Tetrahedron Lett.* ***1992***, *33*, 4759.

[488]Kelly, B.G.; Gilheany; D.G. *Tetrahedron Lett.* ***2002***, *43*, 887.

[489]For reviews, see Solladié, G., in Morrison, J.D. *Asymmetric Synthesis*, Vol. 2, Academic Press, NY, ***1983***, pp. 157–199, 158–183; Nógrádi, M. *Stereoselective Synthesis*, VCH, NY, ***1986***, pp. 160–193; Noyori, R.; Kitamura, M. *Angew. Chem. Int. Ed.* ***1991***, *30*, 49.

enantioselectivity by addition of Grignard and organolithium compounds to aromatic aldehydes, in the presence of optically active amino alcohols as ligands.[490]

Diastereoselective addition[491] has been carried out with achiral reagents and chiral substrates,[492] similar to the reduction shown on p. 1802.[493] Because the attacking atom in this case is carbon, not hydrogen, it is also possible to get diastereoselective addition with an achiral substrate and an optically active reagent.[494] Use of suitable reactants creates, in the most general case, two new stereogenic centers, so the product can exist as two pairs of enantiomers:



Even if the organometallic compound is racemic, it still may be possible to get a diastereoselective reaction; that is, one pair of enantiomers is formed in greater amount than the other.[495]

In some cases, the Grignard reaction can be performed intramolecularly.[496] For example, treatment of 5-bromo-2-pentanone with magnesium and a small amount

[490]Mukaiyama, T.; Soai, K.; Sato, T.; Shimizu, H.; Suzuki, K. *J. Am. Chem. Soc.* ***1979***, *101*, 1455; Mazaleyrat, J.; Cram, D.J. *J. Am. Chem. Soc.* ***1981***, *103*, 4585; Eleveld, M.B.; Hogeveen, H. *Tetrahedron Lett.* ***1984***, *25*, 5187; Schön, M.; Naef, R. *Tetrahedron Asymmetry* ***1999***, *10*, 169; Arvidsson, P.I.; Davidsson, Ö.; Hilmersson, G. *Tetrahedron Asymmetry* ***1999***, *10*, 527.

[491]For a review, see Yamamoto, Y.; Maruyama, K. *Heterocycles* ***1982***, *18*, 357. For a discussion of facial selectivity, see Tomoda, S.; Senju, T. *Tetrahedron* ***1999***, *55*, 3871. See Schulze, V.; Nell, P.G.; Burton, A.; Hoffmann, R.W. *J. Org. Chem.* ***2003***, *68*, 4546.

[492]For a review of cases in which the substrate bears a group that can influence the diastereoselectivity by chelating with the metal, see Reetz, M.T. *Angew. Chem. Int. Ed.* ***1984***, *23*, 556. See also, Keck, G.E.; Castellino, S. *J. Am. Chem. Soc.* ***1986***, *108*, 3847.

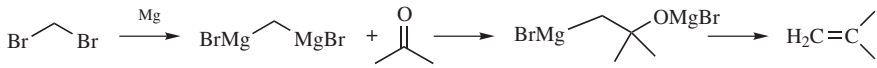
[493]See, for example, Eliel, E.L.; Morris-Natschke, S. *J. Am. Chem. Soc.* ***1984***, *106*, 2937; Reetz, M.T.; Steinbach, R.; Westermann, J.; Peter, R.; Wenderoth, B. *Chem. Ber.* ***1985***, *118*, 1441; Yamamoto, Y.; Matsuoka, K. *J. Chem. Soc., Chem. Commun.* ***1987***, 923; Boireau, G.; Deberly, A.; Abenhaïm, D. *Tetrahedron Lett.* ***1988***, *29*, 2175; Page, P.C.B.; Westwood, D.; Slawin, A.M.Z.; Williams, D.J. *J. Chem. Soc. Perkin Trans. 1* ***1989***, 1158; Soai, K.; Niwa, S.; Hatanaka, T. *Bull. Chem. Soc. Jpn.* ***1990***, *63*, 2129. For examples in which both reactants were chiral, see Roush, W.R.; Halterman, R.L. *J. Am. Chem. Soc.* ***1986***, *108*, 294; Hoffmann, R.W.; Dresely, S.; Hildebrandt, B. *Chem. Ber.* ***1988***, *121*, 2225; Paquette, L.A.; Learn, K.S.; Romine, J.L.; Lin, H. *J. Am. Chem. Soc.* ***1988***, *110*, 879; Brown, H.C.; Bhat, K.S.; Randad, R.S. *J. Org. Chem.* ***1989***, *54*, 1570.

[494]For a review of such reactions with crotylmetallic reagents, see Hoffmann, R.W. *Angew. Chem. Int. Ed.* ***1982***, *21*, 555. For a discussion of the mechanism, see Denmark, S.E.; Weber, E.J. *J. Am. Chem. Soc.* ***1984***, *106*, 7970. For some examples, see Greeves, N.; Pease, J.E. *Tetrahedron Lett.* ***1996***, *37*, 5821; Zweifel, G.; Shoup, T.M. *J. Am. Chem. Soc.* ***1988***, *110*, 5578; Gung, B.W.; Smith, D.T.; Wolf, M.A. *Tetrahedron Lett.* ***1991***, *32*, 13.

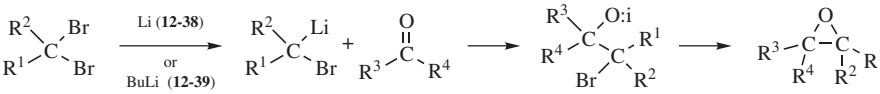
[495]For examples, see Coxon, J.M.; van Eyk, S.J.; Steel, P.J. *Tetrahedron Lett.* ***1985***, *26*, 6121; Mukaiyama, T.; Ohshima, M.; Miyoshi, N. *Chem. Lett.* ***1987***, 1121; Masuyama, Y.; Takahara, J.P.; Kurusu, Y. *Tetrahedron Lett.* ***1989***, *30*, 3437.

[496]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1134–1135.

of mercuric chloride in THF produced 1-methyl-1-cyclobutanol in 60% yield.[497] Other four- and five-membered ring compounds were also prepared by this procedure. Similar closing of five- and six-membered rings was achieved by treatment of a δ- or ε-halocarbonyl compound, not with a metal, but with a dianion derived from nickel tetraphenyporphine.[498]



The *gem*-disubstituted magnesium compounds formed from CH_2Br_2 or CH_2I_2 (**12-38**) react with aldehydes or ketones to give alkenes in moderate-to-good yields.[499] Wittig type reacts also produce alkenes and are discussed in **16-44**. The reaction could not be extended to other *gem*-dihalides. Similar reactions with *gem*-dimetallic compounds prepared with metals other than magnesium have also produced alkenes.[500] An interesting variation is the reaction of methyllithium and CH_2I_2 with an aliphatic aldehyde to give an epoxide,[501] but this reagent reacted with lactones to give a cyclic hemiketal with a pendant iodomethyl unit.[502] Alkylidene oxetanes react with lithium, and then with an aldehyde to give a conjugated ketone.[503] The α,α-dimetallic derivatives of phenyl sulfones ($PhSO_2CM_2R$) (M = Li or Mg) react with aldehydes or ketones $R'COR^2$ to give good yields of the α,β-unsaturated sulfones $PhSO_2CR{=}CR'R^2$,[504] which can be reduced with aluminum amalgam (see **10-67**) or with $LiAlH_4$-$CuCl_2$ to give the alkenes $CHR{=}CR'R^2$.[505] On the other hand, *gem*-dihalides treated with a carbonyl compound and Li or BuLi give epoxides[506] (see also, **16-46**).



[497]Leroux, Y. *Bull. Soc. Chim. Fr.* ***1968***, 359.

[498]Corey, E.J.; Kuwajima, I. *J. Am. Chem. Soc.* ***1970***, *92*, 395. For another method, see Molander, G.A.; McKie, J.A. *J. Org. Chem.* ***1991***, *56*, 4112, and references cited therein.

[499]Bertini, F.; Grasselli, P.; Zubiani, G.; Cainelli, G.*Tetrahedron* ***1970***, *26*, 1281.

[500]For example, see Zweifel, G.; Steele, R.B. *Tetrahedron Lett.* ***1966***, 6021; Cainelli, G.; Bertini, F.; Grasselli, P.; Zubiani, G. *Tetrahedron Lett.* ***1967***, 1581; Takai, K.; Hotta, Y.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* ***1980***, *53*, 1698; Knochel, P.; Normant, J.F. *Tetrahedron Lett.* ***1986***, *27*, 1039; Barluenga, J.; Fernández-Simón, J.L.; Concellón, J.M.; Yus, M. *J. Chem. Soc., Chem. Commun.* ***1986***, 1665; Okazoe, T.; Takai, K.; Utimoto, K. *J. Am. Chem. Soc.* ***1987***, *109*, 951; Piotrowski, A.M.; Malpass, D.B.; Boleslawski, M.P.; Eisch, J.J. *J. Org. Chem.* ***1988***, *53*, 2829; Tour, J.M.; Bedworth, P.V.; Wu, R. *Tetrahedron Lett.* ***1989***, *30*, 3927; Lombardo, L. *Org. Synth. 65*, 81.

[501]Concellón, J.M.; Cuervo, H.; Fernández-Fano, R. *Tetrahedron* ***2001***, *57*, 8983.

[502]Bessieres, B.; Morin, C. *Synlett* ***2000***, 1691.

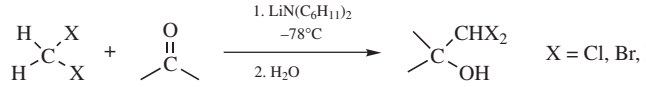
[503]Hashemsadeh, M.; Howell, A.R. *Tetrahedron Lett.* ***2000***, *41*, 1855, 1859.

[504]Pascali, V.; Tangari, N.; Umani-Ronchi, A. *J. Chem. Soc. Perkin Trans. 1* ***1973***, 1166.

[505]Pascali, V.; Umani-Ronchi, A. *J. Chem. Soc., Chem. Commun.* ***1973***, 351.

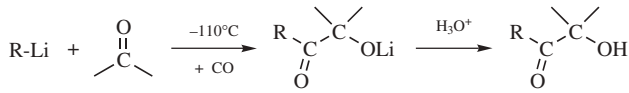
[506]Cainelli, G.; Tangari, N.; Umani-Ronchi, A. *Tetrahedron* ***1972***, *28*, 3009, and references cited therein.

In other uses of *gem*-dihalo compounds, aldehydes and ketones add the CH_2I group [$R_2CO \rightarrow R_2C(OH)CH_2I$] when treated with CH_2I_2 in the presence of SmI_2,[507] and the CHX_2 group when treated with methylene halides and lithium dicyclohexylamide at low temperatures.[508]



A hydroxymethyl group can be added to an aldehyde or ketone with the masked reagent $Me_2((i\text{Pr})O)SiCH_2MgCl$, which with R_2CO gives $R_2C(OH)CH_2$-$Si(O{-}(i\text{Pr}))Me_2$, but with H_2O_2 give 1,2-diols $R_2C(OH)CH_2OH$.[509]

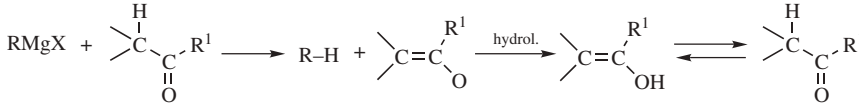
It is possible to add an acyl group to a ketone to give (after hydrolysis) an α-hydroxy ketone.[510] This can be done by adding RLi and CO to the ketone at −110°C:[511]



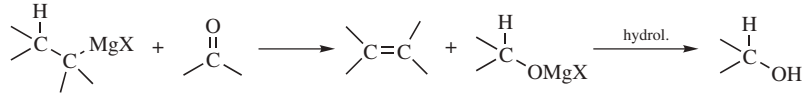
When the same reaction is carried out with carboxylic esters ($R'COOR^2$), α-diketones ($RCOCOR'$) are obtained.[511]

Most aldehydes and ketones react with most Grignard reagents, but there are several potential side reactions[512] that occur mostly with hindered ketones and with bulky Grignard reagents. The two most important of these are *enolization* and *reduction*. The former requires that the aldehyde or ketone have an α hydrogen, and the latter requires that the Grignard reagent have a β hydrogen:

Enolization



Reduction



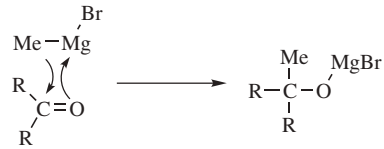
[507]Imamoto, T.; Takeyama, T.; Koto, H. *Tetrahedron Lett.* ***1986***, *27*, 3243.
[508]Taguchi, H.; Yamamoto, H.; Nozaki, H. *Bull. Chem. Soc. Jpn.* ***1977***, *50*, 1588.
[509]Tamao, K.; Ishida, N. *Tetrahedron Lett.* ***1984***, *25*, 4245. For another method, see Imamoto, T.; Takeyama, T.; Yokoyama, M. *Tetrahedron Lett.* ***1984***, *25*, 3225.
[510]For a review, see Seyferth, D.; Weinstein, R.M.; Wang, W.; Hui, R.C.; Archer, C.M. *Isr. J. Chem.* ***1984***, *24*, 167.
[511]Seyferth, D.; Weinstein, R.M.; Wang, W. *J. Org. Chem.* ***1983***, *48*, 1144; Seyferth, D.; Weinstein, R.M.; Wang,W.; Hui, R.C. *Tetrahedron Lett.* ***1983***, *24*, 4907.
[512]Lajis, N. Hj.; Khan, M.N.; Hassan, H.A. *Tetrahedron* ***1993***, *49*, 3405.

Enolization is an acid–base reaction (**12-24**) in which a proton is transferred from the α carbon to the Grignard reagent. The carbonyl compound is converted to its enolate anion form, which, on hydrolysis, gives the original ketone or aldehyde. Enolization is important not only for hindered ketones but also for those that have a relatively high percentage of enol form (e.g., β-keto esters). In reduction, the carbonyl compound is reduced to an alcohol (**16-24**) by the Grignard reagent, which itself undergoes elimination to give an alkene. Two other side reactions are condensation (between enolate ion and excess ketone) and Wurtz-type coupling (**10-64**). Such highly hindered tertiary alcohols as triisopropylcarbinol, tri-*tert*-butylcarbinol, and diisopropylneopentylcarbinol cannot be prepared (or can be prepared only in extremely low yields) by the addition of Grignard reagents to ketones, because reduction and/or enolization become prominent.[513] However, these carbinols can be prepared by the use of alkyllithium reagents at −80°C[514] because enolization and reduction are much less important.[515] Other methods of increasing the degree of addition at the expense of reduction include complexing the Grignard reagent with $LiClO_4$ or $Bu_4N^+ Br^-$,[516] or using benzene or toluene instead of ether as solvent.[517] Both reduction and enolization can be avoided by adding $CeCl_3$ to the Grignard reagent (see above).[518]

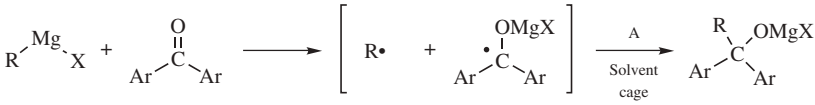
Another way to avoid complications is to add $(RO)_3TiCl$, $TiCl_4$,[519] $(RO)_3ZrCl$, or $(R_2N)_3TiX$ to the Grignard or lithium reagent. This produces organotitanium or organozirconium compounds that are much more selective than Grignard or organolithium reagents.[520] An important advantage of these reagents is that they do not react with NO_2 or CN functions that may be present in the substrate, as Grignard and organolithium reagents do. The reaction of a β-keto amide with $TiCl_4$, for example, gives a complex that allows selective reaction of the ketone unit with MeMgCl—$CeCl_3$ to give the corresponding alcohol.[521] Premixing an allylic Grignard reagent with $ScCl_3$ prior to reaction with the aldehyde gives direct acyl addition without allylic rearrangement as the major product, favoring the trans-alkene unit.[522]

[513]Whitmore, F.C.; George, R.S. *J. Am. Chem. Soc.* ***1942***, *64*, 1239.
[514]Zook, H.D.; March, J.; Smith, D.F. *J. Am. Chem. Soc.* ***1959***, *81*, 1617; Bartlett, P.D.; Tidwell, T.T. *J. Am. Chem. Soc.* ***1968***, *90*, 4421. See also, Lomas, J.S. *Nouv. J. Chim.*, ***1984***, *8*, 365; Molle, G.; Briand, S.; Bauer, P.; Dubois, J.E. *Tetrahedron* ***1984***, *40*, 5113.
[515]Buhler, J.D. *J. Org. Chem.* ***1973***, *38*, 904.
[516]Chastrette, M.; Amouroux, R. *Chem. Commun.* ***1970***, 470; *Bull. Soc. Chim. Fr.* ***1970***, 4348. See also, Richey Jr., H.G.; DeStephano, J.P. *J. Org. Chem.* ***1990***, *55*, 3281.
[517]Canonne, P.; Foscolos, G.; Caron H.; Lemay, G. *Tetrahedron* ***1982***, *38*, 3563.
[518]Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* ***1989***, *111*, 4392.
[519]See Reetz, M.T.; Kyung, S.H.; Hüllmann, M. *Tetrahedron* ***1986***, *42*, 2931.
[520]For a monograph, see Reetz, M.T. *Organotitanium Reagents in Organic Synthesis*, Springer, NY, ***1986***. For reviews, see Weidmann, B.; Seebach, D. *Angew. Chem. Int. Ed.* ***1983***, *22*, 31; Reetz, M.T. *Top. Curr. Chem.* ***1982***, *106*, 1.
[521]Bartoli, G.; Bosco, M.; Marcantoni, E.; Massaccesi, M.; Rinaldi, S.; Sambri, L. *Tetrahedron Lett.* ***2001***, *42*, 6093.
[522]Matsukawa, S.; Funabashi, Y.; Imamoto, T. *Tetrahedron Lett.* ***2003***, *44*, 1007.

There has been much controversy regarding the mechanism of addition of Grignard reagents to aldehydes and ketones.[523] The reaction is difficult to study because of the variable nature of the species present in the Grignard solution (p. 260) and because the presence of small amounts of impurities in the magnesium seems to have a great effect on the kinetics of the reaction, making reproducible experiments difficult.[524] There seem to be two basic mechanisms, depending on the reactants and the reaction conditions. In one of these, the R group is transferred to the carbonyl carbon with its electron pair. A detailed mechanism of this type has been proposed by Ashby and co-workers,[525] based on the discovery that this reaction proceeds by two paths: one first order in MeMgBr and the other first order in Me_2Mg.[526] According to this proposal, both MeMgBr and Me_2Mg add to the carbonyl carbon, though the exact nature of the step by which MeMgBr or Me_2Mg reacts with the substrate is not certain. One possibility is a four-centered cyclic transition state:[527]



The other type of mechanism is a single electron transfer (SET) process[528] with a ketyl intermediate:[529]



Ketyl

This mechanism, which has been mostly studied with diaryl ketones, is more likely for aromatic and other conjugated aldehydes and ketones than it is for

[523]For reviews, see Holm, T. *Acta Chem. Scand. Ser. B* ***1983***, *37*, 567; Ashby, E.C. *Pure Appl. Chem.* ***1980***, *52*, 545; *Bull. Soc. Chim. Fr.* ***1972***, 2133; *Q. Rev. Chem. Soc.* ***1967***, *21*, 259; Ashby, E.C.; Laemmle, J.; Neumann, H.M. *Acc. Chem. Res.* ***1974***, *7*, 272; Blomberg, C. *Bull. Soc. Chim. Fr.* ***1972***, 2143. For a review of the stereochemistry of the reaction, see Ashby, E.C.; Laemmle, J. *Chem. Rev.* ***1975***, *75*, 521. For a review of the effects of the medium and the cation, see Solv'yanov, A.A.; Beletskaya, I.P. *Russ. Chem. Rev.* ***1987***, *56*, 465.

[524]See, for example, Ashby, E.C.; Neumann, H.M.; Walker, F.W.; Laemmle, J.; Chao, L. *J. Am. Chem. Soc.* ***1973***, *95*, 3330.

[525]Ashby, E.C.; Laemmle, J.; Neumann, H.M. *J. Am. Chem. Soc.* ***1972***, *94*, 5421.

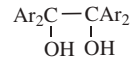
[526]Ashby, E.C.; Laemmle, J.; Neumann, H.M. *J. Am. Chem. Soc.* ***1971***, *93*, 4601; Laemmle, J.; Ashby, E.C.; Neumann, H.M. *J. Am. Chem. Soc.* ***1971***, *93*, 5120.

[527]Tuulmets, A. *Org. React. (USSR)* ***1967***, *4*, 5; House, H.O.; Oliver, J.E. *J. Org. Chem.* ***1968***, *33*, 929; Ashby, E.C.; Yu, S.H.; Roling, P.V. *J. Org. Chem.* ***1972***, *37*, 1918. See also, Billet, J.; Smith, S.G. *J. Am. Chem. Soc.* ***1968***, *90*, 4108; Lasperas, M.; Perez-Rubalcaba, A.; Quiroga-Feijoo, M.L. *Tetrahedron* ***1980***, *36*, 3403.

[528]For a review, see Dagonneau, M. *Bull. Soc. Chim. Fr.* ***1982***, II-269.

[529]There is kinetic evidence that the solvent cage shown may not be necessary: Walling, C. *J. Am. Chem. Soc.* ***1988***, *110*, 6846.

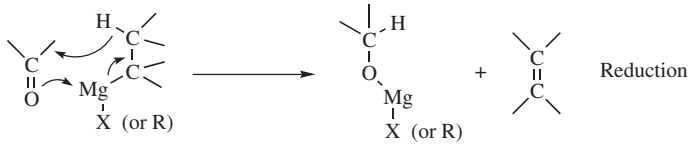
strictly aliphatic ones. Among the evidence[530] for the SET mechanism are ESR spectra[531] and the fact that



side products are obtained (from dimerization of the ketyl).[532] In the case of addition of RMgX to benzil (PhCOCOPh), esr spectra of two different ketyl radicals were observed, both reported to be quite stable at room temperature.[533] Note that a separate study failed to observe freely defusing radicals in the formation of Grignard reagents.[534] Carbon isotope effect studies with Ph^{14}COPh showed that the rate-determining step with most Grignard reagents is the carbon–carbon bond-forming step (marked *A*), though with allylmagnesium bromide it is the initial electron-transfer step.[535] In the formation of Grignard reagents from bromocyclopropane, diffusing cyclopropyl radical intermediates were found.[536] The concerted versus stepwise mechanism has been probed with chiral Grignard reagents.[537]

Mechanisms for the addition of organolithium reagents have been investigated much less.[538] Addition of a cryptand that binds Li^+ inhibited the normal addition reaction, showing that the lithium is necessary for the reaction to take place.[539]

There is general agreement that the mechanism leading to reduction[540] is usually as follows:



[530]For other evidence, see Savin, V.I.; Kitaev, Yu.P. *J. Org. Chem. USSR* ***1975***, *11*, 2622; Ōkubo, M. *Bull. Chem. Soc. Jpn.* ***1977***, *50*, 2379; Ashby, E.C.; Bowers Jr., J.R. *J. Am. Chem. Soc.* ***1981***, *103*, 2242; Holm, T. *Acta Chem. Scand. Ser. B* ***1988***, *42*, 685; Liotta, D.; Saindane, M.; Waykole, L. *J. Am. Chem. Soc.* ***1983***, *105*, 2922; Yamataka, H.; Miyano, N.; Hanafusa, T. *J. Org. Chem.* ***1991***, *56*, 2573.

[531]Fauvarque, J.; Rouget, E. *C. R. Acad. Sci., Ser C*, ***1968***, *267*, 1355; Maruyama, K.; Katagiri, T. *Chem. Lett.* ***1987***, 731, 735; *J. Phys. Org. Chem.* ***1988***, *1*, 21.

[532]Blomberg, C.; Mosher, H.S. *J. Organomet. Chem.* ***1968***, *13*, 519; Holm, T.; Crossland, I. *Acta Chem. Scand.* ***1971***, *25*, 59.

[533]Maruyama, K.; Katagiri, T. *J. Am. Chem. Soc.* ***1986***, *108*, 6263; *J. Phys. Org. Chem.* ***1989***, *2*, 205. See also, Holm, T. *Acta Chem. Scand. Ser. B* ***1987***, *41*, 278; Maruyama, K.; Katagiri, T. *J. Phys. Org. Chem.* ***1991***, *4*, 158.

[534]Walter, R.I. *J. Org. Chem.* ***2000***, *65*, 5014.

[535]Yamataka, H.; Matsuyama, T.; Hanafusa, T. *J. Am. Chem. Soc.* ***1989***, *111*, 4912.

[536]Garst, J.F.; Ungváry, F. *Org. Lett.* ***2001***, *3*, 605.

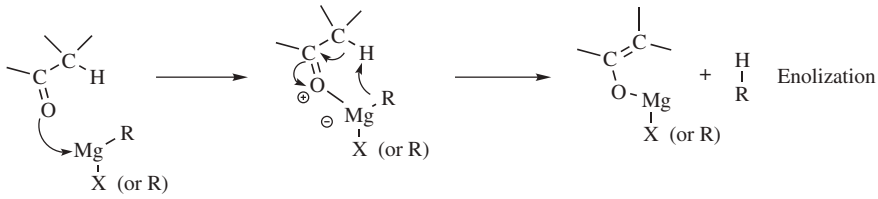
[537]Hoffmann, RW.; Hölzer, B. *Chem. Commun.* ***2001***, 491.

[538]See, for example, Al-Aseer, M.A.; Smith, S.G. *J. Org. Chem.* ***1984***, *49*, 2608; Yamataka, H.; Kawafuji, Y.; Nagareda, K.; Miyano, N.; Hanafusa, T. *J. Org. Chem.* ***1989***, *54*, 4706.

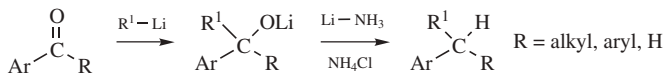
[539]Perraud, R.; Handel, H.; Pierre, J. *Bull. Soc. Chim. Fr.* ***1980***, II-283.

[540]For discussions of the mechanism of reduction, see Singer, M.S.; Salinger, R.M.; Mosher, H.S. *J. Org. Chem.* ***1967***, *32*, 3821; Denise, B.; Fauvarque, J.; Ducom, J. *Tetrahedron Lett.* ***1970***, 335; Cabaret, D.; Welvart, Z. *J. Organomet. Chem.* ***1974***, *80*, 199; Holm, T. *Acta Chem. Scand.* ***1973***, *27*, 1552; Morrison, J.D.; Tomaszewski, J.E.; Mosher, H.S.; Dale, J.; Miller, D.; Elsenbaumer, R.L. *J. Am. Chem. Soc.* ***1977***, *99*, 3167; Okuhara, K. *J. Am. Chem. Soc.* ***1980***, *102*, 244.

There is evidence that the mechanism leading to enolization is also cyclic, but involves prior coordination with magnesium:[541]



Aromatic aldehydes and ketones can be alkylated and reduced in one reaction vessel by treatment with an alkyl- or aryllithium, followed by lithium and ammonia and then by ammonium chloride.[542]

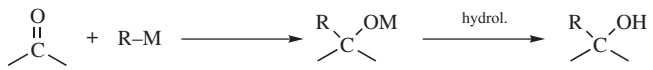


A similar reaction has been carried out with *N,N*-disubstituted amides: $RCONR'_2 \rightarrow RR^2CHNR'_2$.[543]

OS **I**, 188; **II**, 406, 606; **III**, 200, 696, 729, 757; **IV**, 771, 792; **V**, 46, 452, 608, 1058; **VI**, 478, 537, 542, 606, 737, 991, 1033; **VII**, 177, 271, 447; **VIII**, 179, 226, 315, 343, 386, 495, 507, 556; **IX**, 9, 103, 139, 234, 306, 391, 472; **75**, 12; **76**, 214; **X**, 200.

16-25 Addition of Other Organometallics to Aldehydes and Ketones

O-Hydro-*C*-alkyl-addition



A variety of organometallic reagents other than RMgX and RLi add to aldehydes and ketones. A simple example is formation of sodium, or potassium alkyne anions (e.g., RC≡CNa, **16-38**), which undergo acyl addition to ketones or aldehydes to give the propargylic alcohol. For the addition of acetylenic groups, sodium may be the metal used; while vinylic alanes (prepared as in **15-17**) are the reagents of choice for the addition of vinylic groups.[544] A variation includes the use of tetraalkylammonium hydroxide to generate the alkyne anion,[545] and terminal alkynes with CsOH react similarly.[546] A solvent-free reaction was reported that mixed a ketone, a terminal alkyne and potassium *tert*-butoxide.[547] The reagent $Me_3Al/^-C{\equiv}CH$

[541]Pinkus, A.G.; Sabesan, A. *J. Chem. Soc. Perkin Trans. 2* ***1981***, 273.
[542]Lipsky, S.D.; Hall, S.S. *Org. Synth.* ***VI***, 537; McEnroe, F.J.; Sha, C.; Hall, S.S. *J. Org. Chem.* ***1976***, *41*, 3465.
[543]Hwang, Y.C.; Chu, M.; Fowler, F.W. *J. Org. Chem.* ***1985***, *50*, 3885.
[544]Newman, H. *Tetrahedron Lett.* ***1971***, 4571. Vinylic groups can also be added with 9-vinylic-9-BBN compounds: Jacob III, P.; Brown, H.C. *J. Org. Chem.* ***1977***, *42*, 579.
[545]Ishikawa, T.; Mizuta, T.; Hagiwara, K.; Aikawa, T.; Kudo, T.; Saito, S. *J. Org. Chem.* ***2003***, *68*, 3702.
[546]Tzalis, D.; Knochel, P. *Angew. Chem. Int. Ed.* ***1999***, *38*, 1463.
[547]Miyamoto, H.; Yasaka, S.; Tanaka, K. *Bull. Chem. Soc. Jpn.* ***2001***, *74*, 185.

Na^+ also adds to aldehydes to give the ethynyl alcohol.[548] Dialkylzinc reagents have been used for the same purpose, and in the presence of a chiral titanium complex the propargylic alcohol was formed with good enantioselectivity.[549] Zinc(II) chloride facilitates the addition of a terminal alkyne to an aldehyde to give a propargylic alcohol.[550] Zinc(II) triflate can also be used for alkyne addition to aldehydes,[551] and in the presence of a chiral ligand leads to good enantioselectivity in the propargyl alcohol product.[552] Terminal alkynes add to aryl aldehydes in the presence of $InBr_3$ and NEt_3[553] or SmI_2.[554] 1-Iodoalkynes react with In metal and an aldehyde to give the propargylic alcohol.[555] Potassium alkynyltrifluoroborates (p. 817) react with aldehydes and a secondary amine, in an ionic liquid, to give a propargylic amine.[556]

Propargylic acetate adds to aldehydes with good anti selectivity in the presence of Et_2Zn and a palladium catalyst.[557] Propargylic bromide add to ketones in the presence of NaI/Dy,[558] In,[559] or Mn/Cr catalyst/TMSCl.[560] Propargylic tin compounds react with aldehydes to give the alcohol, with good antiselectivity.[561]

With other organometallic compounds, active metals, such as alkylzinc reagents,[562] are useful; and compounds such as alkylmercurys do not react. When the reagent is $MeNbCl_4$, ketones (R_2CO) are converted to $R_2C(Cl)Me$.[563]

[548]Joung, M.J.; Ahn, J.H.; Yoon, N.M. *J. Org. Chem.* ***1996***, *61*, 4472.

[549]For a review, see Pu, L. *Tetrahedron* ***2003***, *59*, 9873. For some leading references, see Gao, G.; Moore, D.; Xie, R.-G.; Pu. L. *Org. Lett.*2002, *4*, 4143; Li, Z.-B.; Pu, L. *Org. Lett.* ***2004***, *6*, 1065; Dahmen, S. *Org. Lett.* ***2004***, *6*, 2113; Kamble, R.M.; Singh, V.K. *Tetrahedron Lett.* ***2003***, *44*, 5347; Lu, G.; Li, X.; Chen, G.; Chan, W.L.; Chan, A.S.C. *Tetrahedron Asymmetry* ***2003***, *14*, 449; Kang, Y.-F.; Liu, L.; Wang, R.; Yan, W.-J.; Zhou, Y.-F. *Tetrahedron Asymmetry* ***2004***, *15*, 3155; Lu, G.; Li, X.; Jia, X.; Chan, W.L.; Chan, A.S.C. *Angew. Chem. Int. Ed.* ***2003***, *42*, 5057; Xu, Z.; Wang, R.; Xu, J.; Da, C.-s.; Yan, W.-j.; Chen, C. *Angew. Chem. Int. Ed.* ***2003***, *42*, 5747;.

[550]Jiang, B.; Si, Y.-G. *Tetrahedron Lett.* ***2002***, *43*, 8323

[551]Frantz, D.E.; Fässler, R.; Carreira, E.M. *J. Am. Chem. Soc.* ***2000***, *122*, 1806.

[552]Anand, N.K.; Carreira, E.M. *J. Am. Chem. Soc.* ***2001***, *123*, 9687; Sasaki, H.; Boyall, D.; Carreira, E.M. *Helv. Chim. Acta* ***2001***, *84*, 964; Boyall, D.; Frantz, D.E.; Carreira, E.M. *Org. Lett.* ***2002***, *4*, 2605.; Xu, Z.; Chen, C.; Xu, J.; Miao, M.; Yan, W.; Wang, R. *Org. Lett.* ***2004***, *6*, 1193; Jiang, B.; Chen, Z.; Xiong, W. *Chem. Commun.* ***2002***, 1524. For an example using zinc (II) diflate, see Chen, Z.; Xiong, W.; Jiang, B. *Chem. Commun.* ***2002***, 2098.

[553]Sakai, N.; Hirasawa, M.; Konakahara, T. *Tetrahedron Lett.* ***2003***, *44*, 4171.

[554]Kwon, D.W.; Cho, M.S.; Kim, Y.H. *Synlett* ***2001***, 627.

[555]Augé, J.; Lubin-Germain, N.; Seghrouchni, L. *Tetrahedron Lett.* ***2002***, *43*, 5255.

[556]In bmim BF_4, 1-butyl-3-methylimidazolium tetrafluoroborate: Kabalka, G.W.; Venkataiah, B.; Dong, G. *Tetrahedron Lett.* ***2004***, *45*, 729.

[557]Marshall, J.A.; Adams, N.D. *J. Org. Chem.* ***1999***, *64*, 5201.

[558]Li, Z.; Jia, Y.; Zhou, J. *Synth. Commun.* ***2000***, *30*, 2515.

[559]In the presence of (−)-cinchonidine: Loh, T.-P.; Lin, M.-J.; Tan, K.L. *Tetrahedron Lett.* ***2003***, *44*, 507.

[560]Inoue, M.; Nakada, M. *Org. Lett.* ***2004***, *6*, 2977.

[561]Savall, B.M.; Powell, N.A.; Roush, W.R. *Org. Lett.* ***2001***, *3*, 3057.

[562]For a review with respect to organozinc compounds, see Furukawa, J.; Kawabata, N. *Adv. Organomet. Chem.* ***1974***, *12*, 103. For an example, see Sjöholm, R.; Rairama, R.; Ahonen, M. *J. Chem. Soc., Chem. Commun.* ***1994***, 1217. For a review with respect to organocadmium compounds, see Jones, P.R.; Desio, P.J. *Chem. Rev.* ***1978***, *78*, 491.

[563]Kauffmann, T.; Abel, T.; Neiteler, G.; Schreer, M. *Tetrahedron Lett.* ***1990***, 503.

Furthermore, organotitanium reagents can be made to add chemoselectively to aldehydes in the presence of ketones.[564] Organomanganese compounds are also chemoselective in this way.[565] Aryl halides that have a pendant ketone unit react with a palladium catalyst to give cyclization via acyl addition.[566] Chiral amides react with aldehydes in the presence of $TiCl_4$ to give syn-selective addition products,[567] and titanium-catalyzed enantioselective additions are known.[568] An alkene-ketone, where the alkene is a vinyl bromide, reacted with $CrCl_2/NiCl_2$ to give a vinyl organometallic, which cyclized to generate a cyclic allylic alcohol with the double bond within the ring.[569] Aryl halides react with a nickel complex under electrolytic conditions to add the aryl group to aldehydes.[570] The C-3 position of an indole adds to aldehydes in the presence of a palladium catalyst.[571] The addition of trifluoromethyl to an aldehyde was accomplished photochemically using CF_3I and $(Me_2N)_2C{=}C(NMe_2)_2$.[572] α-Iodo phosphonate esters react with aldehydes and SmI_2 to give a β-hydroxy phosphonate ester.[573]

Dialkylzinc compounds react with aldehydes to give the secondary alcohol, and R_3ZnLi reagents also add R to a carbonyl.[574] Dimethylzinc and diethylzinc are probably the most common reagents. An intramolecular version is possible by reaction an allene-aldehyde with dimethylzinc. Addition to the allene in the presence of a nickel catalyst[575] or a $CeCl_3$ catalyst[576] is followed by addition of the intermediate organometallic to the aldehyde to give the cyclic product. Aryl halides react with Zn–Ni complexes to give acyl addition of the aryl group to an aldehyde.[577] The reaction of an allylic halide and Zn[578] or Zn/TMSCl[579] leads to acyl addition of aldehydes.

[564]Reetz, M.T. *Organotitanium Reagents in Organic Synthesis*, Springer, NY, ***1986*** (monograph), pp. 75–86. See also, Reetz, M.T.; Maus, S. *Tetrahedron* ***1987***, *43*, 101; Kim, S.-H.; Rieke, R.D. *Tetrahedron Lett.* ***1999***, *40*, 4931.

[565]Cahiez, G.; Figadere, B. *Tetrahedron Lett.* ***1986***, *27*, 4445. For other organometallic reagents with high selectivity towards aldehyde functions, see Kauffmann, T.; Hamsen, A.; Beirich, C. *Angew. Chem. Int. Ed.* ***1982***, *21*, 144; Takai, K.; Kimura, K.; Kuroda, T.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* ***1983***, *24*, 5281; Soai, K.; Watanabe, M.; Koyano, M. *Bull. Chem. Soc. Jpn.* ***1989***, *62*, 2124.

[566]Quan, L.G.; Lamrani, M.; Yamamoto, Y. *J. Am. Chem. Soc.* ***2000***, *122*, 4827.

[567]Crimmins, M.T.; Chaudhary, K. *Org. Lett.* ***2000*** *2*, 775.

[568]Walsh, P.J. *Acc. Chem. Res.* ***2003***, *36*, 739.

[569]Trost, B.M.; Pinkerton, A.B. *J. Org. Chem.* ***2001***, *66*, 7714.

[570]Durandetti, M.; Nédélec, J.-Y.; Périchon, J. *Org. Lett.* ***2001***, *3*, 2073.

[571]Hao, J.; Taktak, S.; Aikawa, K.; Yusa, Y.; Hatano, M.; Mikami, K. *Synlett* ***2001***, 1443.

[572]Aït-Mohand, S.; Takechi, N.; Médebielle, M.; Dolbier Jr., W.R. *Org. Lett.* ***2001***, *3*, 4271.

[573]Orsini, F.; Caselli, A. *Tetrahedron Lett.* ***2002***, *43*, 7255.

[574]For a discussion of the electronic and steric effects, see Musser, C.A.; Richey, Jr., H.G. *J. Org. Chem.* ***2000***, *65*, 7750. For a kinetic study of Et3ZnLi and di-*tert*-butyl ketone, see Maclin, K.M.; Richey, Jr., H.G. *J. Org. Chem.* ***2002***, *67*, 4602.

[575]Montgomery, J.; Song, M. *Org. Lett.* ***2002***, *4*, 4009.

[576]Fischer, S.; Groth, U.; Jeske, M.; Schütz, T. *Synlett* ***2002***, 1922.

[577]Majumdar, K.K.; Cheng, C.-H. *Org. Lett.* ***2000***, *2*, 2295.

[578]Yavari, I.; Riazi-Kermani, F. *Synth. Commun.* ***1995***, *25*, 2923; Ranu, B.C.; Majee, A.; Das, A.R. *Tetrahedron Lett.* ***1995***, *36*, 4885; Durant, A.; Delplancke, J.-L.; Winand, R.; Reisse, J. *Tetrahedron Lett.* ***1995***, *36*, 4257; Felpin, F.-X.; Bertrand, M.-J.; Lebreton, J. *Tetrahedron* ***2002***, *58*, 7381.

[579]Ito, T.; Ishino, Y.; Mizuno, T.; Ishikawa, A.; Kobyashi, J.-i. *Synlett* ***2002***, 2116.

Lithium dimethylcopper (Me_2CuLi) reacts with aldehydes[580] and with certain ketones[581] to give the expected alcohols. The RCu(CN)ZnI reagents also react with aldehydes, in the presence of BF_3–etherate, to give secondary alcohols. Vinyltellurium compound react with BF_3•OEt_2 and cyano cuprates [R(2-thienyl)CuCN-Li_2] to give a reagent that adds 1,2- to the carbonyl of a conjugated ketone.[582] Vinyl tellurium compounds also react with *n*-butyllithium to give a reagent that adds to nonconjugated ketones.[583]

Many methods have been reported for the addition of allylic groups,[584] including enantioselective reactions.[585] One of the most common methods is the Barbier reaction, employing metals and metal compounds other than Mg or Li, although the method is not limited to allylic compounds. Allyl indium compounds[586] add to aldehydes or ketones in various solvents.[587] Indium metal is used for the acyl addition of allylic halides with a variety of aldehydes and ketones, including aliphatic aldehydes,[588] aryl aldehydes[589] and α-keto esters.[590] Indium reacts with allylic bromides and ketones in water[591] and in aqueous media. Elimination of the homoallylic alcohol to a conjugated diene can accompany the addition in some cases.[592] The reaction of a propargyl halide, In, and an aldehyde in aq. THF leads to an allenic alcohol.[593] The reaction of benzaldehyde with a propargylic bromide, indium metal and water give the alcohol.[594] Allyl bromide reacts with Mn/TMSCl and an In catalyst in water to give the homoallylic

[580]Barreiro, E.; Luche, J.; Zweig, J.S.; Crabbé, P. *Tetrahedron Lett.* ***1975***, 2353; Zweig, J.S.; Luche; Barreiro, E.; Crabbé, P. *Tetrahedron Lett.* ***1975***, 2355; Reetz, M.T.; Rölfing, K.; Griebenow, N. *Tetrahedron Lett.* ***1994***, *35*, 1969.

[581]House, H.O.; Prabhu, A.V.; Wilkins, J.M.; Lee, L.F. *J. Org. Chem.* ***1976***, *41*, 3067; Matsuzawa, S.; Isaka, M.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* ***1989***, *30*, 1975.

[582]Araújo, M.A.; Barrientos-Astigarraga, R.E.; Ellensohn, R.M.; Comasseto, J.V. *Tetrahedron Lett.* ***1999***, *40*, 5115.

[583]Dabdoub, M.J.; Jacob, R.G.; Ferreira, J.T.B.; Dabdoub, V.B.; Marques, F.de.A. *Tetrahedron Lett.* ***1999***, *40*, 7159.

[584]For a list of reagents and references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1156–1170. For a discussion of a deuterium kinetic isotope effect in the addition of allylic reagents to benzaldehyde, see Gajewski, J.J.; Bocian, W.; Brichford, N.L.; Henderson, J.L. *J. Org. Chem.* ***2002***, *67*, 4236.

[585]For a review, see Denmark, S.E.; Fu, J. *Chem. Rev.* ***2003***, *103*, 2763.

[586]For a review, see Cintas, P. *Synlett* ***1995***, 1087.

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[588]Loh, T.-P.; Tan, K.-T.; Yang, J.-Y.; Xiang, C.-L. *Tetrahedron Lett.* ***2001***, *42*, 8701.

[589]Khan, F.A.; Prabhudas, B. *Tetrahedron* ***2000***, *56*, 7595.

[590]Loh, T.-P.; Huang, J.-M.; Xu, K.-C.; Goh, S.-H.; Vittal, J.J. *Tetrahedron Lett.* ***2000***, *41*, 6511; Kumar, S.; Kaur, P.; Chimni, S.S. *Synlett* ***2002***, 573.

[591]Chan, T.H.; Yang, Y. *J. Am. Chem. Soc.* ***1999***, *121*, 3228; Paquette, L.A.; Bennett, G.D.; Isaac, M.B.; Chhatriwalla, A. *J. Org. Chem.* ***1998***, *63*, 1836; Li, X.-R.; Loh, T.-P. *Tetrahedron Asymmetry* ***1996***, *7*, 1535; Isaac, M.B.; Chan, T.-H. *Tetrahedron Lett.* ***1995***, *36*, 8957.

[592]Kumar, V.; Chimni, S.; Kumar, S. *Tetrahedron Lett.* ***2004***, *45*, 3409.

[593]Lin, M.-J.; Loh, T.-P. *J. Am. Chem. Soc.* ***2003***, *125*, 13042.

[594]Lu, W.; Ma, J.; Yang, Y.; Chan, T.H. *Org. Lett.* ***2000***, *2*, 3469.

alcohols from aldehydes.[595] When allyl iodide is mixed with In and TMSCl, reaction with a conjugated ketone proceed by 1,4-addition, but in the presence of 10% CuI, the major product is that of 1,2-addition.[596] The reaction with indium is compatible with the presence of a variety of other functional groups in the molecule, including phosphonate,[597] propargylic sulfides.[598] Ethyl α-bromoacetate reacts with aldehydes using In with ultrasound.[599] Vinyl epoxides can be added to aldehydes using InI and a palladium catalyst,[600] and vinyl acetates react with indium metal to give a reactive intermediate that adds to the carbonyl of aldehydes.[601] A tandem reaction has been reported in which a bis(indium) reagent, $Br_2InC(=CH_2)–C(=CH_2)InBr_2$, reacts with 2 equivalents of an aldehyde in the presence of ZnF_2 to give a 3-hexyne-1,6-diol derivative.[602] Alkyl halides react with Zn/Cu and an InCl catalyst, in the presence of 0.07 *M* $Na_2Cr_2O_7$ to give an intermediate that adds to aldehydes.[603] Analogous to aldehydes, 1,1-diacetates react with In and allyl bromide in aq. THF to give a homoallylic acetate,[604] as do dimethyl ketals.[605] Allylic alcohols react with InI and a nickel catalyst to give acyl addition of an allylic group to an aldehyde, giving the homoallylic alcohol.[606]

Another important metal for Barbier-type reaction is samarium. Allyl bromide reacts with a ketone and Sm to give the homoallylic alcohol.[607] Samarium compounds, such as SmI_2,[608] can also be used with allylic halides.

Allyltin compounds readily add to aldehydes and ketones.[609] Allylic bromides react with tin to generate the organometallic *in situ*, which then adds to aldehydes.[610] Allylic chlorides react with aldehydes in the presence of ditin compounds such as $Me_3Sn–SnMe_3$ and a palladium catalyst.[611] Allyltrialkyltin compounds[612]

[595]Augé, J.; Lubin-Germain, N.; Thiaw-Woaye, A. *Tetrahedron Lett.* ***1999***, *40*, 9245.
[596]Lee, P.H.; Ahn, H.; Lee. K.; Sung, S.-y.; Kim, S. *Tetrahedron Lett.* ***2001***, *42*, 37.
[597]Ranu, B.C.; Samanta, S.; Hajra, A. *J. Org. Chem.* ***2001***, *66*, 7519.
[598]Mitzel, T.M.; Palomo, C.; Jendza, K. *J. Org. Chem.* ***2002***, *67*, 136.
[599]Lee, P.H.; Bang, K.; Lee, K.; Sung, S.-y.; Chang, S. *Synth. Commun.* ***2001***, *31*, 3781.
[600]Araki, S.; Kameda, K.; Tanaka, J.; Hirashita, T.; Yamamura, H.; Kawai, M. *J. Org. Chem.* ***2001***, *66*, 7919.
[601]Lombardo, M.; Girotti, R.; Morganti, S.; Trombini, C. *Org. Lett.* ***2001***, *3*, 2981.
[602]Miao, W.; Lu, W.; Chan, T.H.; *J. Am. Chem. Soc.* ***2003***, *125*, 2412.
[603]Keh, C.C.K.; Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* ***2003***, *125*, 4062.
[604]Yadav, J.S.; Reddy, B.V.S.; Reddy, G.S.K.K. *Tetrahedron Lett.* ***2000***, *41*, 2695.
[605]Kwon, J.S.; Pae, A.N.; Choi, K.I.; Koh, H.Y.; Kim, Y.; Cho, Y.S. *Tetrahedron Lett.* ***2001***, *42*, 1957.
[606]Hirashita, T.; Kambe, S.; Tsuji, H.; Omori, H.; Araki, S. *J. Org. Chem.* ***2004***, *69*, 5054.
[607]Basu, M.K.; Banik, B.K. *Tetrahedron Lett.* ***2001***, *42*, 187.
[608]Kunishima, M.; Tawaka, S.; Kono, K.; Hioki, K.; Tani, S. *Tetrahedron Lett.* ***1995***, *36*, 3707; Hélion, F.; Namy, J.-L. *J. Org. Chem.* ***1999***, *64*, 2944.
[609]Yasuda, M.; Kitahara, N.; Fujibayashi, T.; Baba, A. *Chem. Lett.* ***1998***, 743; Marshall, J.A.; Palovich, M.R. *J. Org. Chem.* ***1998***, *63*, 4381; Kobayashi, S.; Nagayama, S. *J. Org. Chem.* ***1996***, *61*, 2256.
[610]Tan, K.-T.; Chng, S.-S.; Cheng, H.-S.; Loh, T.-P. *J. Am. Chem. Soc.* ***2003***, *125*, 2958. For a reaction using Sn and ultrasound, see Andres, P.C.; Peatt, A.C.; Raston, C.L. *Tetraheron Lett.* ***2002***, *43*, 7541.
[611]Wallner, O.A.; Szabó, K.J. *J. Org. Chem.* ***2003***, *68*, 2934.
[612]For a high pressure version of this reaction, see Issacs, N.S.; Maksimovic, L.; Rintoul, G.B.; Young, D.J. *J. Chem. Soc., Chem. Commun.* ***1992***, 1749; Isaacs, N.S.; Marshall, R.L.; Young, D.J. *Tetrahedron Lett.* ***1992***, *33*, 3023.

and tetraallyltin react with aldehydes or ketones in the presence of BF_3–etherate,[613] $Cu(OTf)_2$,[614] $CeCl_3$ with NaI,[615] $Bi(OTf)_3$,[616] PbI_2,[617] AgOTf,[618] $Cd(ClO_4)_2$,[619] SnX_2,[620] Ti (IV),[621] $NbCl_5$,[622] $Zr(O\textit{t}\text{-}Bu)_4$,[623] or $La(OTf)_3$.[624] Tetraallyltin reacts via 1,2-addition to conjugated ketones in refluxing methanol.[625] Aluminum catalysts, such as MABR, facilitate addition of allyltributyltin to aldehydes.[626] Selectfluor has been used to induce 1,2-addition of the allyl group of allyltributyltin to a conjugated aldehyde.[627] Allyltributyltin reacts with aldehydes in the presence of aqueous trifluoromethanesulfonic acid to give the homoallylic alcohol.[628] Tetraallyltin reacts with aldehydes in ionic liquids[629] and on wet silica,[630] and allyltributyltin adds to aldehydes in ionic liquids with $InCl_3$.[631] Tetraallyltin adds to ketones or aldehydes to give homoallylic alcohols with good enantioselectivity in the presence of a chiral titanium complex.[632] Allylic alcohols and homoallylic alcohols add to aldehydes in the presence of $Sn(OTf)_2$[633] In/$InCl_3$,[634] or with a rhodium catalyst.[635] Vinyltin regents, such as (2-butadiene)tributyltin, react with aldehydes in the presence of $SnCl_4$ and 3 equivalents of DMF to

[613]Naruta, Y.; Ushida, S.; Maruyama, K. *Chem. Lett.* ***1979***, 919. For a review, see Yamamoto, Y. *Aldrichimica Acta* ***1987***, *20*, 45.
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give the dienyl alcohol.[636] Allenyl tin compounds (CH_2=C=$CHSnBu_3$) also react with aldehydes in the presence of BF_3•OEt_2 to give a 2-dienyl alcohol.[637] The tin compound can be prepared *in situ* using an α-iodo ketone with an aldehyde and Bu_2SnI_2–LiI.[638] A similar addition occurs with $(allyl)_2SnBr_2$ in water.[639] Asymmetric induction has been reported.[640] The use of a chiral rhodium[641] or titanium[642] catalyst leads to enantioselective addition of allyltributyltin to aldehydes. Allyltributyltin reacts with aldehydes in the presence of $SiCl_4$ and a chiral phosphoramide to give the homoallylic alcohol with moderate enantioselectivity.[643] It is noted that tetraallyl germanium adds to aldehydes in a similar manner in the presence of a $Sc(OTf)_3$ catalyst.[644]

A variety of other allylic metal compounds add to aldehydes or ketones.[645] A variety of alkyl and allylic halides add to aldehydes or ketones in the presence of metals or metal compounds; the metal or compounds based on Ti,[646] Mn,[647] Fe,[648] Ga,[649]

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Ge,[650] Zr,[651] Nb,[652] Cd,[653] Sn,[654] Sb,[655] Te,[656] Ba,[657] Ce,[658] Nd,[659] Hg,[660] Bi,[661] and Pb.[662] In addition, $BiCl_3/NaBH_4$,[663] Mg—$BiCl_3$,[664] and $CrCl_2/NiCl_2$,[665] have been used. Allylic alcohols have been converted to organometallic reagents with diethyl zinc and a palladium catalyst[666] or a ruthenium catalyst[667] leading to the homoallylic alcohol upon reaction with an aldehyde. A chiral Cr/Mn complex has been used with allylic bromides in conjunction with trimethylsilyl chloride.[668] Reagents of the type R—Yb have been prepared from RMgX.[669] Vinyl bromides react with $NiBr_2/CrCl_3$/TMSCl to give a reagent that adds to aldehydes to give the allylic alcohol.[670] Vinyl complexes generated from alkynes and SmI_2 add intramolecularly, and eight-membered rings have been formed in this way.[671] Allylic alcohols add to aldehydes in some cases, using $SnCl_2$ and a palladium catalyst.[672] Glyoxal reacted with 2 equivalents of allyl bromide and $SnCl_2$ with KI in water, to give the bis-homoallylic alcohol oct-1,7-diene-4,5-diol.[673] The alkyl group of trialkyl aluminum compounds such as $AlEt_3$ add to aldehydes, enantioselectively in the presence of chiral transition-metal complexes.[674] Certain functional groups (COOEt, $CONMe_2$, CN) can be present in the R group when

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[658]Loh, T.-P.; Zhou, J.-R. *Tetrahedron Lett.* ***1999***, *40*, 9115.
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[661]Miyamoto, H.; Daikawa, N.; Tanaka, K. *Tetrahedron Lett.* ***2003***, *44*, 6963; Wada, S.; Hayashi, N.; Suzuki, H. *Org. Biomol. Chem.* ***2003***, *1*, 2160; Smith, K.; Lock, S.; El-Hiti, G.A.; Wada, M.; Miyoshi, N. *Org. Biomol. Chem.* ***2004***, *2*, 935; Xu, X.; Zha, Z.; Miao, Q.; Wang, Z. *Synlett* ***2004***, 1171.
[662]Zhou, J.-Y.; Jia, Y.; Sun, G.-F.; Wu, S.-H. *Synth. Commun.* ***1997***, *27*, 1899.
[663]Ren, P.-D.; Shao, D.; Dong, T.-W. *Synth. Commun.* ***1997***, *27*, 2569.
[664]Wada, M.; Fukuma, T.; Morioka, M.; Takahashi, T.; Miyoshi, N. *Tetrahedron Lett.* ***1997***, *38*, 8045.
[665]Taylor, R.E.; Ciavarri, J.P. *Org. Lett.* ***1999***, *1*, 467.
[666]Kimura, M.; Shimizu, M.; Shibata, K.; Tazoe, M.; Tamaru, Y. *Angew. Chem. Int. Ed.* ***2003***, *42*, 3392.
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[671]Hölemann, A.; Reissig, H.-U. *Synlett* ***2004***, 2732.
[672]Márquez, F.; Llebaria, A.; Delgado, A. *Tetrahedron Asymmetry* ***2001***, *12*, 1625.
[673]Samoshin, V.V.; Gremyachinskiy, D.E.; Smith, L.I.; Bliznets, I.V.; Gross, P.H. *Tetrahedron Lett.* ***2002***, *43*, 6329.
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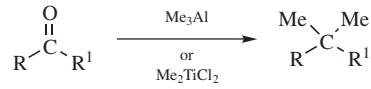
organotin reagents $RSnEt_3$ are added to aldehydes.[675] Trimethylaluminum[676] and dimethyltitanium dichloride[677] exhaustively methylate ketones to give *gem*-dimethyl compounds[678] (see also **10-63**):



The titanium reagent also dimethylates aromatic aldehydes.[679] Triethylaluminum reacts with aldehydes, however, to give the mono-ethyl alcohol, and in the presence of a chiral additive the reaction proceeds with good asymmetric induction.[680] A complex of $Me_3Ti{\bullet}MeLi$ has been shown to be selective for 1,2-addition with conjugated ketones, in the presence of nonconjugated ketones.[681] In other variations, the organometallic reagent is generated *in situ*. 1,4-Dimethoxybenzene reacts with ethyl glyoxylate ($EtO_2C{-}CHO$) in the presence of 5% $Yb(OTf)_3$, to give the alcohol formed by addition of the aryl group to the aldehyde unit.[682]

High ee values have also been obtained with organometallics,[683] including organotitanium compounds (methyl, aryl, allylic) in which an optically active ligand is coordinated to the titanium,[684] allylic boron compounds, and organozinc compounds. As for the organozinc reagents, very high enantioselection was obtained from R_2Zn reagents (R = alkyl)[685] and aromatic[686] aldehydes by the use of a small

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[678]For the *gem*-diallylation of anhydrides, with an indium reagent, see Araki, S.; Katsumura, N.; Ito, H.; Butsugan, Y. *Tetrahedron Lett.* ***1989***, *30*, 1581.

[679]Reetz, M.T.; Kyung, S. *Chem. Ber.* ***1987***, *120*, 123.

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[682]Zhang, W.; Wang, P.G. *J. Org. Chem.* ***2000***, *65*, 4732.

[683]For examples involving other organometallic compounds, see Abenhaïm, D.; Boireau, G.; Deberly, A. *J. Org. Chem.* ***1985***, *50*, 4045; Minowa, N.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* ***1987***, *60*, 3697; Takai, Y.; Kataoka, Y.; Utimoto, K. *J. Org. Chem.* ***1990***, *55*, 1707.

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[685]For a discussion of transition states in the amino alcohol promoted reaction, see Rasmussen, T.; Norrby, P.-O. *J. Am. Chem. Soc.* ***2001***, *123*, 2464.

[686]For catalysts that are also successful for aliphatic aldehydes, see Takahashi, H.; Kawakita, T.; Yoshioka, M.; Kobayashi, S.; Ohno, M. *Tetrahedron Lett.* ***1989***, *30*, 7095; Tanaka, K.; Ushio, H.; Suzuki, H. *J. Chem. Soc., Chem. Commun.* ***1989***, 1700; Soai, K.; Yokoyam, S.; Hayasaka, T. *J. Org. Chem.* ***1991***, *56*, 4264.

amount of various catalysts.[687] The enantioselectivity is influenced by additives, such as LiCl.[688] Silica-immobilized chiral ligands[689] can be used in conjunction with dialkylzinc reagents, and polymer-supported ligands have been used.[690]. Chiral dendritic titanium catalysts have been used to give moderate enantioselectivity.[691]

Enantioselective reaction of a carbonyl with a dialkylzinc is possible when other functional groups are present in the molecule. Examples include keto esters.[692] An enzyme-mediated addition of dialkylzinc reagents to aldehydes has also been reported.[693] When benzaldehyde was treated with Et_2Zn in the presence of the optically active catalyst 1-piperidino-3,3-dimethyl-2-butanol, a surprising result was obtained. Although the catalyst had only 10.7% excess of one enantiomer, the

[687]For a review, see Pu, L.; Yu, H.-B. *Chem. Rev.* ***2001***, *101*, 757. See also, Richmond, M.I.; Seto, C.T. *J. Org. Chem.* ***2003***, *68*, 7505; Sprout, C.M.; Seto, C.T. *J. Org. Chem.* ***2003***, *68*, 7788; Nugent, W.A. *Org. Lett.* ***2002***, *4*, 2133; García, C.; Walsh, P.J. *Org. Lett.* ***2003***, *5*, 3641; Kang, S.-W.; Ko, D.-H.; Kim, K.H.; Ha, D.-C. *Org. Lett.* ***2003***, *5*, 4517; Mao, J.; Wan, B.; Wang, R.; Wu, F.; Lu, S. *J. Org. Chem.* ***2004***, *69*, 9123; Superchi, S.; Giorgio, E.; Scafato, P.; Rosini, C. *Tetrahedron Asymmetry* ***2002***, *13*, 1385; Bastin, S.; Ginj, M.; Brocarrd, J.; Pélinski, L.; Novogrocki, G. *Tetrahedron Asymmetry* ***2003***, *14*, 1701; Joshi, S.N.; Malhotra, S.V. *Tetrahedron Asymmetry* ***2003***, *14*, 1763; Prieto, O.; Ramón, D.J.; Yus, M. *Tetrahedron Asymmetry* ***2003***, *14*, 1955; Lesma, G.; Danieli, B.; Passarella, D.; Sacchetti, A.; Silovani, A. *Tetrahedron Asymmetry* ***2003***, *14*, 2453; Danilova, T.I.; Rozenberg, V.I.; Starikova, Z.A.; Bräse, S. *Tetrahedron Asymmetry* ***2004***, *15*, 223; Scarpi, D.; Lo Galbo, F.; Occhiato, E.G.; Guarna, A. *Tetrahedron Asymmetry* ***2004***, *15*, 1319; Funabashi, K.; Jachmann, M.; Kanai, M.; Shibasaki, M. *Angew. Chem. Int. Ed.* ***2003***, *42*, 5489; Lake, F.; Moberg, C. *Eur. J. Org. Chem.* ***2002***, 3179; Reddy, K.S.; Solà, L.; Huang, W.-S.; Pu, L. *J. Org. Chem.* ***1999***, *64*, 4222; Paleo, M.R.; Cabeza, I.; Sardina, F.J. *J. Org. Chem.* ***2000***, *65*, 2108; Yang, L.; Shen, J.; Da, C.; Wang, R.; Choi, M.C.K.; Yang, L.; Wong, K.-y. *Tetrahedron Asymmetry* ***1999***, *10*, 133; Shi, M.; Jiang, J.-K. *Tetrahedron Asymmetry* ***1999***, *10*, 1673; Kawanami, Y.; Mitsuie, T.; Miki, M.; Sakamoto, T.; Nishitani, K. *Tetrahedron* ***2000***, *56*, 175; Hanyu, N.; Aoki, T.; Mino, T.; Sakamoto, M.; Fujita, T. *Tetrahedron Asymmetry* ***2000***, *11*, 2971; Arroyo, N.; Haslinger, U.; Mereiter, K.; Widhalm, M. *Tetrahedron Asymmetry* ***2000***, *11*, 4207; Jimeno, C.; Moyano, A.; Pericàs, M.A.; Riera, A. *Synlett* ***2001***, 1155; Hermsen, P.J.; Cremers, J.G.O.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* ***2001***, *42*, 4243; Xu, Q.; Wang, H.; Pan, X.; Chan, A.S.C.; Yang, T.-k. *Tetrahedron Lett.* ***2001***, *42*, 6171; Yang, X.-w.; Shen, J.-h.; Da, C.-s.; Wang, H.-s.; Su, W.; Liu, D.-x.; Wang, R.; Choi, M.C.K.; Chan, A.S.C. *Tetrahedron Lett.* ***2001***, *42*, 6573; Ohga, T.; Umeda, S.; Kawanami, Y. *Tetrahedron* ***2001***, *57*, 4825; Zhao, G.; Li, X.-G.; Wang, X.-R. *Tetrahedron Asymmetry* ***2001***, *12*, 399; You, J.-S.; Shao, M.-Y.; Gau, H.-M. *Tetrahedron Asymmetry* ***2001***, *12*, 2971; Priego, J.; Mancheño, O.G.; Cabrera, S.; Carretero, J.C. *Chem. Commun.* ***2001***, 2026; Bolm, C.; Kesselgruber, M; Hermanns, N.; Hildebrand, J.P.; Raabe, G. *Angew. Chem. Int. Ed.* ***2001***, *40*, 1488; Wipf, P.; Wang, X. *Org. Lett.* ***2002***, *4*, 1197; Braga, A.L.; Milani, P.; Paixão, M.W.; Zeni, G.; Rodrigues, O.E.D.; Alves, E.F. *Chem. Commun.* ***2004***, 2488; Sibi, M.P.; Stanley, L.M. *Tetrahedron Asymmetry* ***2004***, *15*, 3353; Tseng, S.-L.; Yang, T.-K. *Tetrahedron Asymmetry* ***2004***, *15*, 3375; Harada, T.; Kanda, K.; Hiraoka, Y.; Marutani, Y.; Nakatsugawa, M. *Tetrahedron Asymmetry* ***2004***, *15*, 3879; Casey, M.; Smyth, M.P. *Synlett* ***2003***, 102.

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[692]DiMauro, E.F.; Kozlowski, M.C. *Org. Lett.* ***2002***, *4*, 3781.

[693]Yang, W.K.; Cho, B.T. *Tetrahedron Asymmetry* ***2000***, *11*, 2947.

product PhCH(OH)Me had an ee of 82%.[694] When the catalyst ee was increased to 20.5%, the product ee rose to 88%. The question is, how could a catalyst produce a product with an ee much higher than itself? One possible explanation[695] is that (*R*) and (*S*) molecules of the catalyst form a complex with each other, and that only the uncomplexed molecules are actually involved in the reaction. Since initially the number of (*R*) and (*S*) molecules was not the same, the (*R/S*) ratio of the uncomplexed molecules must be considerably higher (or lower) than that of the initial mixture.

Although organoboranes do not generally add to aldehydes and ketones,[696] allylic boranes are exceptions.[697] When they add, an allylic rearrangement always takes place. Allylic rearrangements take place with the other reagents as well. The use of a chiral catalyst leads to asymmetric induction[698] and chiral allylic boranes have been prepared.[699] It is noted that chloroboranes (R_2BCl) react with aldehydes via acyl addition of the alkyl group, giving the corresponding alcohol after treatment with water.[700] A variation is the reaction of a diketone, where one carbonyl is conjugated. Treatment with catecholborane gives addition to the conjugated ketone, and subsequent cyclization of the resulting organometallic at the nonconjugated ketone gives a cyclic alcohol with a pendant ketone unit, after treatment with methanol.[701] In the presence of ruthenium complexes, $RB(OH)_2$ and arylboronic acids $ArB(OH)_2$ (p. 815) add to aldehydes to give the corresponding alcohol.[702] Polymer-bound aryl borates add an aryl group to aldehydes in the presence of a rhodium catalyst.[703] An intramolecular version of the phenylboronic acid-induced reaction is known, where a molecule with ketone and conjugated ketone units is converted to a cyclic alcohol using a chiral rhodium catalyst.[704] Allylic boronates add to aldehydes.[705]

[694]Oguni, N.; Matsuda, Y.; Kaneko, T. *J. Am. Chem. Soc.* ***1988***, *110*, 7877.

[695]See Wynberg, H. *Chimia* ***1989***, *43*, 150.

[696]For another exception, involving a vinylic borane, see Satoh, Y.; Tayano, T.; Hara, S.; Suzuki, A. *Tetrahedron Lett.* ***1989***, *30*, 5153.

[697]For reviews, see Hoffmann, R.W.; Niel, G.; Schlapbach, A. *Pure Appl. Chem.* ***1990***, *62*, 1993; Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, ***1988***, pp. 310–318. For a review of allylic boranes, see Bubnov, Yu.N. *Pure Appl. Chem.* ***1987***, *21*, 895. For an example that proceeds with asymmetric induction, see Buynak, J.D.; Geng, B.; Uang, S.; Strickland, J.B. *Tetrahedron Lett.* ***1994***, *35*, 985.

[698]Ishiyama, T.; Ahiko, T.-a.; Miyaura, N. *J. Am. Chem. Soc.* ***2002***, *124*, 12414; Wada, R.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* ***2004***, *126*, 8910.

[699]Lachance, H.; Lu, X.; Gravel, M.; Hall, D.G. *J. Am. Chem. Soc.* ***2003***, *125*, 10160; Ramachandran, P.V.; Krezeminski, M.P.; Reddy, M.V.R.; Brown, H.C. *Tetrahedron Asymmetry* ***1999***, *10*, 11; Roush, W.R.; Pinchuk, A.N.; Micalizio, G.C. *Tetrahedron Lett.* ***2000***, *41*, 9413; Wu, T.R.; Shen, L.; Chong, J.M. *Org. Lett.* ***2004***, *6*, 2701.

[700]Kabalka, G.W.; Wu, Z.; Ju, Y. *Tetrahedron* ***2001***, *57*, 1663; Kabalka, G.W.; Wu, Z.; Ju, Y. *Tetrahedron* ***2002***, *58*, 3243.

[701]Huddleston, R.R.; Cauble, D.F.; Krische, M.J. *J. Org. Chem.* ***2003***, *68*, 11.

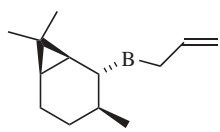
[702]Ueda, M.; Miyaura, N. *J. Org. Chem.* ***2000***, *65*, 4450 and references cited therein.

[703]Pourbaix, C.; Carreaux, F.; Carboni, B. *Org. Lett.* ***2001***, *3*, 803; Rudolph, J.; Schmidt, F.; Bolm, C. *Synthesis* ***2005***, 840.

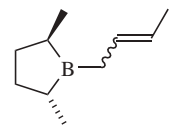
[704]Cauble, D.F.; Gipson, J.D.; Krische, M.J. *J. Am. Chem. Soc.* ***2003***, *125*, 1110.

[705]For a review of the scandium-catalyzed enantioselective addition, see Gravel, M.; Lachance, H.; Lu, X.; Hall, D.G. *Synthesis* ***2004***, 1290.

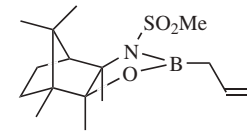
A number of optically active allylic boron compounds have been used, including[706] B-allylbis(2-isocaranyl)borane (**30**),[707] (*E*)- and (*Z*)-crotyl-(*R*,*R*)-2,5-dimethylborolanes (**31**),[708] and the borneol



30



31



32

derivative **32**,[709] all of which add an allyl group to aldehydes, with good enantioselectivity. Where the substrate possesses an aryl group or a triple bond, enantioselectivity is enhanced by using a metal carbonyl complex of the substrate.[710]

Alkenes and alkynes add to aldehydes or ketones by conversion to a reactive organometallic. A radical-type addition is possible using alkenes with BEt_3. Benzaldehyde reacted with isoprene in the presence of BEt_3 and $Ni(acac)_2$ to give an anti-Markovnikov-type addition to the carbonyl, C=C–C(Me)=C + PhCHO → C=CCHMeCH$_2$CH(OH)Ph.[711] Alkynes add to aldehydes elsewhere in the same molecule in the presence of BEt_3 and a nickel catalyst to give a cyclic allylic alcohol.[712] Alkene aldehydes react similarly using Me_3SiOTf.[713] In a similar manner, dienes add to aldehydes in the presence of a nickel catalyst.[714] Propargylic halides add to aldehydes to give an allenic alcohol using β-SnO[Rd(cod)Cl]$_2$.[715] Allylic acetates react with ketones to give the homoallylic alcohol under electrochemical conditions that include bipyridyl, tetrabutylammonium tetrafluoroborate and $FeBr_2$.[716] Terminal alkynes react with zirconium complexes and Me_2Zn to give an allylic tertiary alcohol.[717] Internal alkynes also give allylic alcohols in the presence of BEt_3 and a nickel catalysts.[718] Reaction of an aldehyde containing a conjugated diene unit with diethylzinc and a nickel catalyst leads to cyclic

[706]For some others, see Hoffmann, R.W. *Pure Appl. Chem.* ***1988***, *60*, 123; Corey, E.J.; Yu, C.; Kim, S.S. *J. Am. Chem. Soc.* ***1989***, *111*, 5495; Roush, W.R.; Ando, K.; Powers, D.B.; Palkowitz, A.D.; Halterman, R.L. *J. Am. Chem. Soc.* ***1990***, *112*, 6339; Brown, H.C.; Randad, R.S. *Tetrahedron Lett.* ***1990***, *31*, 455; Stürmer, R.; Hoffmann, R.W. *Synlett* ***1990***, 759.

[707]Racherla, U.S.; Brown, H.C. *J. Org. Chem.* ***1991***, *56*, 401, and references cited therein.

[708]Garcia, J.; Kim, B.M.; Masamune, S. *J. Org. Chem.* ***1987***, *52*, 4831.

[709]Reetz, M.T.; Zierke, T. *Chem. Ind. (London)* ***1988***, 663.

[710]Roush, W.R.; Park, J.C. *J. Org. Chem.* ***1990***, *55*, 1143.

[711]Kimura, M.; Fujimatsu, H.; Ezoe, A.; Shibata, K.; Shimizu, M.; Matsumoto, S.; Tamaru, Y. *Angew. Chem. Int. Ed.* ***1999***, *38*, 397.

[712]Miller, K.M.; Huang, W.-S.; Jamison, T.F. *J. Am. Chem. Soc.* ***2003***, *125*, 3442; Miller, K.M.; Luanphaisarnnont, T.; Molinaro, C.; Jamison, T.F. *J. Am. Chem. Soc.* ***2004***, *126*, 4130.

[713]Suginome, M.; Iwanami, T.; Yamamoto, A.; Ito, Y. *Synlett* ***2001***, 1042.

[714]Sawaki, R.; Sato, Y.; Mori, M. *Org. Lett.* ***2004***, *6*, 1131.

[715]Banerjee, M.; Roy, S. *Org. Lett.* ***2004***, *6*, 2137.

[716]Durandetti, M.; Meignein, C.; Périchon, J. *J. Org. Chem.* ***2003***, *68*, 3121.

[717]Li, H.; Walsh, P.J. *J. Am. Chem. Soc.* ***2004***, *126*, 6538.

[718]Miller, K.M.; Jamison, T.F. *J. Am. Chem. Soc.* ***2004***, *126*, 15342.

alcohols having a pendant allylic unit.[719] A similar reaction was reported using a copper catalyst.[720] Vinyl iodides also react with Cp_2ZrCl_2 to give a vinylzirconium complex that reacts with aldehydes.[721] The intramolecular addition of an alkene to an aldehyde leads to a saturated cyclic alcohol using $PhSiH_3$ and a cobalt catalyst.[722] Intramolecular addition of a conjugated ester (via the β-carbon) to an aldehyde generates a cyclic ketone.[723] This type of coupling has been called the *Stetter reaction*,[724] which actually involves the addition of aldehydes to activated double bonds (**15-34**), mediated by a catalytic amount of thiazolium salt in the presence of a weak base. The intramolecular addition of the allene moiety to an aldehyde is catalyzed by a palladium complex in the presence of $Me_3SiSnBu_3$.[725] A highly enantio- and diastereoselective intramolecular Stetter reaction has been developed.[726] Alkynyl aldehydes react with silanes such as Et_3SiH and a nickel catalyst to give a cyclic compound having a silyl ether and an exocyclic vinylidene unit.[727] Alkene-aldehydes give cyclic alcohols via intramolecular addition of the C=C unit to the carbonyl under electrolytic conditions using a phase-transfer catalyst.[728] A similar cyclization was reported using $SnCl_4$.[729] Vinylidene cycloalkanes react with aldehydes in the presence of a palladium catalyst to give a homoallylic alcohol where addition occurs at the carbon exocyclic to the ring.[730] Alkenes having an allylic hydrogen react with α-keto aldehydes, with a cobalt catalyst, to give α-hydroxy ketones where the alcohol is homoallylic relative to the C=C unit.[731] Allenes react with benzaldehyde using $HCl{-}SnCl_2$ with a palladium catalyst.[732] Silyl allenes react with aldehydes in the presence of a chiral scandium catalyst to give homopropargylic alcohols with good enantioselectivity.[733] Intramolecular addition of an allene to aldehyde via addition of phenyl when treated with PhI and a palladium catalyst.[734] Allenes add to ketones

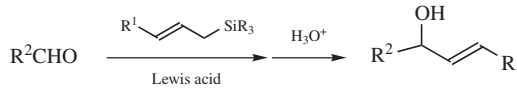
[719]Shibata, K.; Kimura, M.; Shimizu, M.; Tamaru, Y. *Org. Lett.* ***2001***, *3*, 2181.
[720]Agapiou, K.; Cauble, D.F.; Krische, M.J. *J. Am. Chem. Soc.* ***2004***, *126*, 4528.
[721]Namba, K.; Kishi, Y. *Org. Lett.* ***2004***, *6*, 5031.
[722]Baik, T.-G.; Luis, A.L.; Wang, L.-C.; Krische, M.J. *J. Am. Chem. Soc.* ***2001***, *123*, 5112.
[723]Kerr, M.S.; Rovis, T. *J. Am. Chem. Soc.* ***2004***, *126*, 8876.
[724]Stetter, H.; Schreckenberg, M. *Angew. Chem., Int. Ed* ***1973***, *12*, 81; Stetter, H. *Angew. Chem., Int. Ed.* ***1976***, *15*, 639; Stetter, H.; Kuhlmann, H. *Org. React.* ***1991***, *40*,407; Enders, D.; Breuer, K.; Runsink, J.; Teles, J.H. *Helv. Chim. Acta* ***1996***, *79*, 1899; Kerr, M.S.; Rovis, T. *J. Am. Chem. Soc.* ***2004***, *126*, 8876; Pesch, J.; Harms, K.; Bach, T. *Eur. J. Org. Chem.* ***2004***, 2025; Mennen, S.; Blank, J.; Tran-Dube, M.B.; Imbriglio, J.E.; Miller, S.J. *Chem. Commun.* ***2005***, 195. For examples of the Stetter reaction with acyl silanes, see Mattson, A.E.; Bharadwaj, A.R.; Scheidt, K.A. *J. Am. Chem. Soc.* ***2004***, *126*, 2314.
[725]Kang, S.-K.; Ha, Y.-H.; Ko, B.-S.; Lim, Y.; Jung, J. *Angew. Chem. Int. Ed.* ***2002***, *41*, 343.
[726]Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* ***2005***, *127*, 6284; Kerr, M.S.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* ***2002***, *124*, 10298.
[727]Tang, X.-Q.; Montgomery, J. *J. Am. Chem. Soc.* ***1999***, *121*, 6098.
[728]Locher, C.; Peerzada, N. *J. Chem. Soc., Perkin Trans. 1* ***1999***, 179.
[729]Alcaide, B.; Pardo, C.; Rodríguez-Ranera, C.; Rodríguez-Vicente, A. *Org. Lett.* ***2001***, *3*, 4205.
[730]Hao, J.; Hatano, M.; Mikami, K. *Org. Lett.* ***2000***, *2*, 4059.
[731]Kezuka, S.; Ikeno, T.; Yamada, T. *Org. Lett.* ***2001***, *3*, 1937.
[732]Chang, H.-M.; Cheng, C.-H. *Org. Lett.* ***2000***, *2*, 3439.
[733]Evans, D.A.; Sweeney, Z.K.; Rovis, T.; Tedrow, J.S. *J. Am. Chem. Soc.* ***2001***, *123*, 12095.
[734]Kang, S.-K.; Lee, S.-W.; Jung, J.; Lim, Y. *J. Org. Chem.* ***2002***, *67*, 4376.

to give homoallylic alcohols in the presence of SmI_2 and HMPA.[735] Allenes add to carbonyl groups in the presence of 2.2 equivalents of SmI_2 and an excess of HMPA.[736] Alkenes have an allylic methyl group add to formaldehyde, in the presence of BF_3•OEt_2, to give a homoallylic alcohol.[737] Conjugated dienes react with aldehyde via acyl addition of a terminal carbon of the diene, in the presence of $Ni(acac)_2$ and Et_2Zn.[738] Aldehydes having an allylic acetate unit elsewhere in the molecule undergo cyclization in CO and a ruthenium catalyst to give a cyclic alcohol with a pendant vinyl group.[739]

Allylic trifluoroborates (p. 817) react with aldehydes to give the homoallylic alcohol. Pivaldehyde reacts with potassium 2-butenyltrifluoroborate and a catalytic amount of tetrabutylammonium iodide to give 2,2,4-trimethylhex-5-en-3-ol.[740] Aliphatic aldehydes react with this reagent, in the presence of BF_3•OEt_2, to give the homoallylic alcohol with allylic rearrangement and a preference for the syn diastereomer,[741] and aryl aldehydes react as well.[742]

16-26 Addition of Trialkylallylsilanes to Aldehydes and Ketones

O-Hydro-*C*-alkyl-addition



Allylic trialkyl, trialkoxy, and trihalosilanes add to aldehydes to give the homoallylic alcohols in the presence of a Lewis acid[743] (including $TaCl_5$[744] and $YbCl_3$[745]), Me_3SiOTf,[746] fluoride ion,[747] proazaphosphatranes,[748] or a catalytic amount of iodine.[749] The mechanism of this reaction has been examined.[750] A ruthenium catalyst has also been used in conjunction with an arylsilane and an aldehyde.[751]

[735]Hölemann, A.; Reissig, H.-U. *Org. Lett.* ***2003***, *5*, 1463.
[736]Hölemann, A.; Reißig, H.-U. *Chem. Eur. J.* ***2004***, *10*, 5493.
[737]Okachi, T.; Fujimoto, K.; Onaka, M. *Org. Lett.* ***2002***, *4*, 1667.
[738]Loh, T.-P.; Song, H.-Y.; Zhou, Y. *Org. Lett.* ***2002***, *4*, 2715.
[739]Yu, C.-M.; Lee, S.; Hong, Y.-T.; Yoon, S.-K. *Tetrahedron Lett.* ***2004***, *45*, 6557.
[740]Thadani, A.N.; Batey, R.A. *Org. Lett.* ***2002***, *4*, 3827.
[741]Batey, R.A.; Thadani, A.N.; Smil, D.V. *Tetrahedron Lett.* ***1999***, *40*, 4289.
[742]Batey, R.A.; Thadani, A.N.; Smil, D.V.; Lough, A.J. *Synthesis* ***2000***, 990.
[743]For reviews, see Fleming, I.; Dunoguès, J.; Smithers, R. *Org. React.* ***1989***, *37*, 57, 113–125, 290–328; Parnes, Z.N.; Bolestova, G.I. *Synthesis* ***1984***, 991, see pp. 997–1000. For studies of the mechanism, see Denmark, S.E.; Weber, E.J.; Wilson, T.; Willson, T.M. *Tetrahedron* ***1989***, *45*, 1053; Keck, G.E.; Andrus, M.B.; Castellino, S. *J. Am. Chem. Soc.* ***1989***, *111*, 8136. For examples, see Aggarwal, V.K.; Vennall, G.P. *Tetrahedron Lett.* ***1996***, *37*, 3745.
[744]Chandrasekhar, S.; Mohanty, P.K.; Raza, A. *Synth. Commun.* ***1999***, *29*, 257.
[745]Fang, X.; Watkin, J.G.; Warner, B.P. *Tetrahedron Lett.* ***2000***, *41*, 447.
[746]Davis, A.P.; Jaspars, M. *Angew. Chem. Int. Ed.* ***1992***, *31*, 470.
[747]See Cossy, J.; Lutz, F.; Alauze, V.; Meyer, C. *Synlett* ***2002***, 45.
[748]Wang, Z.; Kisanga, P.; Verkade, J.G. *J. Org. Chem.* ***1999***, *64*, 6459.
[749]Yadav, J.S.; Chand, P.K.; Anjaneyulu, S. *Tetrahedron Lett.* ***2002***, *43*, 3783.
[750]Bottoni, A.; Costa, A.L.; DiTommaso, D.; Rossi, I.; Tagliavini, E. *J. Am. Chem. Soc.* ***1997***, *119*, 12131.
[751]Fujii, T.; Koike, T.; Mori, A.; Osakada, K. *Synlett* ***2002***, 298.

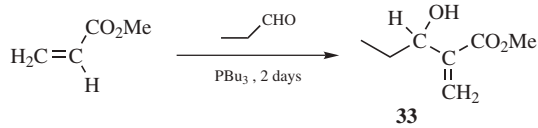
The reaction of an allene aldehyde with Et_3SiH, CO and a rhodium catalyst leads to addition to the alkene followed by intramolecular addition to the aldehyde to give the cyclic alcohol.[752] Allyl(trimethoxy)silane adds an allyl group to aldehydes using a CdF_2[753] catalyst or a chiral AgF complex.[754] Allyltrichlorosilanes have also been used in addition reactions with aldehydes.[755] Hünig's base ($i Pr_2NEt$) and a sulfoxide have also been used to facilitate the addition of an allyl group to an aldehyde from allyltrichlorosilane.[756]

Allyltrichlorosilane reacts with benzaldehyde in the presence of Bu_4NF to give 1-phenylbut-3-en-1ol,[757] and with a chiral additive the reaction proceeds with good enantioselectivity. When chiral titanium complexes are used in the reaction, allylic alcohols are produced with good asymmetric induction.[758] Other chiral additives have been used,[759] as well as chiral catalysts,[760] and chiral complexes of allyl silanes.[761] Chiral allylic silyl derivatives add to aldehydes to give the chiral homoallylic alcohol.[762]

Allylic silanes react with *gem*-diacetates in the presence of $InCl_3$ to give a homoallylic acetate[763] or with dimethyl acetals and TMSOTf in an ionic liquid to give the homoallylic methyl ether.[764] Allylic alcohols can be treated with TMS—Cl and NaI, and then Bi to give an organometallic reagent that adds to aldehydes.[765]

16-27 Addition of Conjugated Alkenes to Aldehydes (the Baylis–Hillman Reaction)[766]

O-Hydro-*C*-alkenyl-addition



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[752]Kang, S.-K.; Hong, Y.-T.; Lee, J.-H.; Kim, W.-Y.; Lee. I.; Yu, C.-M. *Org. Lett.* ***2003***, *5*, 2813.
[753]Aoyama, N.; Hamada, T.; Manabe, K.; Kobayashi, S. *Chem. Commun.* ***2003***, 676.
[754]Yanagisawa, A.; Kageyama, H.; Nakatsuka, Y.; Asakawa, K.; Matsumoto, Y.; Yamamoto, H. *Angew. Chem. Int. Ed.* ***1999***, *38*, 3701.
[755]Kobayashi, S.; Nishio, K. *J. Org. Chem.* ***1994***, *59*, 6620.
[756]Massa, A.; Malkov, A.V.; Kočovský, P.; Scettri, A. *Tetrahedron Lett.* ***2003***, *44*, 7179.
[757]Malkov, A.V.; Bell, M.; Orsini, M.; Pernazza, D.; Massa, A.; Herrmann, P.; Meghani, P.; Kočovský, P. *J. Org. Chem.* ***2003***, *68*, 9659.
[758]Gauthier Jr., D.R.; Carreira, E.M. *Angew. Chem. Int. Ed.* ***1996***, *35*, 2363.
[759]Angell, R.M.; Barrett, A.G.M.; Braddock, D.C.; Swallow, S.; Vickery, B.D. *Chem. Commun.* ***1997***, 919.
[760]Malkov, A.V.; Dufková, L.; Farrugia, L.; Kočovský, P. *Angew. Chem Int. Ed.* ***2003***, *42*, 3802; Bode, J.W.; Gauthier, Jr., D.R.; Carreira, E.M. *Chem. Commun.* ***2001***, 2560.
[761]Zhang, L.C.; Sakurai, H.; Kira, M. *Chem. Commun.* ***1997***, 129; Iseki, K.; Mizuno, S.; Kuroki, Y.; Kobayashi, Y. *Tetrahedron* ***1999***, *55*, 977
[762]Wang, X.; Meng, Q.; Nation, A.J.; Leighton, J.L. *J. Am. Chem. Soc.* ***2002***, *124*, 10672; Kubota, K.;l Leighton, J.L. *Angew. Chem. Int. Ed.* ***2003***, *42*, 946; Hackman, B.M.; Lombardi, P.J.; Leighton, J.L. *Org. Lett.* ***2004***, *6*, 4375.
[763]Yadav, J.S.; Reddy, B.V.S.; Madhuri, Ch.; Sabitha, G. *Chem. Lett.* ***2001***, 18.
[764]In bmim PF_6, 1-butyl-3-methylimidazolium hexafluorophosphate: Zerth, H.M.; Leonard, N.M.; Mohan, R.S. *Org. Lett.* ***2003***, *5*, 55.
[765]Miyoshi, N.; Nishio, M.; Murakami, S.; Fukuma, T.; Wada, M. *Bull. Chem. Soc. Jpn.* ***2000***, *73*, 689.
[766]For a review, see Basavaih, D.; Rao, A.J.; Satyanarayana, T. *Chem. Rev.* ***2003***, *103*, 811.

In the presence of a base,[767] such as 1,4-diazabicyclo[2.2.2]octane (DABCO) or trialkylphosphines, conjugated carbonyl compounds (ketones, esters,[768] thioesters,[769] and amides[770]) add to aldehydes via the α-carbon to give α-alkenyl-β-hydroxy esters or amides. This sequence is called the *Baylis–Hillman reaction*,[771] and a simple example is the formation of **33**.[772] It was observed that methyl vinyl ketone gave other products in the Baylis–Hillman reaction, whereas conjugated esters did not.[773] Methods that are catalytic in base have been developed for the Baylis–Hillman reaction.[774] Both microwave irradiation[775] and ultrasound[776] have been used to induce the reaction. Under certain conditions, rate enhancements have been observed.[777] Rate acceleration occurs with bis-aryl(thio)ureas in a DABCO-promoted reaction.[778] The reaction has been done in ionic liquids[779] and polyethylene glycol (PEG)[780] or sulpholane.[781] Alkynyl carbonyl compounds can be used as partners in the Baylis–Hillman reaction.[782] Transition metal compounds can facilitate the Baylis–Hillman reaction, and $BF_3{\bullet}OEt_2$ has been used.[783] With the boron trifluoride

[767]For an example using NaOMe, see Luo, S.; Mi, X.; Xu, H.; Wang, P.G.; Cheng, J.-P. *J. Org. Chem.* ***2004***, *69*, 8413.

[768]For an example with a conjugated lactone, see Karur, S.; Hardin, J.; Headley, A.; Li, G. *Tetrahedron Lett.* ***2003***, *44*, 2991.

[769]Pei, W.; Wei, H.-X.; Li, G. *Chem. Commun.* ***2002***, 1856.

[770]See Yu, C.; Hu, L. *J. Org. Chem.* ***2002***, *67*, 219; Faltin, C.; Fleming, E.M.; Connon, S.J. *J. Org. Chem.* ***2004***, *69*, 6496.

[771]Baylis, A.B.; Hillman, M.E.D. Ger. Offen. 2,155,133 *Chem. Abstr.*, ***1972***, *77*, 34174q [U.S. Patent 3,743,668]; Drewes, S.E.; Roos, G.H.P. *Tetrahedron* ***1988***, *44*, 4653. For a review, see Basavaiah, D.; Rao, P.D.; Hyma, R.S. *Tetrahedron* ***1996***, *52*, 8001.

[772]Rafel, S.; Leahy, J.W. *J. Org. Chem.* ***1997***, *62*, 1521. Also see, Drewes, S.E.; Rohwer, M.B. *Synth. Commun.* ***1997***, *27*, 415.

[773]Shi, M.; Li, C.-Q.; Jiang, J.-K. *Chem. Commun.* ***2001***, 833.

[774]With imidazole: Gatri, R.; El Gaïed, M.M. *Tetrahedron Lett.* ***2002***, *43*, 7835. With azoles: Luo, S.; Mi, X.; Wang, P.G.; Cheng, J.-P. *Tetrahedron Lett.* ***2004***, *45*, 5171. With proazaphosphatranes/$TiCl_4$: You, J.; Xu, J.; Verkade, J.G. *Angew. Chem. Int. Ed.* ***2003***, *42*, 5054. See Leadbeater, N.E.; van der Pol, C. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 2831. For a discussion of pK_a and reactivity, see Aggarwal, V.K.; Emme, I.; Fulford, S.Y. *J. Org. Chem.* ***2003***, *68*, 692.

[775]Kundu, M.K.; Mukherjee, S.B.; Balu, N.; Padmakumar, R.; Bhat, S.V. *Synlett* ***1994***, 444.

[776]Coelho, F.; Almeida, W.P.; Veronese, D.; Mateus, C.R.; Lopes, E.C.S.; Rossi, R.C.; Silveira, G.P.C.; Pavam, C.H. *Tetrahedron* ***2002***, *58*, 7437.

[777]See Rafel, S.; Leahy, J.W. *J. Org. Chem.* ***1997***, *62*, 1521; Lee, W.-D.; Yang, K.-S.; Chen, K. *Chem. Commun.* ***2001***, 1612. For rate acceleration in water or aqueous media, see Augé, J.; Lubin, N.; Lubineau, A. *Tetrahedron Lett.* ***1994***, *35*, 7947; Luo, S.; Wang, P.G.; Cheng, J.-P. *J. Org. Chem.* ***2004***, *69*, 555; Cai, J.; Zhou, Z.; Zhao, G.; Tang, C. *Org. Lett.* ***2002***, *4*, 4723. For rate acceleration in polar solvents, see Aggarwal, V.K.; Dean, D.K.; Mereu, A.; Williams, R. *J. Org. Chem.* ***2002***, *67*, 510. For a discussion of salt effects, see Kumar, A.; Pawar, S.S. *Tetrahedron* ***2003***, *59*, 5019.

[778]Maher, D.J.; Connon, S.J. *Tetrahedron Lett.* ***2004***, *45*, 1301.

[779]Rosa, J.N.; Afonso, C.A.M.; Santos, A.G. *Tetrahedron* ***2001***, *57*, 4189. For an example in a chiral ionic liquid, see Pégot, B.; Vo-Thanh, G.; Gori, D.; Loupy, A. *Tetrahedron Lett.* ***2004***, *45*, 6425.

[780]Chandrasekhar, S.; Narsihmulu, Ch.; Saritha, B.; Sultana, S.S. *Tetrahedron Lett.* ***2004***, *45*, 5865.

[781]Krishna, P.R.; Manjuvani, A.; Kannan, V.; Sharma, G.V.M. *Tetrahedron Lett.* ***2004***, *45*, 1183.

[782]Matsuya, Y.; Hayashi, K.; Nemoto, H. *J. Am. Chem. Soc.* ***2003***, *125*, 646; Wei, H.-X.; Jasoni, R.L.; Hu, J.; Li, G.; Paré, P.W. *Tetrahedron* ***2004***, *60*, 10233; Shi, M.; Wang, C.-J. *Helv. Chim. Acta* ***2002***, *85*, 841.

[783]Walsh, L.M.; Winn, C.L.; Goodman, J.M. *Tetrahedron Lett.* ***2002***, *43*, 8219.

induced reaction between an aldehyde and a conjugated ketone, a saturated β-hydroxy ketone was formed with good antiselectivity.[784] The coupling of aldehydes with conjugated ketones was accomplished with $TiCl_4$,[785] dialkylaluminum halides,[786] and with (polymethyl)hydrosiloxane and a copper catalyst.[787] Conjugated esters were coupled to aldehydes with DABCO and a lanthanum catalyst.[788] Aldehydes were coupled to conjugated nitriles with $TiCl_4$.[789] The reaction of a conjugated ester, an aldehyde and $LiClO_4$, with 15% DABCO gave the allylic alcohol product.[790] *N*-Tosyl imines can be used in place of aldehydes, and the reaction of the imine, a conjugated ester and DABCO gave the allylic *N*-tosylimine.[791] Aldehydes are coupled to conjugated esters with a chiral quinuclidine catalyst and a titanium catalyst, and in the presence of tosylamine, the final product was the allylic *N*-tosylamine formed with modest enantioselectivity.[792]

An intramolecular version of the Baylis–Hillman reaction generated cyclopentenone derivatives from alkyne-aldehydes and a rhodium catalyst.[793] Another intramolecular reaction gave cyclopentenols via cyclization of an aldehyde-conjugated thioester upon treatment with DBU and DMAP.[794] Cyclization of a conjugated ester using DABCO, where the ''alcohol'' group contained an aldehyde unit (an α-hydroxy aldehyde derivative) gave a lactone with an hydroxy unit at C3 relative to the carbonyl and an α-vinylidene.[795] A ''double Baylis–Hillman'' reaction has also been reported using *N*-tosylimines and conjugated ketones.[796]

Using a chiral auxiliary via an amide[797] or ester[798] leads to asymmetric induction.[799] Aryl aldehydes and conjugated ketones were condensed using proline, leading to modest enantioselectivity.[800] Chiral biaryl catalysts have been used with trialkylphosphines, giving good enantioselectivity.[801] Chiral quinuclidine catalysts lead to

[784]Chandrasekhar, S.; Narsihmulu, Ch.; Reddy, N.R.; Reddy, M.S. *Tetrahedron Lett.* ***2003***, *44*, 2583.
[785]Li, G.; Wei, H.-X.; Gao, J.J.; Caputo, T.D. *Tetrahedron Lett.* ***2000***, *41*, 1; Shi, M.; Jiang, J.-K.; Feng, Y.-S. *Org. Lett.* ***2000***, *2*, 2397.
[786]Pei, W.; Wei, H.X.; Li, G. *Chem. Commun.* ***2002***, 2412.
[787]Arnold, L.A.; Imbos, R.; Mandoli, A.; de Vries, A.H.M.; Naasz, R.; Feringa, B.L. *Tetrahedron* ***2000***, *56*, 2865.
[788]Balan, D.; Adolfsson, H. *J. Org. Chem.* ***2001***, *66*, 6498; Yang, K.-S.; Lee, W.-D.; Pan, J.-F.; Chen, K. *J. Org. Chem.* ***2003***, *68*, 915.
[789]Shi, M.; Feng, Y.-S. *J. Org. Chem.* ***2001***, *66*, 406.
[790]Kawamura, M.; Kobayashi, S. *Tetrahedron Lett.* ***1999***, *40*, 1539.
[791]Xu, Y.-M.; Shi, M. *J. Org. Chem.* ***2004***, *69*, 417.
[792]Balan, D.; Adolfsson, H. *Tetrahedron Lett.* ***2003***, *44*, 2521.
[793]Tanaka, K.; Fu, G.C. *J. Am. Chem. Soc.* ***2001***, *123*, 11492.
[794]Keck, G.E.; Welch, D.S. *Org. Lett.* ***2000***, *4*, 3687.
[795]Krishna, P.R.; Kannan, V.; Sharma, G.V.M. *J. Org. Chem.* ***2004***, *69*, 6467.
[796]Shi, M.; Xu, Y.-M. *J. Org. Chem.* ***2003***, *68*, 4784.
[797]Brzezinski, L.J.; Rafel, S.; Leahy, J.W. *J. Am. Chem. Soc.* ***1997***, *119*, 4317.
[798]Perlmutter, P.; Puniani, E.; Westman, G. *Tetrahedron Lett.* ***1996***, *37*, 1715; Wei, H.-X.; Chen, D.; Xu, X.; Li, G.; Paré, P.W. *Tetrahedron Asymmetry* ***2003***, *14*, 971.
[799]Also see, Markó, I.E.; Giles, P.R.; Hindley, N.J. *Tetrahedron* ***1997***, *53*, 1015.
[800]Imbriglio, J.E.; Vasbinder, M.M.; Miller, S.J. *Org. Lett.* ***2003***, *5*, 3741. See also, Shi, M.; Jiang, J.-K.; L:i, C.-Q. *Tetrahedron Lett.* ***2002***, *43*, 127.
[801]McDougal, N.T.; Schaus, S.E. *J. Am. Chem. Soc.* ***2003***, *125*, 12094.

asymmetric induction.[802] A combination of a chiral sulfinamide, an In catalyst and 3-hydroxyquinuclidine led to the allylic amine derivative with modest enantioselectivity.[803] Sugars have been used as ester auxiliaries, and in reaction with aryl aldehydes and 20% DABCO gave the allylic alcohol with modest enantioselectivity.[804]

The reaction can be modified to give additional products, as with the reaction of *o*-hydroxybenzaldehyde and methyl vinyl ketone with DABCO, where the initial Baylis–Hillman product cyclized via conjugate addition of the phenolic oxygen to the conjugated ketone (**15-31**).[805] Aldehydes and conjugated esters can be coupled with a sulfonamide to give an allylic amine.[806]

A variant of this reaction couples halides with alkenes. α-Bromomethyl esters react with conjugated ketones and DABCO to give a coupling product, **34**.[807] A similar DBU-induced reaction was reported using α-bromomethyl esters and conjugated nitro compounds.[808]

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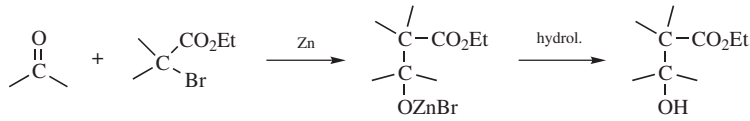
16-28 The Reformatsky Reaction

O-Hydro-*C*-α-ethoxycarbonylalkyl-addition



The *Reformatsky reaction*[809] is very similar to **16-24**. An aldehyde or ketone is treated with zinc and a halide; the halide is usually an α-halo ester or a vinylog of an α-halo ester (e.g., RCHBrCH=CHCOOEt), though α-halo nitriles,[810] α-halo ketones,[811] and α-halo *N,N*-disubstituted amides have also been used. Especially

[802]Shi, M.; Jiang, J.-K. *Tetrahedron Asymmetry* ***2002***, *13*, 1941. See Shi, M.; Xu, Y.-M. *Angew. Chem. Int. Ed.* ***2002***, *41*, 4507.

[803]Aggarwal, V.K.; Castro, A.M.M.; Mereu, A.; Adams, H. *Tetrahedron Lett.* ***2002***, *43*, 1577.

[804]Filho, E.P.S.; Rodrigues, J.A.R.; Moran, P.J.S. *Tetrahedron Asymmetry* ***2001***, *12*, 847.

[805]Kaye, P.T.; Nocanda, X.W. *J. Chem. Soc., Perkin Trans. 1* ***2000***, 1331.

[806]Balan, D.; Adolfsson, H. *J. Org. Chem.* ***2002***, *67*, 2329.

[807]Basavaiah, D.; Sharada, D.S.; Kumaragurubaran, N.; Reddy, R.M. *J. Org. Chem.* ***2002***, *67*, 7135.

[808]Ballini, R.; Barboni, L.; Bosica, G.; Fiorini, D.; Mignini, E.; Palmieri, A. *Tetrahedron* ***2004***, *60*, 4995.

[809]For reviews, see Fürstner, A. *Synthesis* ***1989***, 571; Rathke, M.W. *Org. React.* ***1975***, *22*, 423; Gaudemar, M. *Organomet. Chem. Rev. Sect. A* ***1972***, *8*, 183. For a review of the Reformatsky reaction in synthesis, see Ocampo, R.; Dolbier, Jr., W.R. *Tetrahedron* ***2004***, *60*, 9325.

[810]Vinograd, L.Kh.; Vul'fson, N.S. *J. Gen. Chem. USSR* ***1959***, *29*, 248, 1118, 2656, 2659; Palomo, C.; Aizpurua, J.M.; López, M.C.; Aurrekoetxea, N. *Tetrahedron Lett.* ***1990***, *31*, 2205; Zheng, J.; Yu, Y.; Shen, Y. *Synth. Commun.* ***1990***, *20*, 3277.

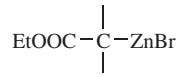
[811]For examples (with R_3Sb and $CrCl_2$, respectively, instead of Zn), see Huang, Y.; Chen, C.; Shen, Y. *J. Chem. Soc. Perkin Trans. 1* ***1988***, 2855; Dubois, J.E.; Axiotis, G.; Bertounesque, E. *Tetrahedron Lett.* ***1985***, *26*, 4371.

high reactivity can be achieved with activated zinc,[812] with zinc/silver-graphite,[813] and with zinc and ultrasound.[814] The reaction is catalytic in zinc in the presence of iodine and ultrasound.[815] Metals other than zinc can be used, including In,[816] Mn,[817] low valent Ti,[818] and metal compounds, such as TiI_4,[819] $TiCl_2$,[820] Cp_2TiCl_2,[821] $(Bu_3Sn)_2/Bu_2SnCl_2$,[822] SmI_2,[823] and $Sc(OTf)_3/PPh_3$.[824] A combination of Zn and an α-bromo ester can be used in conjunction with $BF_3{\bullet}OEt_2$, followed by reaction with dibenzoyl peroxide.[825] The aldehyde or ketone can be aliphatic, aromatic, or heterocyclic or contain various functional groups. Solvents used are generally ethers, including Et_2O, THF, and 1,4-dioxane, although the reaction can be done in water[826] using dibenzoyl peroxide and $MgClO_4$.

Dialkylzinc compounds are an alternative source of zinc in the Reformatsky reaction. When an α-bromo ester, an aldehyde, and diethylzinc were reacted in THF with a rhodium catalyst, the β-hydroxy ester was formed.[827]

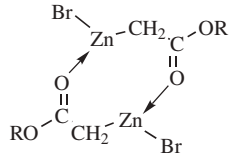
The use of additives, such as germanium, can lead to highly diastereoselective reactions.[828] Using chiral auxiliaries[829] or chiral additives,[830] good enantioselectivity[831] can be achieved.

Formally, the reaction can be regarded as if it were analogous to the Grignard reaction (**16-24**), with



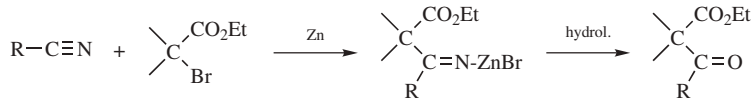
[812]Rieke, R.D.; Uhm, S.J. *Synthesis* ***1975***, 452; Bouhlel, E.; Rathke, M.W. *Synth. Commun.* ***1991***, *21*, 133.
[813]Csuk, R.; Fürstner, A.; Weidmann, H. *J. Chem. Soc., Chem. Commun.* ***1986***, 775.
[814]Han, B.; Boudjouk, P. *J. Org. Chem.* ***1982***, *47*, 5030.
[815]Ross, N.A.; Bartsch, R.A. *J. Org. Chem.* ***2003***, *68*, 360.
[816]Araki, S.; Yamada, M.; Butsugan, Y. *Bull. Chem. Soc. Jpn.* ***1994***, *67*, 1126.
[817]Cahiez, G.; Chavant, P. *Tetrahedron Lett.* ***1989***, *30*, 7373; Suh, Y.S.; Rieke, R.D. *Tetrahedron Lett.* ***2004***, *45*, 1807.
[818]Aoyagi, Y.; Tanaka, W.; Ohta, A. *J. Chem. Soc., Chem. Commun.* ***1994***, 1225.
[819]Shimizu, M.; Kobayashi, F.; Hayakawa, R. *Tetrahedron* ***2001***, *57*, 9591.
[820]Kagayama, A.; Igarashi, K.; Shiina, I.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* ***2000***, *73*, 2579.
[821]Parrish, J.D.; SheHon, D.R.; Little, R.D. *Org. Lett.* ***2003***, *5*, 3615.
[822]Shibata, I.; Kawasaki, M.; Yasuda, M.; Baba, A. *Chem. Lett.* ***1999***, 689.
[823]Utimoto, K.; Matsui, T.; Takai, T.; Matsubara, S. *Chem. Lett.* ***1995***, 197; Arime, T.; Takahashi, H.; Kobayashi, S.; Yamaguchi, S.; Mori, N. *Synth. Commun.* ***1995***, *25*, 389; Park, H.S.; Lee, I.S.; Kim, Y.H. *Tetrahedron Lett.* ***1995***, *36*, 1673; Molander, G.A.; Etter, J.B. *J. Am. Chem. Soc.* ***1987***, *109*, 6556.
[824]Kagoshima, H.; Hashimoto, Y.; Saigo, K. *Tetrahedron Lett.* ***1998***, *39*, 8465.
[825]Chattopadhyay, A.; Salaskar, A. *Synthesis* ***2000***, 561.
[826]Bieber, L.W.; Malvestiti, I.; Storch, E.C. *J. Org. Chem.* ***1997***, *62*, 9061.
[827]Kanai, K.; Wakabyashi, H.; Honda, T. *Org. Lett.* ***2000***, *2*, 2549.
[828]Kagoshima, H.; Hashimoto, Y.; Oguro, D.; Saigo, K. *J. Org. Chem.* ***1998***, *63*, 691.
[829]Fukuzawa, S.-i.; Tatsuzawa, M.; Hirano, K. *Tetrahedron Lett.* ***1998***, *39*, 6899.
[830]Soai, K.; Hirose, Y.; Sakata, S. *Tetrahedron Asymmetry* ***1992***, *3*, 677.
[831]Pini, D.; Uccello-Barretta, G.; Mastantuono, A.; Salvadori, P. *Tetrahedron* ***1997***, *53*, 6065; Andrés, J.M.; Martín, Y.; Pedrosa, R.; Pérez-Encabo, A. *Tetrahedron* ***1997***, *53*, 3787; Mi, A.; Wang, Z.; Zhang, J.; Jiang, Y. *Synth. Commun.* ***1997***, *27*, 1469.; Ribeiro, C.M.R.; de S. Santos, E.; de O. Jardim, A.H.; Maia, M.P.; da Silva, F.C.; Moreira, A.P.D.; Ferreira, V.F. *Tetrahedron Asymmetry* ***2002***, *13*, 1703.

(**35**) as an intermediate analogous to RMgX.[832] There *is* an intermediate derived from zinc and the ester, the structure of which has been shown to be **36**, by X-ray crystallography of the solid intermediate prepared from *t*-BuOCOCH$_2$Br and Zn.[833] As can be seen, it has some of the characteristics of **35**.

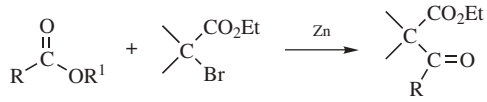


36

After hydrolysis, the alcohol is the usual product, but sometimes (especially with aryl aldehydes) elimination follows directly and the product is an alkene. By the use of Bu_3P along with Zn, the alkene can be made the main product,[834] making this an alternative to the Wittig reaction (**16-44**). The alkene is also the product when K_2CO_3/$NaHCO_3$ is used with 2% PEG–telluride.[835] Since Grignard reagents cannot be formed from α-halo esters, the method is quite useful, though there are competing reactions and yields are sometimes low. A similar reaction (called the *Blaise reaction*) has been carried out on nitriles:[836]



Carboxylic esters have also been used as substrates, but then, as might be expected (p. 1252), the result is substitution and not addition:



The product in this case is the same as with the corresponding nitrile, though the pathways are different. The reaction is compatible with amine substituents, and α-(*N,N*-dibenzyl)amino aldehydes have been used to prepare β-hydroxy-γ-(*N,N*-dibenzylamino) esters with good anti-selectivity.[837]

[832]For a study of transition structures, see Maiz, J.; Arrieta, A.; Lopez, X.; Ugalde, J.M.; Cossio, F.P.; Fakultatea, K.; Unibertsitatea, E.H.; Lecea, B. *Tetrahedron Lett.* ***1993***, *34*, 6111.

[833]Dekker, J.; Budzelaar, P.H.M.; Boersma, J.; van der Kerk, G.J.M.; Spek, A.L. *Organometallics*, ***1984***, *3*, 1403.

[834]Shen, Y.; Xin, Y.; Zhao, J. *Tetrahedron Lett.* ***1988***, *29*, 6119. For another method, see Huang, Y.; Shi, L.; Li, S.; Wen, X. *J. Chem. Soc. Perkin Trans. 1* ***1989***, 2397.

[835]Huang, Z.-Z.; Ye, S.; Xia, W.; Yu, Y.-H.; Tang, Y. *J. Org. Chem.* ***2002***, *67*, 3096.

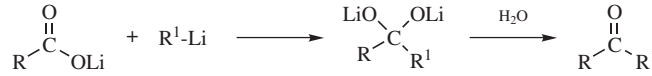
[836]See Cason, J.; Rinehart Jr., K.L.; Thornton, S.D. *J. Org. Chem.* ***1953***, *18*, 1594; Bellassoued, M.; Gaudemar, M. *J. Organomet. Chem.* ***1974***, *81*, 139; Hannick, S.M.; Kishi, Y. *J. Org. Chem.* ***1983***, *48*, 3833.

[837]Andrés, J.M.; Pedrosa, R.; Pérez, A.; Pérez-Encabo, A. *Tetrahedron* ***2001***, *57*, 8521.

For an alternative approach involving ester enolates (see **16-36**).
OS **III**, 408; **IV**, 120, 444; **IX**, 275.

16-29 The Conversion of Carboxylic Acid Salts to Ketones with Organometallic Compounds

Alkyl-de-oxido-substitution



Good yields of ketones can often be obtained by treatment of the lithium salt of a carboxylic acid with an alkyllithium reagent, followed by hydrolysis.[838] The R′ group may be aryl or primary, secondary, or tertiary alkyl and R may be alkyl or aryl. The compounds MeLi and PhLi have been employed most often. Tertiary alcohols are side products. Lithium acetate can be used, but generally gives low yields.

A variation of this transformation reacts the acid with lithium naphthalenide in the presence of 1-chlorobutane. The product is the ketone.[839] A related reaction treats the lithium carboxylate with lithium metal and the alkyl halide, with sonication, to give the ketone.[840] Phenylboronic acid (p. 815) reacts with aryl carboxylic acids in the presence of a palladium catalyst and disuccinoyl carbonate to give a diaryl ketone.[841]

OS **V**, 775.

16-30 The Addition of Organometallic Compounds to CO_2 and CS_2

***C*-Alkyl-*O*-halomagnesio-addition**

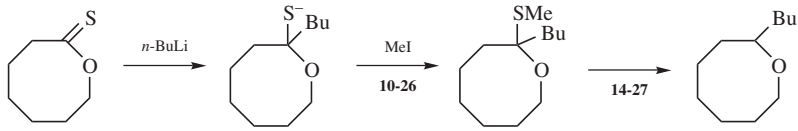
Grignard reagents add to one C=O bond of CO_2 exactly as they do to an aldehyde or a ketone.[842] Here, of course, the product is the salt of a carboxylic acid. The reaction is usually performed by adding the Grignard reagent to dry ice. Many carboxylic acids have been prepared in this manner, and this constitutes an important way of increasing a carbon chain by one unit. Since labeled CO_2 is commercially

[838]For a review, see Jorgenson, M.J. *Org. React.* ***1970***, *18*, 1. For an improved procedure, see Rubottom, G.M.; Kim, C. *J. Org. Chem.* ***1983***, *48*, 1550.
[839]Alonso, F.; Lorenzo, E.; Yus, M. *J. Org. Chem.*, ***1996***, *61*, 6058.
[840]Aurell, M.J.; Danhui, Y.; Einhorn, J.; Einhorn, C.; Luche, J.L. *Synlett* ***1995***, 459. Also see, Aurell, M.J.; Einhorn, C.; Einhorn, J.; Luche, J.L. *J. Org. Chem.* ***1995***, *60*, 8.
[841]Gooßen, L.J.; Ghosh, K. *Chem. Commun.* ***2001***, 2084.
[842]For reviews of the reaction between organometallic compounds and CO_2, see Volpin, M.E.; Kolomnikov, I.S. *Organomet. React.* ***1975***, *5*, 313; Sneeden, R.P.A., in Patai, S. *The Chemistry of Carboxylic Acids and Esters*, Wiley, NY, ***1969***, pp. 137–173; Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood Cliffs, NJ, ***1954***, pp. 913–948. For a more general review, see Lapidus, A.L.; Ping, Y.Y. *Russ. Chem. Rev.* ***1981***, *50*, 63.

available, this is a good method for the preparation of carboxylic acids labeled in the carboxyl group. Other organometallic compounds have also been used (RLi,[843] RNa, RCaX, RBa,[844] etc.), but much less often. The formation of the salt of a carboxylic acid after the addition of CO_2 to a reaction mixture is regarded as a positive test for the presence of a carbanion or of a reactive organometallic intermediate in that reaction mixture (see also, **16-42**).

When chiral additives, such as (−)-sparteine, have added to the initial reaction with the organolithium reagent, quenching with CO_2 produces carboxylic acids with good asymmetric induction.[845]

In a closely related reaction, Grignard reagents add to CS_2 to give salts of dithiocarboxylic acids.[846] These salts can be trapped with amines to form thioamides.[847] Two other reactions are worthy of note. (*1*) Lithium dialkylcopper reagents react with dithiocarboxylic esters to give tertiary thiols[848] (*2*) Thiono lactones can be converted to cyclic ethers,[849] for example:



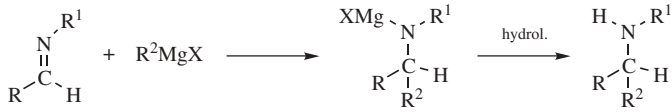
This is a valuable procedure because medium and large ring ethers are not easily made, while the corresponding thiono lactones can be prepared from the readily available lactones (see, e.g., **16-63**) by reaction **16-11**.

A terminal alkyne can be converted to the anion under electrolytic conditions, in the presence of CO_2, to give propargylic acids, R—C≡C—COOH.[850]

OS **I**, 361, 524; **II**, 425; **III**, 413, 553, 555; **V**, 890, 1043; **VI**, 845; **IX**, 317.

16-31 The Addition of Organometallic Compounds to C=N Compounds

N-Hydro-*C*-alkyl-addition



[843]The kinetics of this reaction have been studied, see Nudelman, N.S.; Doctorovich, F. *J. Chem. Soc. Perkin Trans. 2* ***1994***, 1233.

[844]Yanagisawa, A.; Yasue, K.; Yamamoto, H. *Synlett* ***1992***, 593.

[845]Park, Y.S.; Beak, P. *J. Org. Chem.* ***1997***, *62*, 1574.

[846]For a review of the addition of Grignard reagents to C=S bonds, see Paquer, D. *Bull. Soc. Chim. Fr.* ***1975***, 1439. For a review of the synthesis of dithiocarboxylic acids and esters, see Ramadas, S.R.; Srinivasan, P.S.; Ramachandran, J.; Sastry, V.V.S.K. *Synthesis* ***1983***, 605.

[847]Katritzky, A.R.; Moutou, J.-L.; Yang, Z. *Synlett* ***1995***, 99.

[848]Bertz, S.H.; Dabbagh, G.; Williams, L.M. *J. Org. Chem.* ***1985***, *50*, 4414.

[849]Nicolaou, K.C.; McGarry, D.G.; Somers, P.K.; Veale, C.A.; Furst, G.T. *J. Am. Chem. Soc.* ***1987***, *109*, 2504.

[850]Köster, F.; Dinjus, E.; Duñach, E. *Eur. J. Org. Chem.* ***2001***, 2507.

Aldimines can be converted to secondary amines by treatment with Grignard reagents.[851] Ketimines generally give reduction instead of addition. However, organolithium compounds give the normal addition product with both aldimines and ketimines.[852] For the addition of an organometallic compound to an imine to give a primary amine, R′ in RCH=NR′ would have to be H, and such compounds are seldom stable. However, the conversion has been done, for R = aryl, by the use of the masked reagents $(ArCH{=}N)_2SO_2$ [prepared from an aldehyde RCHO and sulfamide $(NH_2)_2SO_2$]. Addition of R^2MgX or R^2Li to these compounds gives $ArCHR^2NH_2$ after hydrolysis.[853] An intramolecular version of the addition or organolithium reagents is known, and treatment of the *N*-(3-chloropropyl)aldimine of benzaldehyde with lithium and DTBB, followed by hydrolysis with water, gave 2-phenylpyrrolidine.[854] Grignard regents add to imines in the presence of various transition metal catalysts, including $Sc(OTf)_3$[855] or Cp_2ZrCl_2.[856] When chiral additives are used in conjunction with the organolithium reagent, chiral amines are produced[857] with good asymmetric induction.[858] Chiral auxiliaries have been used in addition reactions to imines,[859] and to oxime derivatives.[860] Chiral catalysts lead to enantioselective addition of alkynes to imines to give a homopropargylic amine.[861]

Zinc metal reacts with allylic bromides to form an allylic zinc complex, which reacts with imines to give the homoallylic amine.[862] This reaction is catalyzed by TMSCl.[863] Allylzinc bromide adds to imines.[864] Dialkylzinc reagents add to imines to give the amine, and in the presence of a chiral ligand the reaction proceeds with

[851]For reviews of the addition of organometallic reagents to C=N bonds, see Harada, K., in Patai, S. *The Chemistry of the Carbon–Nitrogen Double Bond*, Wiley, NY, ***1970***, pp. 266–272; Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood Cliffs, NJ, ***1954***, pp. 1204–1227. For recent examples, see Wang, D.-K.; Dai, L.-X.; Hou, X.-L.; Zhang, Y. *Tetrahedron Lett.* ***1996***, *37*, 4187; Bambridge, K.; Begley, M.J.; Simpkins, N.S. *Tetrahedron Lett.* ***1994***, *35*, 3391.

[852]Huet, J. *Bull. Soc. Chim. Fr.* ***1964***, 952, 960, 967, 973.

[853]Davis, F.A.; Giangiordano, M.A.; Starner, W.E. *Tetrahedron Lett.* ***1986***, *27*, 3957.

[854]Yus, M.; Soler, T.; Foubelo, F. *J. Org. Chem.* ***2001***, *66*, 6207.

[855]Saito, S.; Hatanaka, K.; Yamamoto, H. *Synlett* ***2001***, 1859.

[856]Gandon, V.; Bertus, P.; Szymoniak, J. *Eur. J. Org. Chem.* ***2001***, 3677.

[857]For a review see Enders, D.; Reinhold, U. *Tetrahedron Asymmetry*, ***1997***, *8*, 1895.

[858]Andersson, P.G.; Johansson, F.; Tanner, D. *Tetrahedron* ***1998***, *54*, 11549; Tomioka, K.; Inoue, I.; Shindo, M.; Koga, K. *Tetrahedron Lett.* ***1991***, *32*, 3095; Denmark, S.E.; Stiff, C.M. *J. Org. Chem.* ***2000***, *65*, 5875; Chrzanowska, M.; Sokołowska, J. *Tetrahedron Asymmetry* ***2001***, *12*, 1435.

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[861]Benaglia, M.; Negri, D.; Dell'Anna, G. *Tetrahedron Lett.* ***2004***, *45*, 8705.

[862]Lee, C.-L.K.; Ling, H.-Y.; Loh, T.-P. *J. Org. Chem.* ***2004***, *69*, 7787.

[863]Legros, J.; Meyer, F.; Coliboeuf, M.; Crousse, B.; Bonnet-Delpon, D.; Bégué, J.-P. *J. Org. Chem.* ***2003***, *68*, 6444.

[864]van der Sluis, M.; Dalmolen, J.; de Lange, B.; Kaptein, B.; Kellogg, R.M.; Broxterman, Q.B. *Org. Lett.* ***2001***, *3*, 3943.

good enantioselectivity.[865] Dialkylzinc reagents add to *N*-tosyl imines using a copper catalyst, and with a chiral ligand leads to good enantioselectivity.[866] α-Bromo esters are converted to an organometallic reagent with Zn/Cu, and addition to *N*-arylimines gives *N*-aryl β-amino esters.[867] The reaction of imines, such as $ArN{=}CHCO_2Et$, where R = a chiral benzylic substituent, and $ZnBr_2$, followed by R′ZnBr leads to a chiral α-amino ester.[868] Terminal alkynes add to imines using $ZnCl_2$ and TMSCl, and with a chiral ligand attached to nitrogen the reaction proceeds with some enantioselectivity.[869]

Other organometallic compounds,[870] including allylic stannanes,[871] allylic samarium, [872] allylic germanium,[873] and allylic indium compounds[874] add to aldimines in the same manner. Aryltrialkylstannanes also add the aryl group to *N*-tosyl imines using a rhodium catalyst and sonication.[875] Catalytic enantioselective addition reactions are well known,[876] including reactions in an ionic liquid.[877] Allylic

[865]For an example using a Zr catalyst with a chiral ligand, see Porter J.R.; Traverse, J.F.; Hoveyda, A.H.; Snapper, M.L. *J. Am. Chem. Soc.* ***2001***, *123*, 984. With a Pd catalyst, see Inoue, A.; Shinokubo, H.; Oshima, K. *J. Am. Chem. Soc.* ***2003***, *125*, 1484. With a Zr catalyst, see Porter, J.R.; Traverse, J.F.; Hoveyda, A.H.; Snapper, M.L. *J. Am. Chem. Soc.* ***2001***, *123*, 10409. See also, Zhang, X.-M.; Zhang, H.-L.; Lin, W.-Q.; Gong, L.-Z.; Mi, A.-Q.; Cui, X.; Jiang, Y.-Z.; Yu, K.B. *J. Org. Chem.* ***2003***, *68*, 4322; Jensen, D.R.; Schultz, M.J.; Mueller, J.A.; Sigman, M.S. *Angew. Chem. Int. Ed.* ***2003***, *42*, 3810.

[866]Fujihara, H.; Nagai, K.; Yomioka, K. *J. Am. Chem. Soc.* ***2000***, *122*, 12055. See Wang, C.-J.; Shi, M. *J. Org. Chem.* ***2003***, *68*, 6229.

[867]Adrian Jr., J.C.; Barkin, J.L.; Hassib, L. *Tetrahedron Lett.* ***1999***, *40*, 2457.

[868]Chiev, K.P.; Roland, S.; Mangeney, P. *Tetrahedron Asymmetry* ***2001***, *13*, 2205.

[869]Jiang, B.; Si, Y.-G. *Tetrahedron Lett.* ***2003***, *44*, 6767.

[870]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 847–863.

[871]Keck, G.E.; Enholm, E.J. *J. Org. Chem.* ***1985***, *50*, 146; Nakamura, H.; Nakamura, K.; Yamamoto, Y. *J. Am. Chem. Soc.* ***1998***, *120*, 4242; Kobayashi, S.; Iwamoto, S.; Nagayama, S. *Synlett* ***1997***, 1099; Wang, D.-K.; Dai, L.-X.; Hou, X.-L. *Tetrahedron Lett.* ***1995***, *36*, 8649. Catalytic amounts of metal compounds can be used with the allyl stannane, including: **Pd**: Nakamura, H.; Iwama, H.; Yamamoto, Y. *Chem. Commun.* ***1996***, 1459 and Fernandes, R.A.; Yamamoto, Y. *J. Org. Chem.* ***2004***, *69*, 3562; **Zr**: Gastner, T.; Ishitani, H.; Akiyama, R.; Kobayashi, S. *Angew. Chem. Int. Ed.* ***2001***, *40*, 1896; **Ta**: Shibata, I.; Nose, K.; Sakamoto, K.; Yasuda, M.; Baba, A. *J. Org. Chem.* ***2004***, *69*, 2185; **La**: Aspinall, H.C.; Bissett, J.S.; Greeves, N.; Levin, D. *Tetrahedron Lett.* ***2002***, *43*, 323; **Al**: Niwa, Y.; Shimizu, M. *J. Am. Chem. Soc.* ***2003***, *125*, 3720; **Nb**: Andrade, C.K.Z.; Oliveira, G.R. *Tetrahedron Lett.* ***2002***, *43*, 1935; Akiyama, T.; Onuma, Y. *J. Chem. Soc., Perkin Trans. 1* ***2002***, 1157. With **$LiClO_4$**: Yadav, J.S.; Reddy, B.V.S.; Reddy, P.S.R.; Rao, M.S. *Tetrahedron Lett.* ***2002***, *43*, 6245.

[872]Wang, J.; Zhang, Y.; Bao, W. *Synth. Commun.* ***1996***, *26*, 2473. For an example using an allylic bromide with SmI_2, see Kim, B.; Han, R.; Park, R.; Bai, K.; Jun, Y.; Baik, W. *Synth. Commun.* ***2001***, *31*, 2297.

[873]Akiyama, T.; Iwai, J.; Onuma, Y.; Kagoshima, H. *Chem. Commun.* ***1999***, 2191.

[874]Chan, T.H.; Lu, W. *Tetrahedron Lett.* ***1998***, *39*, 8605; Jin, S.-J.; Araki, S.; Butsugan, Y. *Bull Chem. Soc. Jpn.* ***1993***, *66*, 1528; Beuchet, P.; Le Marrec, N.; Mosset, P. *Tetrahedron Lett.* ***1992***, *33*, 5959; Vilaivan, T.; Winotapan, C.; Shinada, T.; Ohfune, Y. *Tetrahedron Lett.* ***2001***, *42*, 9073.

[875]Ding, R.; Zhao, C.H.; Chen, Y.J.; Lu, L.; Wang, D.; Li, C.J. *Tetrahedron Lett.* ***2004***, *45*, 2995.

[876]For a review, see Kobayashi, Sh.; Ishitani, H. *Chem. Rev.* ***1999***, *99*, 1069.

[877]In bmim BF_4, 1-butyl-3-methylimidazolium tetrafluoroborate: Chowdari, N.S.; Ramachary, D.B.; Barbas III, C.F. *Synlett* ***2003***, 1906.

halides react with imines in the presence of indium metal[878] or $InCl_3$[879] to give the homoallylic amine, and with *N*-sulfonyl imines to give the homoallylic sulfonamide.[880] In this latter reaction, antiselectivity was observed when the reaction was done in water, and syn selectivity when done in aqueous THF.[881] Propargylic halides add to imines in the presence of indium metal, in aq. THF.[882] Imines react with allylic halides and gallium metal, with ultrasound.[883] Imines also react with allylic halides and Yb, in the presence of Me_3SiCl.[884] Aryl iodides add to *N*-aryl imines in the presence of a rhodium catalyst.[885] Titanium enolates add to imines to give β-amino esters.[886] Terminal alkynes react with aryl aldehydes and aryl amines to give propargylic amine without a catalyst,[887] and an iridium[888] or a copper catalyst[889] also leads to a propargylic amine.[890] Terminal alkynes add to imines to give a propargylic amine with high enantioselectivity using a chiral copper complex.[891] Triethylaluminum adds an ethyl group to an imine in the presence of a europium catalyst. Reaction with $PhSnMe_3$ and *N*-tosylimines with a rhodium catalyst, for example, leads to addition of a phenyl group to the carbon of the C=N bond.[892] Other *N*-sulfonyl imines react similarly to give the corresponding sulfonamide, and in the presence of a chiral ligand the reaction proceeds to good enantioselectivity.[893] *N*-Tosyl imines also react with dialkylzinc reagents, giving the sulfonamide with modest enantioselectivity.[894] *N*-Sulfinyl imines, $R_2CH{=}NS(=O)R'$,[895] react with Grignard reagents (R^2MgX) to give the corresponding *N*-sulfinylamine, $R_2CH(R^2)NHS(=O)R'$.[896] Enolate anions, generated by reaction of dimethylaminopyridine and a conjugated ketone, add to *N*-tosylimines.[897] *N*-Carbamoyl imines add acetonitrile (via carbon) using DBU and a ruthenium catalyst.[898]

[878]Choucair, B.; Léon, H.; Miré, M.-A.; Lebreton, C.; Mosset, P. *Org. Lett.* ***2000***, *2*, 1851. See Hirashita, T.; Hayashi, Y.; Mitsui, K.; Araki, S. *J. Org. Chem.* ***2003***, *68*, 1309.
[879]Under electrolysis conditions, see Hilt, G.; Smolko, K.I.; Waloch, C. *Tetrahedron Lett.* ***2002***, *43*, 1437.
[880]Lu, W.; Chan, T.H. *J. Org. Chem.* ***2000***, *65*, 8589.
[881]Lu, W.; Chan, T.H. *J. Org. Chem.* ***2001***, *66*, 3467.
[882]Prajapati, D.; Laskar, D.D.; Gogoi, B.J.; Devi, G. *Tetrahedron Lett.* ***2003***, *44*, 6755.
[883]Andrews, P.C.; Peatt, A.C.; Raston, C.L. *Tetrahedron Lett.* ***2004***, *45*, 243.
[884]Su, W.; Li, J.; Zhang, Y. *Synth. Commun.* ***2001***, *31*, 273.
[885]Ishiyama, T.; Hartwig, J. *J. Am. Chem. Soc.* ***2000***, *122*, 12043.
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[888]Fischer, C.; Carreira, E.M. *Org. Lett.* ***2001***, *3*, 4319; Fischer, C.; Carreira, E.M. *Synthesis* ***2004***, 1497.
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[891]Tsvelikhovsky, D.; Gelman, D.; Molander, G.A.; Blum, J. *Org. Lett.* ***2004***, *6*, 1995.
[892]Oi, S.; Moro, M.; Fukuhara, H.; Kawanishi, T.; Inoue, Y. *Tetrahedron Lett.* ***1999***, *40*, 9259.
[893]Hayashi, T.; Ishigedani, M. *J. Am. Chem. Soc.* ***2000***, *122*, 976.
[894]Soeta, T.; Nagai, K.; Fujihara, H.; Kuriyama, M.; Tomioka, K. *J. Org. Chem.* ***2003***, *68*, 9723.
[895]For a review of these reagents, see Ellman, J.A.; Owens, T.D.; Tang, T.P. *Acc. Chem. Res.* ***2002***, *35*, 984.
[896]Tang, T.P.; Volkman, S.K.; Ellman, J.A. *J. Org. Chem.* ***2001***, *66*, 8772.
[897]Shi, M.; Xu, Y.-M. *Chem. Commun.* ***2001***, 1876.
[898]Kumagai, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* ***2004***, *126*, 13632.

Activated aromatic compounds add to *N*-carbamoyl imines in the presence of copper catalysts, and with good enantioselectivity when a chiral catalyst is used.[899] A combination of $AuCl_3$/AgOTf facilitates the addition of arenes to *N*-tosyl imines.[900] Furan derivatives add via C-2 with good enantioselectivity using a chiral phosphoric acid catalyst.[901] Alkenes add to *N*-tosyl imines with a Yb catalyst[902] an allenes add to *N*-carbamoyl imines in the presence of vanadium catalyst.[903] *N*-Carbamoyl imines, formed *in situ*, react with allylic silanes in the presence of an iodine catalyst.[904] The intramolecular addition of an alkene to an imine, facilitated by Cp_2ZrBu_2, gave a cycloalkyl amine.[905]

Arylboronates (p. 815) add to *N*-sulfonyl imines in the presence of a rhodium catalyst to give the corresponding sulfonamide.[906] Vinyl boronates also add to nitrones in the presence of Me_2Zn, transferring the vinyl group to the C=N unit.[907] Aryl boronic acids (p. 815) add the aryl group to *N*-tosyl imines using a rhodium catalyst.[908] Allylic boronates also add to aldehydes, and subsequent treatment with ammonia give the homoallylic amine.[909]

Allylic silanes, such as allyltrimethylsilane, add to *N*-substituted imines in the presence of a palladium catalyst to give the homoallylic amine.[910] Similar results are obtained when the allylic silane and imine are treated with a catalytic amount of tetrabutylammonium fluoride.[911] *N*-Tosyl imines also react with allylic silanes, and the reaction of $EtO_2C{-}CH{=}NTs$ and allyltrimethylsilane with a chiral copper catalyst gave $EtO_2C{-}CH(NHTs)CH_2CH{=}CH_2$, albeit in poor yield with modest enantioselectivity.[912] Another addition reaction converts aryl aldehydes to the imine using $Me_2N{-}SiMe_3$ and $LiClO_4$, and subsequent reaction with $Me_2PhSiCl$ gave the corresponding amine, $ArCH(SiMe_2Ph)NMe_2$.[913] Allylic trichlorosilanes add to hydrazones to give homoallylic hydrazine derivatives with excellent anti-selectivity[914]

[899]Saaby, S.; Fang, X.; Gathergood, N.; Jørgensen, K.A. *Angew. Chem. Int. Ed.* ***2000***, *39*, 4114. See also, Saaby, S.; Bayón, P.; Aburel, P.S.; Jørgensen, K.A. *J. Org. Chem.* ***2002***, *67*, 4352.
[900]Luo, Y.; Li, C.-J. *Chem. Commun.* ***2004***, 1930.
[901]Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* ***2004***, *126*, 11804. See also, Spanedda, M.V.; Ourévitch, M.; Crouse, B.; Bégué, J.-P.; Bonnet-Delpon, D. *Tetrahedron Lett.* ***2004***, *45*, 5023.
[902]Yamanaka, M.; Nishida, A.; Nakagawa, M. *J. Org. Chem.* ***2003***, *68*, 3112.
[903]Trost, B.M.; Jonasson, C. *Angew. Chem. Int. Ed.* ***2003***, *42*, 2063.
[904]Phukan, P. *J. Org. Chem.* ***2004***, *69*, 4005.
[905]Makabe, M.; Sato, Y.; Mori, M. *J. Org. Chem.* ***2004***, *69*, 6238.
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[907]Pandya, A.; S.U.; Pinet, S.; Chavant, P.Y.; Vallée, Y. *Eur. J. Org. Chem.* ***2003***, 3621.
[908]Kuriyama, M.; Soeta, T.; Hao, X.; Chen, Q.; Tomioka, K. *J. Am. Chem. Soc.* ***2004***, *126*, 8128.
[909]Sugiura, M.; Hirano, K.; Kobayashi, S. *J. Am. Chem. Soc.* ***2004***, *126*, 7182.
[910]Nakamura, K.; Nakamura, H.; Yamamoto, Y. *J. Org. Chem.* ***1999***, *64*, 2614.
[911]Wang, D.-K.; Zhou, Y.-G.; Tang, Y.; Hou, X.-L.; Dai, L.-X. *J. Org. Chem.* ***1999***, *64*, 4233. Tetraallylsilane and TBAF, with a chiral palladium catalyst, gives chiral homoallylic amines, see Fernandes, R.A.; Yamamoto, Y. *J. Org. Chem.* ***2004***, *69*, 735.
[912]Fang, X.; Johannsen, M.; Yao, S.; Gathergood, N.; Hazell, R.G.; Jørgensen, K.A. *J. Org. Chem.* ***1999***, *64*, 4844.
[913]Naimi-Jamal, M.R.; Mojtahedi, M.M.; Ipaktschi, J.; Saidi, M.R. *J. Chem. Soc., Perkin Trans. 1* ***1999***, 3709.
[914]Hirabayashi, R.; Ogawa, C.; Sugiura, M.; Kobayashi, S. *J. Am. Chem. Soc.* ***2001***, *123*, 9493.

and with good enantioselectivity using a chiral ligand.[915] Chiral allyl silane derivatives have been developed, and add to hydrazones with good enantioselectivity.[916]

Aldehydes add via the α-carbon using proline, to give β-amino aldehydes with good selectivity to give chiral β-amino aldehydes.[917] Silyl enol ethers add to hydrazones in the presence of ZnF_2 and a chiral ligand to give chiral β-hydrazino ketones.[918] Nitro compounds add to *N*-carbamoyl imines with a chiral diamine catalyst with some enantioselectivity.[919] Nitro compounds add via carbon using a copper catalyst, and with good enantioselectivity when a chiral ligand is used.[920] Similar addition to imine derivatives was accomplished using ketene silyl acetals and Amberlyst-15.[921] Alternatively, an imine is reacted first with $Zn(OTf)_2$ and then with a ketene silyl acetal.[922] The conjugate bases of nitro compounds (formed by treatment of the nitro compound with BuLi) react with Grignard reagents in the presence of $ClCH{=}NMe_2^+\ Cl^-$ to give oximes: $RCH{=}N(O)OLi + R'MgX \rightarrow RR'C{=}NOH$.[923]

37

Many other C=N systems (phenylhydrazones, oxime ethers, etc.) give normal addition when treated with Grignard reagents; others give reductions; others give miscellaneous reactions. Organocerium reagents add to hydrazones.[924] Oximes can be converted to hydroxylamines (**37**) by treatment with 2 equivalents of an alkyllithium reagent, followed by methanol.[925] Oxime ethers add an allyl group upon reaction with allyl bromide and indium metal in water.[926] Nitrones, $R_2C{=}N^+(R')-O^-$, react with allylic bromides and Sm to give homoallylic oximes,[927] and with terminal alkynes and a zinc catalyst to give propargylic oximes.[928]

[915]Kobayashi, S.; Ogawa, C.; Konishi, H.; Sugiura, M. *J. Am. Chem. Soc.* ***2003***, *125*, 6610.
[916]Berger, R.; Duff, K.; Leighton, J.L. *J. Am. Chem. Soc.* ***2004***, *126*, 5686.
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[918]Hamada, T.; Manabe, K.; Kobayashi, S. *J. Am. Chem. Soc.* ***2004***, *126*, 7768. For a similar reaction using a bismuth catalyst, see Ollevier, T.; Nadeau, E. *J. Org. Chem.* ***2004***, *69*, 9292.
[919]Nugent, B.M.; Yoder, R.A.; Johnston, J.N. *J. Am. Chem. Soc.* ***2004***, *126*, 3418.
[920]Nishiwaki, N.; Knudson, K.R.; Gothelf, K.V.; Jørgensen, K.A. *Angew. Chem. Int. Ed.* ***2001***, *40*, 2992.
[921]Shimizu, M.; Itohara, S.; Hase, E. *Chem. Commun.* ***2001***, 2318.
[922]Ishimaru, K.; Kojima, T. *J. Org. Chem.* ***2003***, *68*, 4959.
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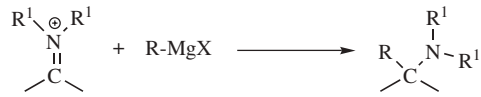
[926]Bernardi, L.; Cerè, V.; Femoni, C.; Pollicino, S.; Ricci, A. *J. Org. Chem.* ***2003***, *68*, 3348.
[927]Laskar, D.D.; Prajapati, D.; Sandu, J.S. *Tetrahedron Lett.* ***2001***, *42*, 7883.
[928]Frantz, D.E.; Fässler, R.; Carreira, E.M. *J. Am. Chem. Soc.* ***1999***, *121*, 11245. See Pinet, S.; Pandya, S.U.; Chavant, P.Y.; Ayling, A.; Vallee, Y. *Org. Lett.* ***2002***, *4*, 1463.

Grignard reagents also add to nitrones.[929] Nitrones react with $CH_2{=}CHCH_2InBr$ in aq. DMF to give the homoallylic oxime[930] and silyl ketene acetals add in the presence of a chiral titanium catalyst to good enantioselectivity.[931] Hydrazone derivatives react with iodoalkenes in the presence of $InCl_3$ and $Mn_2(CO)_{10}$ under photochemical conditions to give the hydrazine derivative.[932] Indium metal promotes the addition of alkyl iodides to hydrazones.[933] A hydrazone can be formed *in situ* by reacting an aldehyde with a hydrazine derivative, and in the presence of tetrallyltin and a scandium catalysts, homoallylic hydrazine derivatives are formed.[934] Ketene dithioacetals add to hydrazones using a chiral zirconium catalyst to give a pyrazolidine.[935]

Radical addition to imines is known. Carbon-centered radicals add to imines.[936] The reaction of an alkyl halide with BEt_3 in aqueous methanol, for example, gives the imine addition product, an alkylated amine.[937] Secondary alkyl iodides add to *O*-alkyl oximes in the presence of BEt_3 and AIBN, and this methodology was used to convert $MeO_2C{-}CH{=}NOBn$ to $MeO_2C{-}CH(R)NOBn$.[938] Benzylic halides adds to imines under photochemical conditions, and in the presence of 1-benzyl-1,4-dihydronicotinamide[939] or with BEt_3 in aqueous methanol.[940] Tertiary alkyl iodides add to oxime ethers using $BF_3{\bullet}OEt_2$ in the presence of BEt_3/O_2.[941]

Iminium salts[942] give tertiary amines directly, with just R adding:



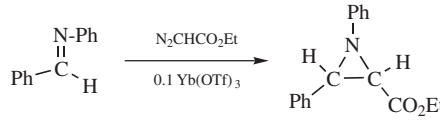
Chloroiminium salts $ClCH{=}NR'_2\,Cl^-$ (generated *in situ* from an amide $HCONR'_2$ and phosgene $COCl_2$) react with 2 equivalents of a Grignard reagent RMgX, one adding to the C=N and the other replacing the Cl, to give tertiary amines $R_2CHNR'_2$.[943]

OS **IV**, 605; **VI**, 64. Also see OS **III**, 329.

[929]See Merino, P.; Tejero, T. *Tetrahedron* ***2001***, *57*, 8125.
[930]Kumar, H.M.S.; Anjaneyulu, S.; Reddy, E.J.; Yadav, J.S. *Tetrahedron Lett.* ***2000***, *41*, 9311.
[931]Murahashi, S.-I.; Imada, Y.; Kawakami, T.; Harada, K.; Yonemushi, Y.; Tomita, N. *J. Am. Chem. Soc.* ***2002***, *124*, 2888.
[932]Friedstad, G.K.; Qin, J. *J. Am. Chem. Soc.* ***2001***, *123*, 9922.
[933]Miyabe, H.; Ueda, M.; Nishimura, A.; Naito, T. *Tetrahedron* ***2004***, *60*, 4227.
[934]Kobayashi, S.; Hamada, T.; Manabe, K. *Synlett* ***2001***, 1140.
[935]Yamshita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* ***2004***, *126*, 11279.
[936]For a review, see Friestad, G.K. *Tetrahedron* ***2001***, *57*, 5461.
[937]Miyabe, H.; Ueda, M.; Naito, T. *J. Org. Chem.* ***2000***, *65*, 5043.
[938]Miyabe, H.; Ueda, M.; Yoshioka, N.; Yamakawa, K.; Naito, T. *Tetrahedron* ***2000***, *56*, 2413.
[939]Jin, M.; Zhang, D.; Yang, L.; Liu, Y.; Liu, Z. *Tetrahedron Lett.* ***2000***, *41*, 7357.
[940]McNabb, S.B.; Ueda, M.; Naito, T. *Org. Lett.* ***2004***, *6*, 1911.
[941]Halland, N.; Jørgensen, K.A. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 1290.
[942]For a review of nucleophilic addition to iminium salts, see Paukstelis, J.V.; Cook, A.G., in Cook, A.G. *Enamines*, 2nd ed., Marcel Dekker, NY, ***1988***, pp. 275–356.
[943]Wieland, G.; Simchen, G. *Liebigs Ann. Chem.* ***1985***, 2178.

16-32 Addition of Carbenes and Diazoalkanes to C=N Compounds

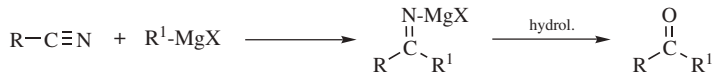
In the presence of metal catalysts such as $Yb(OTf)_3$, diazoalkanes add to imines to generate aziridines. An example is:[944]



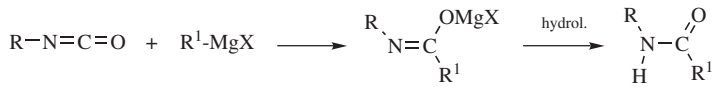
The reaction is somewhat selective for the cis-diastereomer. The use of chiral additives in this reaction leads to aziridines enantioselectively.[945] Imines can be formed by the reaction of an aldehyde and an amine, and subsequent treatment with Me_3SiI and butyllithium gives an aziridine.[946] *N*-Tosyl imines react with diazoalkenes to form *N*-tosyl aziridines, with good cis-selectivity[947] and modest enantioselectivity in the presence of a chiral copper catalyst,[948] but excellent enantioselectivity with a chiral rhodium catalyst.[949]. It is noted that *N*-tosyl aziridines are formed by the reaction of an alkene with PhI=NTs and a copper catalyst.[950] The reaction of alkenes with diazo compounds is discussed in **15-53**.

16-33 The Addition of Grignard Reagents to Nitriles and Isocyanates

Alkyl,oxo-de-nitrilo-tersubstitution (Overall transformation)



***N*-Hydro-*C*-alkyl-addition**



Ketones can be prepared by addition of Grignard reagents to nitriles, followed by hydrolysis of the initially formed imine anion. Many ketones have been made in this manner, though when both R groups are alkyl, yields are not high.[951] Yields

[944]Nagayama, S.; Kobayashi, S. *Chem Lett.* ***1998***, 685. Also see, Rasmussen, K.G.; Jørgensen, K.A. *J. Chem. Soc., Chem. Commun.* ***1995***, 1401.

[945]Hansen, K.B.; Finney, N.S.; Jacobsen, E.N. *Angew. Chem. Int. Ed.* ***1995***, *34*, 676.

[946]Reetz, M.T.; Lee, W.K. *Org. Lett.* ***2001***, *3*, 3119.

[947]Aggarwal, V.K.; Ferrara, M. *Org. Lett.* ***2000***, *2*, 4107; Hori, R.; Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* ***2000***, *41*, 9455; Krumper, J.R.; Gerisch, M.; Suh, J.M.; Bergman, R.G.; Tilley, T.D. *J. Org. Chem.* ***2003***, *68*, 9705; Williams, A.L.; Johnston, J.N. *J. Am. Chem. Soc.* ***2004***, *126*, 1612; Sun, W.; Xia, C.-G.; Wang, H.-W. *Tetrahedron Lett.* ***2003***, *44*, 2409.

[948]Juhl, K.; Hazell, R.G.; Jørgensen, K.A. *J. Chem. Soc., Perkin Trans. 1* ***1999***, 2293.

[949]Aggarwal, V.K.; Alonso, E.; Fang, G.; Ferrara, M.; Hynd, G.; Porcelloni, M. *Angew. Chem. Int. Ed.* ***2001***, *40*, 1433.

[950]Handy, S.T.; Czopp, M. *Org. Lett.* ***2001***, *3*, 1423.

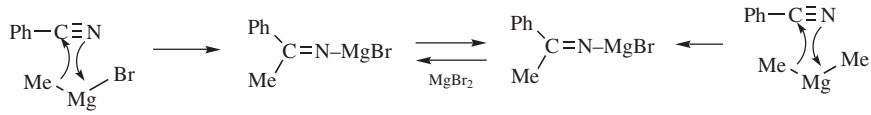
[951]For a review, see Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood Cliffs, NJ, ***1954***, pp. 767–845.

can be improved by the use of Cu(I) salts[952] or by using benzene containing one equivalent of ether as the solvent, rather than ether alone.[953] The ketimine salt does not in general react with Grignard reagents: Hence tertiary alcohols or tertiary alkyl amines are not often side products.[954] By careful hydrolysis of the salt it is sometimes possible to isolate ketimines,[955]

especially when R and R′ = aryl. The addition of Grignard reagents to the C≡N group is normally slower than to the C=O group, and cyano group containing aldehydes add the Grignard reagent without disturbing the CN group.[956] Other metal compounds have been used, including Sm with allylic halides[957] and organocerium compounds such as $MeCeCl_2$.[958] Allylic halides react with an excess of zinc metal in the presence of 40% $AlCl_3$, and in the presence of a nitrile homoallylic ketones are produced after hydrolysis.[959] Benzonitrile reacts as with iodopropane and a mixture of SmI_2 and NiI_2 catalysts to give 1-phenyl-1-butanone.[960]

Addition of Grignard reagents[961] or organolithium reagents[962] to ω-halo nitriles leads to 2-substituted cyclic imines.

The following mechanism has been proposed for the reaction of the methyl Grignard reagent with benzonitrile:[963]



Arenes add to nitriles in the presence of a palladium catalyst in DMSO/trifluoroacetic acid to give a diaryl ketone.[964]

The addition of Grignard reagents to isocyanates gives, after hydrolysis, *N*-substituted amides.[965] This is a very good reaction and can be used to prepare

[952]Weiberth, F.J.; Hall, S.S. *J. Org. Chem.* ***1987***, *52*, 3901.
[953]Canonne, P.; Foscolos, G.B.; Lemay, G. *Tetrahedron Lett.* ***1980***, 155.
[954]For examples where tertiary amines have been made the main products, see Alvernhe, G.; Laurent, A. *Tetrahedron Lett.* ***1973***, 1057; Gauthier, R.; Axiotis, G.P.; Chastrette, M. *J. Organomet. Chem.* ***1977***, *140*, 245.
[955]Pickard, P.L.; Toblert, T.L. *J. Org. Chem.* ***1961***, *26*,4886.
[956]Cason, J.; Kraus, K.W.; McLeod Jr., W.D. *J. Org. Chem.* ***1959***, *24*, 392.
[957]Yu, M.; Zhang, Y.; Guo, H. *Synth. Commun.* ***1997***, *27*, 1495.
[958]Ciganek, E. *J. Org. Chem.* ***1992***, *57*, 4521.
[959]Lee, A.S.-Y.; Lin, L.-S. *Tetrahedron Lett.* ***2000***, *41*, 8803.
[960]Kang, H.-Y.; Song, S.-E. *Tetrahedron Lett.* ***2000***, *4*1, 937.
[961]Fry, D.F.; Fowler, C.B.; Dieter, R.K. *Synlett* ***1994***, 836.
[962]Gallulo, V.; Dimas, L.; Zezza, C.A.; Smith, M.B. *Org. Prep. Proceed. Int.* ***1989***, *21*, 297.
[963]Ashby, E.C.; Chao, L.; Neumann, H.M. *J. Am. Chem. Soc.* ***1973***, *95*, 4896, 5186.
[964]Zhou, C.; Larock, R.C. *J. Am. Chem. Soc.* ***2004***, *126*, 2302.
[965]For a review of this and related reactions, see Screttas, C.G.; Steele, B.R. *Org. Prep. Proced. Int.* ***1990***, *22*, 271.

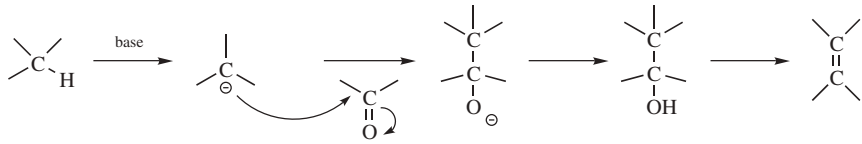
derivatives of alkyl and aryl halides. The reaction has also been performed with alkyllithium compounds.[966] Isothiocyanates give *N*-substituted thioamides. Other organometallic compounds add to isocyanates. Vinyltin reagents lead to conjugated amides.[967]

It is noted that terminal alkynes add to the carbon of an isonitrile in the presence of a uranium complex, giving a propargylic imine.[968]

OS **III**, 26, 562; **V**, 520.

G. Carbon Attack by Active Hydrogen Compounds

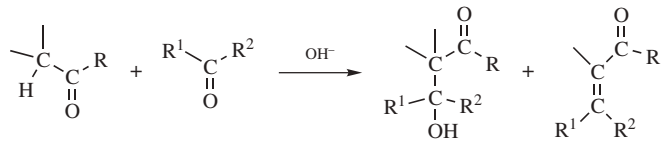
Reactions **16-34**–**16-50** are base-catalyzed condensations (although some of them are also catalyzed to acids).[969] In **16-34**–**16-44**, a base removes a C—H proton to give a carbanion, which then adds to a C=O. The oxygen acquires a proton, and the resulting alcohol may or may not be dehydrated, depending on whether an α hydrogen is present and on whether the new double bond would be in conjugation with double bonds already present:



The reactions differ in the nature of the active hydrogen component and the carbonyl component. Table 16.2 illustrates the differences. Reaction **16-50** is an analogous reaction involving addition to C≡N.

16-34 The Aldol Reaction[970]

***O*-Hydro-*C*-(α-acylalkyl)-addition; α-Acylalkylidine-de-oxo-bisubstitution**



(If α H was present)

[966]LeBel, N.A.; Cherluck, R.M.; Curtis, E.A. *Synthesis* ***1973***, 678; Cooke, Jr., M.P.; Pollock, C.M. *J. Org. Chem.* ***1993***, *58*, 7474. For another method, see Einhorn, J.; Luche, J.L. *Tetrahedron Lett.* ***1986***, *27*, 501.
[967]Niestroj, M.; Neumann, W.P.; Thies, O. *Chem. Ber.* ***1994***, *127*, 1131.
[968]Barnea, E.; Andrea, T.; Kapon, M.; Berthet, J.-C.; Ephritikhine, M.; Eisen, M.S. *J. Am. Chem. Soc.* ***2004***, *126*, 10860.
[969]For reviews, see House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 629–682; Reeves, R.L., in Patai, S. *The Chemistry of the Carbonyl Group*, pt. 1, Wiley, NY, ***1966***, pp. 567–619. See also, Stowell, J.C. *Carbanions in Organic Synthesis*, Wiley, NY, ***1979***.
[970]See Smith, M.B. *Organic Synthesis*, 2nd ed., McGraw-Hill, NY, ***2001***, pp. 740–745.

TABLE 16.2. Base-Catalyzed Condensations Showing the Active-Hydrogen Components and the Carbonyl Compounds

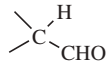
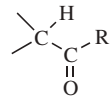
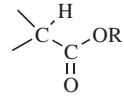
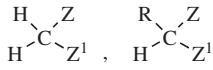
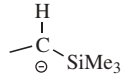
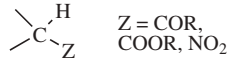
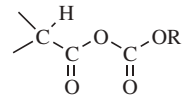
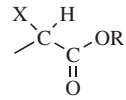
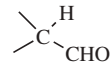
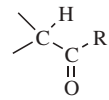
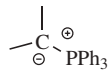
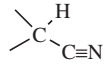
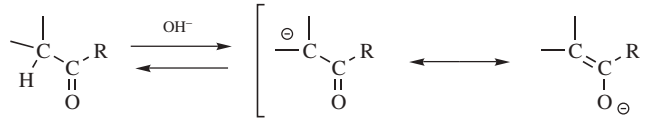
Reaction	Active-Hydrogen Component	Carbonyl Component	Subsequent Reaction
16-34	Aldehyde  Ketone 	Aldehyde, ketone	Dehydration may follow
Aldol reaction			
16-36	Ester 	Aldehyde, ketone (usually without α-hydrogens)	Dehydration may follow
16-38	 and similar molecules	Aldehyde, ketone (usually without α-hydrogens)	Dehydration (usually follows)
Knoevenagel reaction			
16-41		Aldehyde, ketone may follow	Dehydration
Peterson reaction			
16-42		CO_2, CS_2	
16-39	Anhydride 	Aromatic aldehyde usually follows	Dehydration
Perkin reaction			
16-40	α-Halo Ester 	Aldehyde, Ketone (S_N reaction) follows	Epoxidation
Darzen's reaction			
16-43	Aldehyde  Ketone 	Formaldehyde reaction follows	Crossed-Cannizzaro

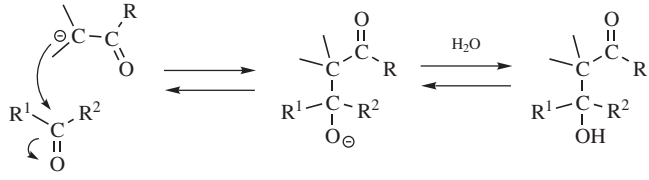
TABLE 16.2. (*Continued*)

Reaction	Active-Hydrogen Component	Carbonyl Component	Subsequent Reaction
Tollens' reaction			
16-44	Phosphorous ylid 	Aldehyde, ketone	"Dehydration" always follows
Wittig reaction			
16-50	Nitrile 	Nitrile	
Thorpe reaction			

In the *aldol reaction*,[971] the α carbon of one aldehyde or ketone molecule adds to the carbonyl carbon of another.[972] Although acid-catalyzed aldol reactions are known,[973] the most common form of the reaction uses a base. There is evidence that an SET mechanism can intervene when the substrate is an aromatic ketone.[974] Although hydroxide was commonly used in early versions of this reaction, stronger bases, such as alkoxides (RO^-) or amides (R_2N^-), are also common. Amine bases have been used.[975] Hydroxide ion is not a strong enough base to convert substantially all of an aldehyde or ketone molecule to the corresponding enolate ion, that is., the equilibrium lies well to the left, for both aldehydes and



ketones. Nevertheless, enough enolate ion is present for the reaction to proceed:



[971]This reaction is also called the *aldol condensation*, though, strictly speaking, this term applies to the formation only of the α,β-unsaturated product, and not the aldol.

[972]For reviews, see Thebtaranonth, C.; Thebtaranonth, Y., in Patai, S.; Rappoport, Z. *The Chemistry of Enones*, pt. 1, Wiley, NY, ***1989***, pp. 199–280, 199–212; Hajos, Z.G., in Augustine, R.L. *Carbon–Carbon Bond Formation*, Vol. 1; Marcel Dekker, NY, ***1979***; pp. 1–84; Nielsen, A.T.; Houlihan, W.J. *Org. React.* ***1968***, *16*, 1.

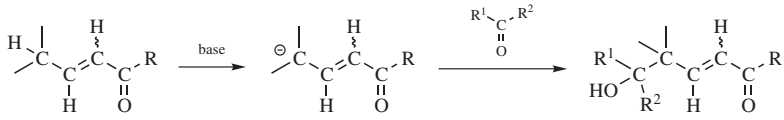
[973]For example, see Mahrwald, R.; Gündogan, B. *J. Am. Chem. Soc.* ***1998***, *120*, 413.

[974]Ashby, E.C.; Argyropoulos, J.N. *J. Org. Chem.* ***1986***, *51*, 472.

[975]Trost, B.M.; Silcoff, E.R.; Ito, H. *Org. Lett.* ***2001***, *3*, 2497.

This equilibrium lies further to the right with alkoxide and especially with amide bases, depending on the solvent. Protic solvents, such as water or alcohol, are acidic enough to react with the enolate anion and shift the equilibrium to the left. In an aprotic solvent, such as ether or THF, with a strong amide base, such as lithium diisopropylamide (LDA, p. 389), the equilibrium lies more to the right.[976] A variety of amide bases can be used to deprotonate the ketone or aldehyde, and in the case of an unsymmetrical ketone removal of the more acidic proton leads to the kinetic enolate anion.[977] Note that a polymer-bound amide base has been used[978] and solid-phase chiral lithium amides are known.[979] A polymer-supported phosphoramide has been used as a catalyst for the aldol condensation.[980] The product is a β-hydroxy aldehyde (called an *aldol*) or ketone, which in some cases is dehydrated during the course of the reaction. In aprotic solvents with a mild workup procedure, however, the aldol is readily isolated unless the substrate is an aromatic aldehyde or ketone. The aldol reaction has been done in ionic liquids.[981] Even if the dehydration is not spontaneous, it can usually be done easily, since the new double bond is in conjugation with the C=O bond; so that this is a method of preparing α,β-unsaturated aldehydes and ketones, as well as β-hydroxy aldehydes and ketones. One-pot procedures have been reported to give the conjugated product.[982] The entire reaction is an equilibrium (including the dehydration step), and α,β-unsaturated and β-hydroxy aldehydes and ketones can be cleaved by treatment with $^-$OH (the *retrograde aldol reaction*). The *retro*-aldol condensation has been exploited for crossed-aldol reactions.[983] A vinylogous aldol reaction is known[984] as is a 1"double" aldol.[985] Enzyme-mediated aldol reactions have been reported using two aldehydes, including formaldehyde.[986]

Under the principle of vinylogy, the active hydrogen can be one in the γ position of an α,β-unsaturated carbonyl compound:



[976]For a discussion of solvent and temperature effects, see Cainelli, G.; Galletti, P.; Giacomini, D.; Orioli, P. *Tetrahedron Lett.* ***2001***, *42*, 7383.

[977]See Xie, L.; Vanlandeghem, K.; Isenberger, K.M.; Bernier, C. *J. Org. Chem.* ***2003***, *68*, 641; Zhao, P.; Lucht, B.L.; Kenkre, S.L.; Collum, D.B. *J. Org. Chem.* ***2004***, *69*, 242; Zhao, P.; Condo, A.; Keresztes, I.; Collum, D.B. *J. Am. Chem. Soc.* ***2004***, *126*, 3113.

[978]Seki, A.; Ishiwata, F.; Takizawa, Y.; Asami, M. *Tetrahedron* ***2004***, *60*, 5001.

[979]Johansson, A.; Abrahamsson, P.; Davidsson, Ö. *Tetrahedron Asymmetry* ***2003***, *14*, 1261.

[980]Flowers II, R.A.; Xu, X.; Timmons, C.; Li, G. *Eur. J. Org. Chem.* ***2004***, 2988.

[981]In bmim BF_4, 1-butyl-3-methylimidazolium tetrafluoroborate: Zheng, X.; Zhang, Y. *Synth. Commun.* ***2003***, 161.

[982]Kourouli, T.; Kefalas, P.; Ragoussis, N.; Ragoussis, V. *J. Org. Chem.* ***2002***, *67*, 4615.

[983]For an example, see Simpura, I.; Nevalainen, V. *Angew. Chem. Int. Ed.* ***2000***, *39*, 3422.

[984]For reviews, see Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G.; *Chem. Rev.* ***2000***, *100*, 1929; Casiraghi, G.; Zanardi, E.; Rassu, G. *Pure Appl. Chem.* ***2000***, *72*, 1645.

[985]For a discussion of the mechanism of this reaction see Abiko, A.; Inoue, T.; Masamune, S. *J. Am. Chem. Soc.* ***2002***, *124*, 10759.

[986]Demir, A.S.; Ayhan, P.; Igdir, A.C.; Duygu, A.N. *Tetrahedron* ***2004***, *60*, 6509.

The scope of the aldol reaction may be discussed under five headings:

1. *Reaction between Two Molecules of the Same Aldehyde*. Hydroxide or alkoxide bases are used in protic solvents,[987] and the reaction is quite feasible. Many aldehydes have been converted to aldols and/or their dehydration products in this manner. The most effective catalysts are basic ion-exchange resins. Of course, the aldehyde must possess an α hydrogen.
2. *Reaction between Two Molecules of the Same Ketone*. With hydroxide or alkoxide bases in protic solvents the equilibrium lies well to the left,[988] and the reaction is feasible only if the equilibrium can be shifted. This can often be done by allowing the reaction to proceed in a Soxhlet extractor (e.g., see OS **I**, 199). Two molecules of the same ketone can also be condensed without a Soxhlet extractor,[989] by treatment with basic Al_2O_3.[990] Unsymmetrical ketones condense on the side that has more hydrogens. An exception is butanone, which reacts at the CH_2 group with acid catalysts, though with basic catalysts, it too reacts at the CH_3 group.

   Alternatively, the use of an amide base, such as LDA or lithium hexamethyldisilazide (p. 389), in aprotic solvents, such as ether or THF, at low temperatures, generates an enolate anion under conditions where the equilibrium lies more to the right. A second equivalent of the ketone can then be added. Clearly, this technique is effective in reactions of aldehydes.
3. *Reaction between Two Different Aldehydes*. In the most general case, this will produce a mixture of four products (eight, if the alkenes are counted). However, if one aldehyde does not have an α hydrogen, only two aldols are possible, and in many cases the crossed product is the main one. The crossed-aldol reaction is often called the *Claisen–Schmidt reaction*.[991] The crossed aldol is readily accomplished using amide bases in aprotic solvent. The first aldehyde is treated with LDA in THF at −78°C, for example, to form the enolate anion. Subsequent treatment with a second aldehyde leads to the mixed aldol product. The crossed aldol of two aldehydes has been done using potassium *tert*-butoxide and $Ti(OBu)_4$.[992]
4. *Reaction between Two Different Ketones*. This is seldom attempted with hydroxide or alkoxide bases in protic solvents since similar considerations apply to those discussed for aldehydes. This reaction is commonly done with amide bases in aprotic solvents, but with somewhat more difficulty than with aldehydes.

[987]For discussions of equilibrium constants in aldol reactions, see Guthrie, J.P.; Wang, X. *Can. J. Chem.* ***1991***, *69*, 339; Guthrie, J.P. *J. Am. Chem. Soc.* ***1991***, *113*, 7249, and references cited therein.
[988]The equilibrium concentration of the product from acetone in pure acetone was determined to be 0.01%: Maple, S.R.; Allerhand, A. *J. Am. Chem. Soc.* ***1987***, *109*, 6609.
[989]For another method, see Barot, B.C.; Sullins, D.W.; Eisenbraun, E.J. *Synth. Commun.* ***1984***, *14*, 397.
[990]Muzart, J. *Synthesis* ***1982***, 60; *Synth. Commun.* ***1985***, *15*, 285.
[991]For an aqueous version, see Buonora, P.T.; Rosauer, K.G.; Dai, L. *Tetrahedron Lett.* ***1995***, *36*, 4009.
[992]Han, Z.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* ***2000***, *41*, 4415.

5. *Reaction between an Aldehyde and a Ketone*. This is usually feasible with hydroxide or alkoxides bases in protic solvents, particularly when the aldehyde has no α hydrogen, since there is no competition from ketone condensing with itself.[993] This is also called the *Claisen–Schmidt reaction*. Even when the aldehyde has an α hydrogen, it is generally the α carbon of the ketone that adds to the carbonyl of the aldehyde, not the other way around. Mixtures are usually produced, however. If the ketone or the aldehyde is treated with an amide base in aprotic solvents, a second aldehyde or ketone can be added to give the aldolate with high regioselectivity. The reaction can be also made regioselective by preparing an enol derivative of the ketone separately[994] and then adding this to the aldehyde (or ketone). Other types of preformed derivatives that react with aldehydes and ketones are enamines (with a Lewis acid catalyst),[995] and enol borinates $R'CH{=}CR^2{-}OBR_2$[996] (which can be synthesized by **15-27**) or directly from an aldehyde or ketone[997]). Preformed metallic enolates are also used. For example, lithium enolates[998] (prepared by **12-23**) react with the substrate in the presence of $ZnCl_2$;[999] in this case the aldol product is stabilized by chelation of its two oxygen atoms with the zinc ion.[1000] Other metallic enolates can be used for aldol reactions, either preformed or generated *in situ* with a catalytic amount of a metal compound. Metals used for this purpose include Mg,[1001] Ti,[1002] Zr,[1003] Pd,[1004]

[993]For a study of the rate and equilibrium constants in the reaction between acetone and benzaldehyde, see Guthrie, J.P.; Cossar, J.; Taylor, K.F. *Can. J. Chem.* ***1984***, *62*, 1958. For a microwave induced reaction using aqueous NaOH, see Kad, G.L.; Kaur, K.P.; Singh, V.; Singh, J. *Synth. Commun.* ***1999***, *29*, 2583.

[994]For some other aldol reactions with preformed enol derivatives, see Mukaiyama, T. *Isr. J. Chem.* ***1984***, *24*, 162; Caine, D., in Augustine, R.L., *Carbon–Carbon Bond Formation*, Vol. 1, Marcel Dekker, NY, ***1979***, pp. 264–276.

[995]Takazawa, O.; Kogami, K.; Hayashi, K. *Bull. Chem. Soc. Jpn.* ***1985***, *58*, 2427.

[996]Inoue, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* ***1980***, *53*, 174; Hooz, J.; Oudenes, J.; Roberts, J.L.; Benderly, A. *J. Org. Chem.* ***1987***, *52*, 1347; Nozaki, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* ***1988***, *29*, 1041. For a review, see Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, ***1988***, pp. 324–333. For an *ab initio* study see Murga, J.; Falomir, E.; Carda, M.; Marco, J.A. *Tetrahedron* ***2001***, *57*, 6239.

[997]For conversion of ketones to either (*Z*) or (*E*) enol borinates, see, for example, Evans, D.A.; Nelson, J.V.; Vogel, E.; Taber, T.R. *J. Am. Chem. Soc.* ***1981***, *103*, 3099; Brown, H.C.; Dhar, R.K.; Bakshi, R.K.; Pandiarajan, P.K.; Singaram, B. *J. Am. Chem. Soc.* ***1989***, *111*, 3441; Brown, H.C.; Ganesan, K. *Tetrahedron Lett.* ***1992***, *33*, 3421.

[998]For a complete structure–energy analysis of one such reaction, see Arnett, E.M.; Fisher, F.J.; Nichols, M.A.; Ribeiro, A.A. *J. Am. Chem. Soc.* ***1990***, *112*, 801.

[999]House, H.O.; Crumrine, D.S.; Teranishi, A.Y.; Olmstead, H.D. *J. Am. Chem. Soc.* ***1973***, *95*, 3310.

[1000]It has been contended that such stabilization is not required: Mulzer, J.; Brüntrup, G.; Finke, J.; Zippel, M. *J. Am. Chem. Soc.* ***1979***, *101*, 7723.

[1001]Wei, H.-X.; Jasoni, R.L.; Shao, H.; Hu, J.; Paré, P.W. *Tetrahedron* ***2004***, *60*, 11829.

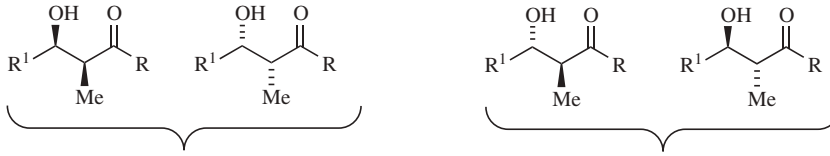
[1002]Stille, J.R.; Grubbs, R.H. *J. Am. Chem. Soc.* ***1983***, *105*, 1664; Mahrwald, R.; Costisella, B.; Gündogan, B. *Tetrahedron Lett.* ***1997***, *38*, 4543. For the use of $Ti(OiPr)_4$ to modify syn/anti ratios of aldol products, see Mahrwald, R.; Costisella, B.; Gündogan, B. *Synthesis* ***1998***, 262.

[1003]Evans, D.A.; McGee, L.R. *Tetrahedron Lett.* ***1980***, *21*, 3975; *J. Am. Chem. Soc.* ***1981***, *103*, 2876.

[1004]Nokami, J.; Mandai, T.; Watanabe, H.; Ohyama, H.; Tsuji, J. *J. Am. Chem. Soc.* ***1989***, *111*, 4126.

In,[1005] Sn,[1006] La,[1007] and Sm,[1008] all of which give products with moderate to excellent diastereoselectivity[1009] and regioselectivity. α-Alkoxy ketones react with lithium enolates particularly rapidly.[1010] A bis(aldol) condensation has been reported with epoxy ketones and aldehydes using SmI_2.[1011] Vinyl silanes react with aldehydes in the presence of a copper catalyst to vie the aldol product.[1012]

The reactions with preformed enol derivatives provide a way to control the stereoselectivity of the aldol reaction.[1013] As with the Michael reaction (**15-24**), the aldol reaction creates two new stereogenic centers, and, in the most general case, there are four stereoisomers of the aldol product (two racemic diastereomers), which can be represented as



syn (or erythro) (±) pair anti (or threo) (±) pair

Among the preformed enol derivatives used for diastereoselective aldol condensations have been enolates of Li,[1014] Mg, Ti,[1015] Zr,[343] and Sn,[1016] silyl enol

[1005]Loh, T.-P.; Wei, L.-L.; Feng, L.-C. *Synlett* ***1999***, 1059. For an example using ultrasound and $InCl_3$, see Loh, T.-P.; Feng, L.-C.; Wei, L.-L. *Tetrahedron* ***2001***, *57*, 4231.

[1006]Yanagisawa, A.; Kimura, K.; Nakatsuka, Y.; Yamamoto, H. *Synlett* ***1998***, 958.

[1007]Kobayashi, S.; Hachiya, I.; Takahori, T. *Synthesis* ***1993***, 371.

[1008]Yokoyama, Y.; Mochida, K. *Synlett* ***1996***, 445; Sasai, H.; Arai, S.; Shibasaki, M. *J. Org.Chem.* ***1994***, *59*, 2661. Also see, Bao, W.; Zhang, Y.; Wang, J. *Synth. Commun.* ***1996***, *26*, 3025.

[1009]For a review, see Mahrwald, R. *Chem. Rev.* ***1999***, *99*, 1095.

[1010]Das, G.; Thornton, E.R. *J. Am. Chem. Soc.* ***1990***, *112*, 5360.

[1011]Mukaiyama, T.; Arai, H.; Shiina, I. *Chem. Lett.* ***2000***, 580.

[1012]Yang, B.-Y.; Chen, X.-M.; Deng, G.-J.; Zhang, Y.-L.; Fan, Q.-H. *Tetrahedron Lett.* ***2003***, *44*, 3535.

[1013]For reviews, see Heathcock, C.H. *Aldrichimica Acta* ***1990***, *23*, 99; *Science* ***1981***, *214*, 395; Nógrádi, M. *Stereoselective Synthesis*, VCH, NY, ***1986***, pp. 193–220; Heathcock, C.H., in Morrison, J.D. *Asymmetric Synthesis*, Vol. 3, Academic Press, NY, ***1984***, pp. 111–212; Heathcock, C.H., in Buncel, E.; Durst, T. *Comprehensive Carbanion Chemistry*, pt. B, Elsevier, NY, ***1984***, pp. 177–237; Evans, D.A.; Nelson, J.V.; Taber, T.R. *Top. Stereochem.* ***1982***, *13*, 1; Evans, D.A. *Aldrichimica Acta* ***1982***, *15*, 23; Braun, M.; Sacha, H.; Galle, D.; Baskaran, S. *Pure Appl. Chem.* ***1996***, *68*, 561. For a discussion of how configuration and conformation influence the stereochemistry of aldols, see Kitamura, M.; Nakano, K.; Miki, T.; Okada, M.; Noyori, R. *J. Am. Chem. Soc.* ***2001***, *123*, 8939.

[1014]Fellmann, P.; Dubois, J.E. *Tetrahedron* ***1978***, *34*, 1349; Heathcock, C.H.; Pirrung, M.C.; Montgomery, S.H.; Lampe, J. *Tetrahedron* ***1981***, *37*, 4087; Masamune, S.; Ellingboe, J.W.; Choy, W. *J. Am. Chem. Soc.* ***1982***, *104*, 5526; Ertas, M.; Seebach, D. *Helv. Chim. Acta* ***1985***, *68*, 961.

[1015]Nerz-Stormes, M.; Thornton, E.R. *Tetrahedron Lett.* ***1986***, 897; Evans, D.A.; Rieger, D.L.; Bilodeau, M.T.; Urpí, F. *J. Am. Chem. Soc.* ***1991***, *113*, 1047; Cosp. A.; Larrosa, I.; Vilasís, I.; Romea, P.; Urpí, F.; Vilarrasa, J. *Synlett* ***2003***, 1109.

[1016]Mukaiyama, T.; Iwasawa, N.; Stevens, R.W.; Haga, T. *Tetrahedron* ***1984***, *40*, 1381; Labadie, S.S.; Stille, J.K. *Tetrahedron* ***1984***, *40*, 2329; Yura, T.; Iwasawa, N.; Mukaiyama, T. *Chem. Lett.* ***1986***, 187. See also, Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* ***1983***, *24*, 3347.

ethers,[1017] enol borinates,[1018] and enol borates $R'CH{=}CR^2{-}OB(OR)_2$.[1019] The nucleophilicity of silyl enol ethers has been examined.[1020] Base-induced formation of the enolate anion generally leads to a mixture of (*E*)- and (*Z*)-isomers, and dialkyl amide bases are used in most cases. The (*E*/*Z*) stereoselectivity depends on the structure of the lithium dialkylamide base, with the highest (*E*/*Z*) ratios obtained with LiTMP-butyllithium mixed aggregates in THF.[1021] The use of LiHMDS resulted in a reversal of the (*E*/*Z*) selectivity. In general, metallic (*Z*) enolates give the syn (or erythro) pair, and this reaction is highly useful for the diastereoselective synthesis of these products.[1022] The (*E*) isomers generally react nonstereoselectively. However, anti (or threo) stereoselectivity has been achieved in a number of cases, with titanium enolates,[1023] with magnesium enolates,[1024] with certain enol borinates,[1025] and with lithium enolates at −78°C.[1026] Enolization accounts for syn–anti isomerization of aldols.[1027] In another variation, a β-keto Weinreb amide (see **16-82**) reacted with $TiCl_4$ and Hünig's base (iPr$_2$NEt) and then an aldehyde to give the β-hydroxy ketone.[1028]

[1017]Matsuda, I.; Izumi, Y. *Tetrahedron Lett.* ***1981***, *22*, 1805; Yamamoto, Y.; Maruyama, K.; Matsumoto, K. *J. Am. Chem. Soc.* ***1983***, *105*, 6963; Sakurai, H.; Sasaki, K.; Hosomi, A. *Bull. Chem. Soc. Jpn.* ***1983***, *56*, 3195; Hagiwara, H.; Kimura, K.; Uda, H. *J. Chem. Soc., Chem. Commun.* ***1986***, 860.

[1018]Evans, D.A.; Nelson, J.V.; Vogel, E.; Taber, T.R. *J. Am. Chem. Soc.* ***1981***, *103*, 3099; Evans, D.A.; Bartroli, J.; Shih, T.L. *J. Am. Chem. Soc.* ***1981***, *103*, 2127; Masamune, S.; Choy, W.; Kerdesky, F.A.J.; Imperiali, B. *J. Am. Chem. Soc.* ***1981***, *103*, 1566; Paterson, I.; Goodman, J.M.; Lister, M.A.; Schumann, R.C.; McClure, C.K.; Norcross, R.D. *Tetrahedron* ***1990***, *46*, 4663; Walker, M.A.; Heathcock, C.H. *J. Org. Chem.* ***1991***, *56*, 5747. For reviews, see Paterson, I. *Chem. Ind. (London)* ***1988***, 390; Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, ***1988***, p. 324.

[1019]Hoffmann, R.W.; Ditrich, K.; Fröch, S. *Liebigs Ann. Chem.* ***1987***, 977.

[1020]Patz, M.; Mayr, H. *Tetrahedron Lett.* ***1993***, *34*, 3393.

[1021]Pratt, L. M.; Newman, A.; Cyr, J. S.; Johnson, H.; Miles, B.; Lattier, A.; Austin, E.; Henderson, S.; Hershey, B.; Lin, M.; Balamraju, Y.; Sammonds, L.; Cheramie, J.; Karnes, J.; Hymel, E.; Woodford, B.; Carter, C. *J. Org. Chem.* ***2003***, *68*, 6387.

[1022]For discussion of transition-state geometries in this reaction, see Hoffmann, R.W.; Ditrich, K.; Froech, S.; Cremer, D. *Tetrahedron* ***1985***, *41*, 5517; Anh, N.T.; Thanh, B.T. *Nouv. J. Chim.*, ***1986***, *10*, 681; Li, Y.; Paddon-Row, M.N.; Houk, K.N. *J. Org. Chem.* ***1990***, *55*, 481; Denmark, S.E.; Henke, B.R. *J. Am. Chem. Soc.* ***1991***, *113*, 2177.

[1023]See Murphy, P.J.; Procter, G.; Russell, A.T. *Tetrahedron Lett.* ***1987***, *28*, 2037; Nerz-Stormes, M.; Thornton, E.R. *J. Org. Chem.* ***1991***, *56*, 2489.

[1024]Swiss, K.A.; Choi, W.; Liotta, D.; Abdel-Magid, A.F.; Maryanoff, C.A. *J. Org. Chem.* ***1991***, *56*, 5978.

[1025]Masamune, S.; Sato, T.; Kim, B.M.; Wollmann, T.A. *J. Am. Chem. Soc.* ***1986***, *108*, 8279; Danda, H.; Hansen, M.M.; Heathcock, C.H. *J. Org. Chem.* ***1990***, *55*, 173. See also, Corey, E.J.; Kim, S.S. *Tetrahedron Lett.* ***1990***, *31*, 3715.

[1026]Hirama, M.; Noda, T.; Takeishi, S.; Itô, S. *Bull. Chem. Soc. Jpn.* ***1988***, *61*, 2645; Majewski, M.; Gleave, D.M. *Tetrahedron Lett.* ***1989***, *30*, 5681.

[1027]Ward, D.E.; Sales, M.; Sasmal, P.K. *Org. Lett.* ***2001***, *3*, 3671; Ward, D.E.; Sales, M.; Sasmal, P.K. *J. Org. Chem.* ***2004***, *69*, 4808.

[1028]Calter, M.A.; Guo, X.; Liao, W. *Org. Lett.* ***2001***, *3*, 1499.

These reactions can also be made enantioselective[1029] (in which case only one of the four isomers predominates)[1030] by using[1031] chiral enol derivatives,[1032] chiral aldehydes or ketones,[1033] or both.[1034] Chiral bases[1035] can be used, such as proline,[1036] proline derivatives,[1037] or chiral additives, used in conjunction with the base.[1038] A chiral binaphthol dianion has been used to catalyze the reaction.[1039] Chiral auxiliaries[1040] have been developed that can be used in conjunction with the aldol condensation, as well as chiral catalysts[1041] and chiral ligands[1042]

[1029]For a review, see Allemann, C.; Gordillo, R.; Clemente, F.R.; Cheong, P.H.-Y.; Houk, K.N. *Acc. Chem. Res.* ***2004***, *37*, 558; Saito, S.; Yamamoto, H. *Acc. Chem. res.* ***2004***, *37*, 570. For a discussion of chelation versus nonchelation control, see Yan, T.-H.; Tan, C.-W.; Lee, H.-C.; Lo, H.-C.; Huang, T.-Y. *J. Am. Chem. Soc.* ***1993***, *115*, 2613. For the effects of lithium salts on enantioselective deprotonation, see Majewski, M.; Lazny, R.; Nowak, P. *Tetrahedron Lett.* ***1995***, *36*, 5465. Also see, Smith, M.B. *Organic Synthesis*, 2nd ed., McGraw-Hill, NY, ***2001***, pp. 779–790.

[1030]For anti-selective aldol reactions, see Oppolzer, W.; Lienard, P. *Tetrahedron Lett.* ***1993***, *34*, 4321. For a "non-Evans" *syn*-aldol, see Yan, T.-H.; Lee, H.-C.; Tan, C.-W. *Tetrahedron Lett.* ***1993***, *34*, 3559.

[1031]For reviews, see Klein, J., in Patai, S. *Supplement A: The Chemistry of Double-Bonded Functional Groups*, Vol. 2, pt. 1, Wiley, NY, ***1989***, pp. 567–677; Braun, M. *Angew. Chem. Int. Ed.* ***1987***, *26*, 24.

[1032]For examples, see Eichenauer, H.; Friedrich, E.; Lutz, W.; Enders, D. *Angew. Chem. Int. Ed.* ***1978***, *17*, 206; Meyers, A.I.; Yamamoto, Y. *Tetrahedron* ***1984***, *40*, 2309; Ando, A.; Shioiri, T. *J. Chem. Soc., Chem. Commun.* ***1987***, 1620; Muraoka, M.; Kawasaki, H.; Koga, K. *Tetrahedron Lett.* ***1988***, *29*, 337; Paterson, I.; Goodman, J.M. *Tetrahedron Lett.* ***1989***, *30*, 997; Siegel, C.; Thornton, E.R. *J. Am. Chem. Soc.* ***1989***, *111*, 5722; Gennari, C.; Molinari, F.; Cozzi, P.; Oliva, A. *Tetrahedron Lett.* ***1989***, *30*, 5163; Faunce, J.A.; Grisso, B.A.; Mackenzie, P.B. *J. Am. Chem. Soc.* ***1991***, *113*, 3418.

[1033]For example, see Ojima, I.; Yoshida, K.; Inaba, S. *Chem. Lett.* ***1977***, 429; Heathcock, C.H.; Flippin, L.A. *J. Am. Chem. Soc.* ***1983***, *105*, 1667; Reetz, M.T.; Kesseler, K.; Jung, A. *Tetrahedron* ***1984***, *40*, 4327.

[1034]For example, see Heathcock, C.H.; White, C.T.; Morrison, J.J.; VanDerveer, D. *J. Org. Chem.* ***1981***, *46*, 1296; Short, R.P.; Masamune, S. *Tetrahedron Lett.* ***1987***, *28*, 2841.

[1035]For a review, see Notz, W.; Tanaka, F.; Barbas III, C.F. *Acc. Chem. Res.* ***2004***, *37*, 580.

[1036]Notz, W.; List, B. *J. Am. Chem. Soc.* ***2000***, *122*, 7386; List, B.; Pojarliev, P.; Castello, C. *Org. Lett.* ***2001***, *3*, 573; Sakthivel, K.; Notz, W.; Bui, T.; Barbas III, C.F. *J. Am. Chem. Soc.* ***2001***, *123*, 5260; Northrup, A.B.; MacMillan, D.W.C. *J. Am. Chem. Soc.* ***2002***, *124*, 6798. See Peng, Y.-Y.; Ding, Q.-P.; Li, Z.; Wang, P.G.; Cheng, J.-P. *Tetrahedron Lett.* ***2003***, *44*, 3871; Darbre, T.; Machuqueiro, M. *Chem. Commun.* ***2003***, 1090; Nyberg, A.I.; Usano, A.; Pihko, P.M. *Synlett* ***2004***, 1891. For an example with formaldehyde, see Casas, J.; Sundén, H.; Córdova, A. *Tetrahedron Lett.* ***2004***, *45*, 6117. For a proline-catalyzed high pressure reaction, see Sekiguchi, Y.; Sasaoka, A.; Shimomoto, A.; Fujioka, S.; Kotsuki, H. *Synlett* ***2003***, 1655.

[1037]Tang, Z.; Jiang, F.; Yu, L.-T.; Cui, X.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D. *J. Am. Chem. Soc.* ***2003***, *125*, 5262; Zhong, G.; Fan, J.; Barbas III, C.F. *Tetrahedron Lett.* ***2004***, *45*, 5681.

[1038]See Mahrwald, R. *Org. Lett.* ***2000***, *2*, 4011.

[1039]Nakajima, M.; Orito, Y.; Ishizuka, T.; Hashimoto, S. *Org. Lett.* ***2004***, *6*, 3763.

[1040]Hein, J.E.; Hultin, P.G. *Synlett* ***2003***, 635.

[1041]Suzuki, T.; Yamagiwa, N.; Matsuo, Y.; Sakamoto, S.; Yamaguchi, K.; Shibasaki, M.; Noyori, R. *Tetrahedron Lett.* ***2001***, *42*, 4669. For a review, see Alcaidi, B.; Almendros, P. *Eur. J. Org. Chem.* ***2002***, 1595.

[1042]Trost, B.M.; Ito, H. *J. Am. Chem. Soc.* ***2000***, *122*, 12003.

in catalytic reactions. Aldehydes are condensed with ketones with potassium hexamethyldisilazide (KHMDS) and 8% of a chiral lithium catalyst, giving the aldol product with moderate enantioselectivity.[1043] Structural variations in the aldehyde or ketone are compatible with many enantioselective condensation reactions. An α-hydroxy ketone was condensed with an aldehyde using a chiral zinc catalyst to give the aldol (an α,β-dihydroxy ketone) with good syn selectivity and good enantioselectivity.[1044] A catalytic amount of a nicotine metabolite allows an enantioselective reaction in aqueous media.[1045] Chiral vinylogous aldol reactions have been reported.[1046]

Silyl enol ethers react with aldehydes in the presence of chiral boranes[1047] or other additives[1048] to give aldols with good asymmetric induction (see the Mukaiyama aldol reaction in **16-35**). Chiral boron enolates have been used.[1049] Since both new stereogenic centers are formed enantioselectively, this kind of process is called *double asymmetric synthesis*.[1050] Where both the enolate derivative and substrate were achiral, carrying out the reaction in the presence of an optically active boron compound[1051] or a diamine coordinated with a tin compound[1052] gives the aldol product with excellent enantioselectivity for one stereoisomer. Formation of the magnesium enolate anion of a chiral amide, adds to aldehydes to give the alcohol enantioselectively.[1053]

Diamine protonic acids have been used for catalytic asymmetric aldol reaction.[1054] Boron triflate derivatives, R_2BOTf, have been used for the condensation of ketals and ketone to give β-alkoxy ketones.[1055]

[1043]Yoshikawa, N.; Yamada, Y.M.A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* ***1999***, *121*, 4168.

[1044]Kumagai, N.; Matsunaga, S.; Yoshikawa, N.; Ohshima, T.; Shibasaki, M. *Org. Lett.* ***2001***, *3*, 1539; Yoshikawa, N.; Kumagai, N.; Matsunaga, S.; Moll, G.; Ohshma, T.; Suzuki, T.; Shibasaki, M. *J. Am. Chem. Soc.* ***2001***, *123*, 2466; Trost, B.M.; Ito, H.; Silcoff, E.R. *J. Am. Chem. Soc.* ***2001***, *123*, 3367.

[1045]Dickerson, T.J.; Janda, K.D. *J. Am. Chem. Soc.* ***2002***, *124*, 3220.

[1046]Takikawa, H.; Ishihara, K.; Saito, S.; Yamamoto, H. *Synlett* ***2004***, 732; Denmark, S.E.; Heemstra, Jr., J.R. *Synlett* ***2004***, 2411.

[1047]Ishihara, K.; Maruyama, T.; Mouri, M.; Gao, Q.; Furuta, K.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* ***1993***, *66*, 3483.

[1048]Corey, E.J.; Cywin, C.L.; Roper, T.D. *Tetrahedron Lett.* ***1992***, *33*, 6907.

[1049]See Yoshida, K.; Ogasawara, M.; Hayashi, T. *J. Org. Chem.* ***2003***, *68*, 1901.

[1050]For a review, see Masamune, S.; Choy, W.; Petersen, J.S.; Sita, L.R. *Angew. Chem. Int. Ed.* ***1985***, *24*, 1.

[1051]Corey, E.J.; Kim, S.S. *J. Am. Chem. Soc.* ***1990***, *112*, 4976; Furuta, K.; Maruyama, T.; Yamamoto, H. *J. Am. Chem. Soc.* ***1991***, *113*, 1041; Kiyooka, S.; Kaneko, Y.; Komura, M.; Matsuo, H.; Nakano, M. *J. Org. Chem.* ***1991***, *56*, 2276. For a review, see Bernardi, A.; Gennari, C.; Goodman, J.M.; Paterson, I. *Tetrahedron Asymmetry* ***1995***, *6*, 2613.

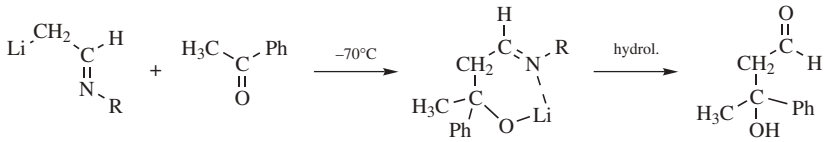
[1052]Mukaiyama, T.; Uchiro, H.; Kobayashi, S. *Chem. Lett.* ***1990***, 1147.

[1053]Evans, D.A.; Tedrow, J.S.; Shaw, J.T.; Downey, C.W. *J. Am. Chem. Soc.* ***2002***, *124*, 392.

[1054]Saito, S.; Nakadai, M.; Yamamoto, H. *Synlett* ***2001***, 1245; Trost, B.M.; Fettes, A.; Shireman, B.T. *J. Am. Chem. Soc.* ***2004***, *126*, 2660.

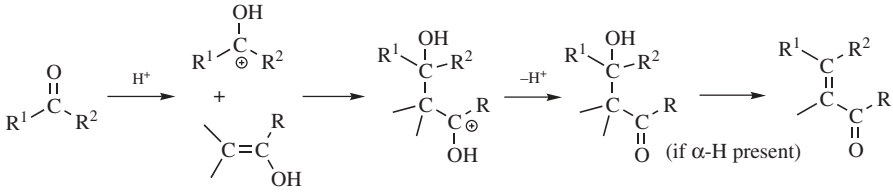
[1055]Li, L.-S.; Das, S.; Sinha, S.C. *Org. Lett.* ***2004***, *6*, 127.

It is possible to make the α carbon of the aldehyde add to the carbonyl carbon of the ketone, by using an imine instead of an aldehyde, and $LiN(iPr)_2$ as the base:[1056]



This is known as a *directed aldol reaction*. Similar reactions have been performed with α-lithiated dimethylhydrazones of aldehydes or ketones[1057] and with α-lithiated aldoximes.[1058]

The aldol reaction can also be performed with acid catalysts, as mentioned above, in which case dehydration usually follows. Here, there is initial protonation of the carbonyl group, which attacks the α carbon of the *enol* form of the other molecule:[1059]



With respect to the enol, this mechanism is similar to that of halogenation (**12-4**). A side reaction that is sometimes troublesome is further condensation, since the product of an aldol reaction is still an aldehyde or ketone. The aldol condensation of aldehydes has also been done using a mixture of pyrrolidine and benzoic acid.[1060]

The intramolecular aldol condensation is well known, and aldol reactions are often used to close five- and six-membered rings. Because of the favorable entropy (p. 303), such ring closures generally take place with ease[1061] when using hydroxide or alkoxide bases in protic solvents. In aprotic solvents with amide bases,

[1056]Wittig, G.; Frommeld, H.D.; Suchanek, P. *Angew. Chem. Int. Ed.* ***1963***, *2*, 683. For reviews, see Mukaiyama, T. *Org. React.* ***1982***, *28*, 203; Wittig, G. *Top. Curr. Chem.* ***1976***, *67*, 1; *Rec. Chem. Prog.* ***1967***, *28*, 45; Wittig, G.; Reiff, H. *Angew. Chem. Int. Ed.* ***1968***, *7*, 7; Reiff, H. *Newer Methods Prep. Org. Chem.* ***1971***, *6*, 48.

[1057]Corey, E.J.; Enders, D. *Tetrahedron Lett.* ***1976***, 11. See also, Beam, C.F.; Thomas, C.W.; Sandifer, R.M.; Foote, R.S.; Hauser, C.R. *Chem. Ind. (London)* ***1976***, 487; Sugasawa, T.; Toyoda, T.; Sasakura, K. *Synth. Commun.* ***1979***, *9*, 515; Depezay, J.; Le Merrer, Y. *Bull. Soc. Chim. Fr.* ***1981***, II-306.

[1058]Hassner, A.; Näumann, F. *Chem. Ber.* ***1988***, *121*, 1823.

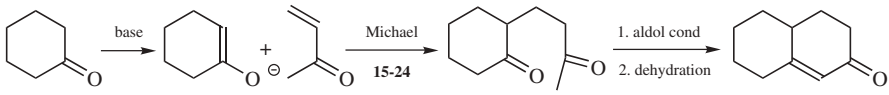
[1059]There is evidence (in the self-condensation of acetaldehyde) that a water molecule acts as a base (even in concentrated H_2SO_4) in assisting the addition of the enol to the protonated aldehyde: Baigrie, L.M.; Cox, R.A.; Slebocka-Tilk, H.; Tencer, M.; Tidwell, T.T. *J. Am. Chem. Soc.* ***1985***, *107*, 3640.

[1060]Ishikawa, T.; Uedo, E.; Okada, S.; Saito, S. *Synlett* ***1999***, 450.

[1061]For rate and equilibrium constants, see Guthrie, J.P.; Guo, J. *J. Am. Chem. Soc.* ***1996***, *118*, 11472. For neighboring-group effects, see Eberle, M.K. *J. Org. Chem.* ***1996***, *61*, 3844.

formation of the enolate anion occurs by deprotonation of the more acidic site, followed by cyclization to the second carbonyl. The acid-catalyzed intramolecular aldol condensation is known, and the mechanism has been studied.[1062] Stereoselective proline-catalyzed intramolecular aldol reactions give the cyclize product with good enantioselectivity.[1063]

An important extension of the intramolecular aldol condensation is the *Robinson annulation* reaction,[1064] which has often been used in the synthesis of steroids and terpenes. In original versions of this reaction, a cyclic ketone is converted to another cyclic ketone under equilibrium conditions using hydroxide or alkoxide bases in a protic solvent, forming one additional six-membered ring containing a double bond. The reaction can be done in a stepwise manner using amide bases in aprotic solvents. In the reaction with hydroxide or alkoxide bases in alcohol or water solvents, the substrate is treated with methyl vinyl ketone (or a simple derivative of methyl vinyl ketone) and a base.[1065] The enolate ion of the substrate adds to the methyl vinyl ketone in a Michael reaction (**15-24**) to give a diketone that undergoes or is made to undergo an internal aldol



reaction and subsequent dehydration to give the product.[1066] The Robinson annulation can be combined with alkylation.[1067] Enantioselective Robinson annulation techniques have been developed, including a proline-catalyzed reaction.[1068] The Robinson annulation has been done in ionic liquids[1069] and a solvent-free version of the reaction is known.[1070]

Because methyl vinyl ketone has a tendency to polymerize, precursors are often used instead, that is., compounds that will give methyl vinyl ketone when treated with a base. One common example, $MeCOCH_2CH_2NEt_2Me^+\ I^-$ (see **17-9**), is easily prepared by quaternization of $MeCOCH_2CH_2NEt_2$, which itself is prepared

[1062]Bouillon, J.-P.; Portella, C.; Bouquant, J.; Humbel, S. *J. Org. Chem.* ***2000***, *65*, 5823.

[1063]Bahmanyar, S.; Houk, K.N. *J. Am. Chem. Soc.* ***2001***, *123*, 12911; Pidathala, C.; Hoang, L.; Vignola, N.; List, B. *Angew. Chem. Int. Ed.* ***2003***, *42*, 2785.

[1064]For reviews of this and related reactions, see Gawley, R.E. *Synthesis* ***1976***, 777; Jung, M.E. *Tetrahedron* ***1976***, *32*, 1; Mundy, B.P. *J. Chem. Educ.* ***1973***, *50*, 110. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1356–1358.

[1065]Acid catalysis has also been used: see Heathcock, C.H.; Ellis, J.E.; McMurry, J.E.; Coppolino, A. *Tetrahedron Lett.* ***1971***, 4995.

[1066]For improved procedures, see Sato, T.; Wakahara, Y.; Otera, J.; Nozaki, H. *Tetrahedron Lett.* ***1990***, *31*, 1581, and references cited therein.

[1067]Tai, C.-L.; Ly, T.W.; Wu, J.-D.; Shia, K.-S.; Liu, H.-J. *Synlett* ***2001***, 214.

[1068]Bui, T.; Barbas III, C.F. *Tetrahedron Lett.* ***2000***, *41*, 6951; Rajagopal, D.; Narayanan, R.; Swaminathan, S. *Tetrahedron Lett.* ***2001***, *42*, 4887.

[1069]Morrison, D.W.; Forbes, D.C.; Davis Jr., J.H. *Tetrahedron Lett.* ***2001***, *42*, 6053.

[1070]Miyamoto, H.; Kanetaka, S.; Tanaka, K.; Yoshizawa, K.; Toyota, S.; Toda, F. *Chem. Lett.* ***2000***, 888.

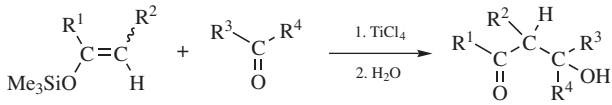
by a Mannich reaction (**16-19**) involving acetone, formaldehyde, and diethylamine. α-Silylated vinyl ketones $RCOC(SiMe_3)=CH_2$ have also been used successfully in annulation reactions.[1071] The $SiMe_3$ group is easily removed. 1,5-Diketones prepared in other ways are also frequently cyclized by internal aldol reactions. When the ring closure of a 1,5-diketone is catalyzed by the amino acid (*S*)-proline, the product is optically active with high enantiomeric excess.[1072] *Stryker's reagent* [1073] $[(Ph_3P)CuH]_6$ has been used for an intramolecular addition where ketone enolate anion to a conjugated ketone, giving cyclic alcohol with a pendant ketone unit.[1074]

OS **I**, 77, 78, 81, 199, 283, 341; **II**, 167, 214; **III**, 317, 353, 367, 747, 806, 829; **V**, 486, 869; **VI**, 496, 666, 692, 781, 901; **VII**, 185, 190, 332, 363, 368, 473; **VIII**, 87, 208, 241, 323, 339, 620; **IX**, 432, 610; **X**, 339.

16-35 Mukaiyama Aldol and Related Reactions[1075]

O-Hydro-*C*-(α-acylalkyl)-addition

An important variation of the aldol condensation involves treatment of an aldehyde or ketone with a silyl ketene acetal $R_2C=C(OSiMe_3)OR'$[1076] in the presence of $TiCl_4$[1077], to give **38**. The silyl ketene acetal can be considered a preformed enolate that gives aldol product



38

with $TiCl_4$ in aqueous solution, or with no catalyst at all.[1078] A combination of $TiCl_4$ and a *N*-tosyl imine has also been used to facilitate the Mukaiyama aldol

[1071]Stork, G.; Singh, J. *J. Am. Chem. Soc.* ***1974***, *96*, 6181; Boeckman, Jr., R.K. *J. Am. Chem. Soc.* ***1974***, *96*, 6179.

[1072]Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem. Int. Ed.* ***1971***, *10*, 496; Hajos, Z.G.; Parrish, D.R. *J. Org. Chem.* ***1974***, *39*, 1615. For a review of the mechanism, see Agami, C. *Bull. Soc. Chim. Fr.* ***1988***, 499.

[1073]Mahoney, W.S.; Brestensky, D.M.; Stryker, J.M. *J. Am. Chem. Soc.* ***1988***, *110*, 291; Brestensky, D.M.; Stryker, J.M. *Tetrahedron Lett.* ***1989***, *30*, 5677.

[1074]Chiu, P.; Szeto, C.-P.; Geng, Z.; Cheng, K.-F. *Org. Lett.* ***2001***, *3*, 1901.

[1075]See Smith, M.B. *Organic Synthesis*, 2nd ed., McGraw-Hill, NY, ***2001***, pp.755–759.

[1076]For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1745–1752. For methods of preparing silyl ketene acetals, see Revis, A.; Hilty, T.K. *Tetrahedron Lett.* ***1987***, *28*, 4809, and references cited therein.

[1077]Mukaiyama, T. *Pure Appl. Chem.* ***1983***, *55*, 1749; Kohler, B.A.B. *Synth. Commun.* ***1985***, *15*, 39; Mukaiyama, T.; Narasaka, K. *Org. Synth., 65*, 6. For a discussion of the mechanism, see Gennari, C.; Colombo, L.; Bertolini, G.; Schimperna, G. *J. Org. Chem.* ***1987***, *52*, 2754. For a review of this and other applications of $TiCl_4$ in organic synthesis, see Mukaiyama, T. *Angew. Chem. Int. Ed.* ***1977***, *16*, 817. See also, Reetz, M.T. *Organotitanium Reagents in Organic Synthesis*, Spinger, NY, ***1986***.

[1078]Lubineau, A.; Meyer, E. *Tetrahedron* ***1988***, *44*, 6065; Miura, K.; Sato, H.; Tamaki, K.; Ito, H.; Hosomi, A. *Tetrahedron Lett.* ***1998***, *39*, 2585. For an uncatalyzed reaction under high pressure, see Bellassoued, M.; Reboul, E.; Dumas, F. *Tetrahedron Lett.* ***1997***, *38*, 5631.

reaction.[1079] The mechanism of this reaction has been explored.[1080] Other catalysts have been used for this reaction as well, including $InCl_3$,[1081] SmI_2,[1082] $Sc(OTf)_3$,[1083] HgI_2,[1084] $Yb(OTf)_3$,[1085] $Cu(OTf)_2$,[1086] $[Cp_2Zr(O\textit{t}\text{-Bu})THF]^+[BPh_4]^-$,[1087] $LiClO_4$,[1088] $VOCl_3$,[1089] an iron catalyst,[1090] and $Bi(OTf)_3$.[1091] The reaction can be done in water using a scandium catalyst[1092] or a Montmorillonite K10 clay.[1093] Silyl enol ethers react with aqueous formaldehyde in the presence of TBAF to give the aldol product.[1094] A catalytic amount of Me_3SiCl facilitates the titanium mediated reaction.[1095] Sulfonamides, such as $HNTf_2$, have been used as a catalyst[1096] as has pyridine *N*-oxide.[1097] A combination of Ph_2BOH and benzoic acid in water catalyzes the reaction.[1098] Lithium perchlorate in acetonitrile (5 *M*) can be used for the reaction of an aldehyde and a silyl enol ether.[1099] When the catalyst is dibutyltin bis (triflate) $Bu_2Sn(OTf)_2$, aldehydes react, but not their acetals, while acetals of ketones react, but not the ketones themselves.[1100] Reaction at the carbonyl of saturated carbonyl compounds is significantly faster than 1,2-addition to unsaturated carbonyl compounds.[1101] Propargylic acetals react with silyl enol ethers and a scandium catalyst to give β-alkoxy ketones.[1102] Imines react with silyl enol ethers n the presence of $BF_3{\bullet}OEt_2$ to give β-amino ketones.[1103] α-Silyl silyl enol ethers

[1079]Miura, K.; Nakagawa, T.; Hosomi, A. *J. Am. Chem. Soc.* ***2002***, *124*, 536.
[1080]Hollis, T.K.; Bosnich, B. *J. Am. Chem. Soc.* ***1995***, *117*, 4570. For the transition-state geometry, see Denmark, S.E.; Lee, W. *J. Org. Chem.* ***1994***, *59*, 707.
[1081]Loh, T.-P.; Pei, J.; Cao, G.-Q. *Chem. Commun.* ***1996***, 1819; Kobayashi, S.; Busujima, T.; Nagayama, S. *Tetrahedron Lett.* ***1998***, *39*, 1579. Both $InCl_3$ and $CeCl_3$ have been used in aqueous media, see Muñoz-Muñiz, O.; Quintanar-Audelo, M.; Juaristi, E. *J. Org. Chem.* ***2003***, *68*, 1622.
[1082]Van de Weghe, P.; Collin, J. *Tetrahedron Lett.* ***1993***, *34*, 3881.
[1083]Kobayashi, S.; Wakabayashi, T.; Nagayama, S.; Oyamada, H. *Tetrahedron Lett.* ***1997***, *38*, 4559; Komoto, I.; Kobayashi, S. *Chem. Commun.* ***2001***, 1842; Komoto, I.; Kobayashi, S. *J. Org. Chem.* ***2004***, *69*, 680.
[1084]Dicker, I.B. *J. Org. Chem.* ***1993***, *58*, 2324.
[1085]This catalyst is tolerated in water. See Kobayashi, S.; Hachiya, I. *J. Org. Chem.* ***1994***, *59*, 3590.
[1086]Kobayashi, S.; Nagayama, S.; Busujima, T. *Chem. Lett.* ***1997***, 959.
[1087]Hong, Y.; Norris, D.J.; Collins, S. *J. Org. Chem.* ***1997***, *58*, 3591.
[1088]Reetz, M.T.; Fox, D.N.A. *Tetrahedron Lett.* ***1993***, *34*, 1119.
[1089]Kurihara, M.; Hayshi, T.; Miyata, N. *Chem. Lett.* ***2001***, 1324.
[1090]Bach, T.; Fox, D.N.A.; Reetz, M.T. *J. Chem. Soc., Chem. Commun.* ***1992***, 1634.
[1091]LeRoux, C.; Ciliberti, L.; Laurent-Robert, H.; Laporterie, A.; Dubac, J. *Synlett* ***1998***, 1249.
[1092]Manabe, K.; Kobayashi, S. *Tetrahedron Lett.* ***1999***, *40*, 3773. For a discussion of the effect of surfactants on this reaction, see Tian, H.-Y.; Chen, Y.-J.; Wang, D.; Bu, Y.-P.; Li, C.-J. *Tetrahedron Lett.* ***2001***, *42*, 1803.
[1093]Loh, T.-P.; Li, X.-R. *Tetrahedron* ***1999***, *55*, 10789.
[1094]Ozasa, N.; Wadamoto, M.; Ishihara, K.; Yamamoto, H. *Synlett* ***2003***, 2219.
[1095]Yoshida, Y.; Matsumoto, N.; Hamasaki, R.; Tanabe, Y. *Tetrahedron Lett* ***1999***, *40*, 4227.
[1096]Ishihara, K.; Hiraiwa, Y.; Yamamoto, H. *Synlett* ***2001***, 1851.
[1097]Denmark, S.E.; Fan, Y. *J. Am. Chem. Soc.* ***2002***, *124*, 4233.
[1098]Mori, Y.; Kobayashi, J.; Manabe, K.; Kobayashi, S. *Tetrahedron* ***2002***, *58*, 8263.
[1099]Sudha, R.; Sankararaman, S. *J. Chem. Soc., Perkin Trans. 1* ***1999***, 383.
[1100]Sato, T.; Otera, J.; Nozaki, H. *J. Am. Chem. Soc.* ***1990***, *112*, 901.
[1101]Shirakawa, S.; Maruoka, K. *Tetrahedron Lett.* ***2002***, *43*, 1469.
[1102]Yoshimatsu, M.; Kuribayashi, M.; Koike, T. *Synlett* ***2001***, 1799.
[1103]Akiyama, T.; Takaya, J.; Kagoshima, H. *Chem. Lett.* ***1999***, 947.

$RCH{=}CH(OTMS)SiMe_3$ react with acetals in the presence of $SnCl_4$ to give β-alkoxy silyl ketones.[1104]

An interesting variation in this reaction combined an intermolecular Mukaiyama aldol followed by an intramolecular reaction (a "domino" Mukaiyama aldol) that gave cyclic conjugated ketone products.[1105] Borane derivatives such as $C{=}C{-}OB(NMe_2)_2$ react with aldehydes to give β-amino ketones.[1106]

Silyl enol ethers[1107] derived from esters (silyl ketene acetals) react with aldehydes in the presence of various catalysts to give β-hydroxy esters. Water accelerates the reaction of an aldehyde and a ketene silyl acetal with no other additives.[1108] The reaction is catalyzed by triphenylphosphine[1109] and also by $SiCl_4$ with a chiral bis(phosphoramide) catalyst.[1110] The reaction was done without a catalyst in an ionic liquid.[1111] A vinylogous reaction is known that gives δ-hydroxy-α,β-unsaturated esters.[1112] Under different conditions, silyl ketene acetals of conjugated esters react with aldehydes to give conjugated lactones.[1113] Imines react with silyl ketene acetals in the presence of SmI_3 to give β-amino esters.[1114] Another variation converted a *N*-(1-trimethylsilyloxyvinyl) imine to a conjugated amide by initial reaction with 2 equivalents of *n*-butyllithium and a zirconium complex followed by reaction with an aldehyde.[1115] Silyl ketene acetals also undergo conjugate addition in reactions with conjugated ketones.[1116] Silyl ketene acetals of thio esters also react with aldehydes to give β-hydroxy thioesters.[1117]

Asymmetric Mukaiyama aldol reactions and reactions of silyl ketene acetals have been reported, [1118] usually using chiral additives[1119] although chiral auxiliaries

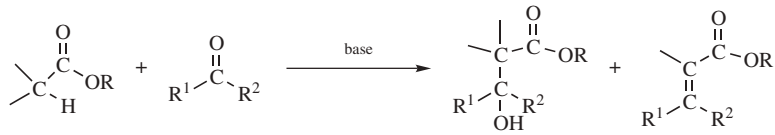
[1104]Honda, M.; Oguchi, W.; Segi, M.; Nakajima, T. *Tetrahedron* ***2002***, *58*, 6815.
[1105]Langer, P.; Köhler, V. *Org. Lett.* ***2000***, *2*, 1597.
[1106]Suginome, M.; Uehlin, L.; Yamamoto, A.; Murakami, M. *Org. Lett.* ***2004***, *6*, 1167.
[1107]For a discussion of enantioselective deprotonation to form chiral silyl enol ethers, see Carswell, E.L.; Hayes, D.; Henderson, K.W.; Kerr, W.J.; Russell, C.J. *Synlett* ***2003***, 1017.
[1108]Loh, T.-P.; Feng, L.-C.; Wei, L.-L. *Tetrahedron* ***2000***, *56*, 7309.
[1109]Matsukawa, S.; Okano, N.; Imamoto, T. *Tetrahedron Lett.* ***2000***, *41*, 103.
[1110]Denmark, S.E.; Heemstra, Jr., J.R. *Org. Lett.* ***2003***, *5*, 2303; Denmark, S.E.; Wynn, T.; Beutner, G.L. *J. Am. Chem. Soc.* ***2002***, *124*, 13405.
[1111]In omim Cl, 1-octyl-3-methylimidazolium chloride or in bmim PF_6, 1-butyl-3-methylimidazolium hexafluorophosphate: Chen, S.-L.; Ji, S.-J.; Loh, T.-P. *Tetrahedron Lett.* ***2004***, *45*, 375.
[1112]Bluet, G.; Campagne, J.-M. *J. Org. Chem.* ***2001***, *66*, 4293; Christmann, M.; Kalesse, M. *Tetrahedron Lett.* ***2001***, *42*, 1269.
[1113]Bluet, G.; Bazán-Tejeda, B.; Campagne, J.-M. *Org. Lett.* ***2001***, *3*, 3807.
[1114]Hayakawa, R.; Shimizu, M. *Chem. Lett.* ***1999***, 591.
[1115]Gandon, V.; Bertus, P.; Szymoniak, J. *Tetrahedron* ***2000***, *56*, 4467.
[1116]Harada, T.; Iwai, H.; Takatsuki, H.; Fujita, K.; Kubu, M.; Oku, A. *Org. Lett.* ***2001***, *3*, 2101.
[1117]Hamada, T.; Manabe, K.; Ishikawa, S.; Nagayama, S.; Shiro, M.; Kobayashi, S. *J. Am. Chem. Soc.* ***2003***, *125*, 2989.
[1118]Bach, T. *Angew. Chem. Int. Ed.* ***1994***, *33*, 417. For a discussion of stereocontrol, see Annunziata, R.; Cinquini, M.; Cozzi, F.; Cozzi, P.G.; Consolandi, E. *J. Org. Chem.* ***1992***, *57*, 456.
[1119]For examples, see Kobayashi, S.; Kawasuji, T.; Mori, N. *Chem. Lett.* ***1994***, 217; Kobayashi, S.; Uchiro, H.; Shiina, I.; Mukaiyama, T. *Tetrahedron* ***1993***, *49*, 1761; Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc.* ***1994***, *116*, 4077; Kaneko, Y.; Matsuo, T.; Kiyooka, S. *Tetrahedron Lett.* ***1994***, *35*, 4107; Kiyooka, S.; Kido, Y.; Kaneko, Y. *Tetrahedron Lett.* ***1994***, *35*, 5243.

have also been used.[1120] Chiral catalysts, usually transition-metal complexes using chiral ligands, are quite effective,[1121] but chiral bis(oxazolones)[1122] and chiral quaternary ammonium salts[1123] have also been used. A zirconium BINOL complex gave good enantioselectivity in reactions of silyl ketene acetals, and also good anti selectivity in the product.[1124] This reaction can also be run with the aldehyde or ketone in the form of its acetal $R^3R^4C(OR')_2$, in which case the product is the ether $R^1COCHR_2CR^3R^4OR'$ instead of **38**.[1125] Trichlorosilyl enol ethers react with aldehydes directly in the presence of a chiral phosphoramide to give the aldol with good syn selectivity and good enantioselectivity.[1126] Vinylogous silyl ketene acetals with a chiral oxazolidinone auxiliary attached to the α-vinylic carbon react with aldehydes and $TiCl_4$ to give a δ-hydroxy-α,β-unsaturated amide (an acyl oxazolidinone).[1127]

Enol acetates and enol ethers also give this product when treated with acetals and $TiCl_4$ or a similar catalyst.[1128] A variation of this condensation uses an enol acetate with an aldehyde in the presence of Et_2AlOEt to give the aldol product.[1129]

16-36 Aldol-Type Reactions between Carboxylic Acid Derivatives and Aldehydes or Ketones

O-Hydro-C-(α-alkoxycarbonylalkyl)-addition; α-Alkoxycarbonylalkylidene-de-oxo-bisubstitution



(if α-H present)

[1120]For an example, see Vasconcellos, M.L.; Desmaële, D.; Costa, P.R.R.; d'Angelo, J. *Tetrahedron Lett.* ***1992***, *33*, 4921.

[1121]Titanium complexes: Imashiro, R.; Kuroda, T. *J. Org. Chem.* ***2003***, *68*, 974. Copper complexes: Kobayashi, S.; Nagayama, S.; Busujima, T. *Tetrahedron* ***1999***, *55*, 8739. Lead complexes: Nagayama, S.; Kobayashi, S. *J. Am. Chem. Soc* ***2000***, *122*, 11531. Cerium complexes: Kobayashi, S.; Hamada, T.; Nagayama, S.; Manabe, K. *Org. Lett.* ***2001***, *3*, 165. Silver complexes: Yanagisawa, A.; Nakatsuka, Y.; Asakawa, K.; Kageyama, H.; Yamamoto, H. *Synlett* ***2001***, 69; Yanigisawa, A.; Nakatsuka, Y.; Asakawa, K.; Wadamoto, M.; Kageyama, H.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* ***2001***, *74*, 1477; Wadamoto, M.; Ozasa, N.; Yanigisawa, A.; Yamamoto, H. *J. Org. Chem.* ***2003***, *68*, 5593. Zirconium complexes: Kobayashi, S.; Ishitani, H.; Yamashita, Y.; Ueno, M.; Shimizu, H. *Tetrahedron* ***2001***, *57*, 861. Scandium complexes: Ishikawa, S.; Hamada, T.; Manabe, K.; Kobayashi, S. *J. Am. Chem. Soc.* ***2004***, *126*, 12236.

[1122]Kobayashi, S.; Nagayama, S.; Busujima, T. *Chem. Lett.* ***1999***, 71.

[1123]Zhang, F.-Y.; Corey, E.J. *Org. Lett.* ***2001***, *3*, 639.

[1124]Ishitani, H.; Yamashita, Y.; Shimizu, H.; Kobayashi, S. *J. Am. Chem. Soc.* ***2000***, *122*, 5403.

[1125]Mukaiyama, T.; Kobayashi, S.; Murakami, M. *Chem. Lett.* ***1984***, 1759; Murata, S.; Suzuki, M.; Noyori, R. *Tetrahedron* ***1988***, *44*, 4259. For a review of cross-coupling reactions of acetals, see Mukaiyama, T.; Murakami, M. *Synthesis* ***1987***, 1043.

[1126]Denmark, S.E.; Pham, S.M. *J. Org. Chem.* ***2003***, *68*, 5045; Denmark, S.E.; Stavenger, R.A. *J. Am. Chem. Soc.* ***2000***, *122*, 8837; Denmark, S.E.; Ghosh, S.K. *Angew. Chem. Int. Ed.* ***2001***, *40*, 4759.

[1127]Shirokawa, S.-i.; Kamiyama, M.; Nakamura, T.; Okada, M.; Nakazaki, A.; Hosokawa, S.; Kobayashi, S. *J. Am. Chem. Soc.* ***2004***, *126*, 13604.

[1128]Kitazawa, E.; Imamura, T.; Saigo, K.; Mukaiyama, T. *Chem. Lett.* ***1975***, 569.

[1129]Mukaiyama, T.; Shibata, J.; Shimamura, T.; Shiina, I. *Chem. Lett.* ***1999***, 951.

In the presence of a strong base, the α carbon of a carboxylic ester or other acid derivative can condense with the carbonyl carbon of an aldehyde or ketone to give a β-hydroxy ester,[1130] amide, and so on., which may or may not be dehydrated to the α,β-unsaturated derivative. This reaction is sometimes called the *Claisen reaction*,[1131] an unfortunate usage since that name is more firmly connected to **16-85**. Early reactions used hydroxide or an alkoxide base in water or alcohol solvents, where self-condensation was the major process. Under such conditions, the aldehyde or ketone was usually chosen for its lack of an α-proton. Much better control of the reaction was achieved when amide bases in aprotic solvents, such as ether or THF, were used. The reaction of *tert*-butyl acetate and LDA[1132] in hexane or more commonly THF at −78°C gives the enolate anion of *tert*-butyl acetate,[1133] (**12-23**, e.g., although self-condensation is occasionally a problem even here. Subsequent reaction a ketone provides a simple rapid alternative to the Reformatsky reaction (**16-28**) as a means of preparing β-hydroxy *tert*-butyl esters. It is also possible for the α carbon of an aldehyde or ketone to add to the carbonyl carbon of a carboxylic ester, but this is a different reaction (**16-86**) involving nucleophilic substitution and not addition to a C=O bond. It can, however, be a side reaction if the aldehyde or ketone has an α hydrogen.

Transition-metal mediated condensation of esters and aldehydes is known. The reaction of a thioester and an aryl aldehyde with $TiCl_4$—NBu_3, for example, gave a β-hydroxy thioester with good syn selectivity.[1134] Selenoamides [$RCH_2C(=Se)NR'_2$] react with LDA and then an aldehyde to give β-hydroxy selenoamides.[1135]

Besides ordinary esters (containing an α hydrogen), the reaction can also be carried out with lactones and, as in **16-34**, with the γ position of α,β-unsaturated esters (vinylogy). The enolate anion of an amide can be condensed with an aldehyde.[1136]

There are a number of variations of the condensation reaction of acid derivatives. The reaction between a cyclic ketone having a pendant alkynyl ester unit and tetrabutylammonium fluoride leads to cyclization to a bicyclic alcohol with an exocyclic allene moiety.[1137] A chain-extension reaction culminates in acyl addition of an ester enolate. The reaction of a β-keto ester, such as methyl 3-oxobutanote and $EtZnCH_2I$, leads to chain extension via a carbenoid-like insertion reaction (p. 803), which reacts with an aldehyde in a second step to give a methyl 3-oxopentanoate derivative with a —CH(OH)R group at C-2 relative to the ester carbonyl.[1138]

[1130]If the reagent is optically active because of the presence of a chiral sulfoxide group, the reaction can be enantioselective. For a review of such cases, see Solladié, G. *Chimia* ***1984***, *38*, 233.

[1131]Because it was discovered by Claisen, L. *Ber.* ***1890***, *23*, 977.

[1132]Huerta, F.F.; Bäckvall, J.-E. *Org. Lett.* ***2001***, *3*, 1209.

[1133]Rathke, M.W.; Sullivan, D.F. *J. Am. Chem. Soc.* ***1973***, *95*, 3050.

[1134]Tanabe, Y.; Matsumoto, N.; Funakoshi, S.; Manta, N. *Synlett* ***2001***, 1959.

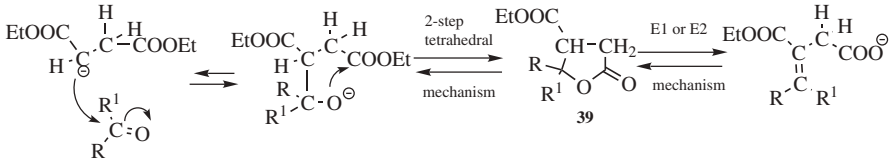
[1135]Murai, T.; Suzuki, A.; Kato, S. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 2711.

[1136]For a case using $CeCl_3$ to promote the reaction, see Shang, X.; Liu, H-J. *Synth. Commun.* ***1994***, *24*, 2485.

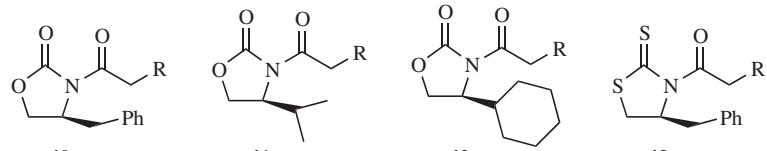
[1137]Wendling, F.; Miesch, M. *Org. Lett.* ***2001***, *3*, 2689.

[1138]Lai, S.; Zercher, C.K.; Jasinski, J.P.; Reid, S.N.; Staples, R.J. *Org. Lett.* ***2001***, *3*, 4169.

For most esters, a much stronger base is needed than for aldol reactions; $(i\text{Pr})_2$-NLi (LDA, p. 389), Ph_3CNa and $LiNH_2$ are among those employed. However, one type of ester reacts more easily, and such strong bases are not needed: diethyl succinate and its derivatives condense with aldehydes and ketones in the presence of bases such as NaOEt, NaH, or $KOCMe_3$. This reaction is called the *Stobbe condensation*.[1139] One of the ester groups (sometimes both) is hydrolyzed in the course of the reaction. The following mechanism accounts for (*1*) the fact the succinic esters react so much better than others; (*2*) one ester group is always cleaved; and (*3*) the alcohol is not the product but the alkene. In addition, intermediate lactones **39** have been isolated from the mixture.[1140] The Stobbe condensation has been extended to di-*tert*-butyl esters of glutaric acid.[1141] The boron-mediated reaction is known.[1142]



Chiral additives, such as diazaborolidines can be added to an ester, and subsequent treatment with a base and then an aldehyde leads to a chiral β-hydroxy ester.[1143] A variety of chiral amide or oxazolidinone derivatives have been used to form amide linkages to carboxylic acid derivatives. These chiral auxiliaries lead to chirality transfer from the enolate anion of such derivatives, in both alkylation reactions and acyl substitution reactions with aldehydes and ketones. The so-called Evans auxiliaries (**40**-**42**) are commonly used and give good enantioselectivity.[1144] A variation is the magnesium halide-catalyzed anti-aldol reaction of chiral *N*-acylthiazolidinethiones (see **43**).[1145] The use of chiral *N*-acyloxazolidinthiones with $TiCl_4$ and sparteine also gave good selectivity in the acyl addition.[1146] Chiral diazaboron derivatives have also been used to facilitate the condensation of a α-phenylthio ester with an aldehyde.[1147]



40 **41** **42** **43**

[1139]For a review, see Johnson, W.S.; Daub, G.H. *Org. React.* ***1951***, *6*, 1.
[1140]Robinson, R.; Seijo, E. *J. Chem. Soc.* ***1941***, 582.
[1141]Puterbaugh, W.H. *J. Org. Chem.* ***1962***, *27*, 4010. See also, El-Newaihy, M.F.; Salem, M.R.; Enayat, E.I.; El-Bassiouny, F.A. *J. Prakt. Chem.* ***1982***, *324*, 379.
[1142]For a review, see Abiko, A. *Acc. Chem. Res.* ***2004***, *37*, 387.
[1143]Corey, E.J.; Choi, S. *Tetrahedron Lett.* ***2000***, *41*, 2769.
[1144]Evans, D.A.; Takacs, J.M. *Tetrahedron Lett.* ***1980***, *21*, 4233; Sonnet, P.E.; Heath, R.R. *J. Org. Chem.* ***1980***, *45*, 3137; Evans, D.A.; Chapman, K.T.; Bisaha, J. *Tetrahedron Lett.* ***1984***, *25*, 4071.
[1145]Evans, D.A.; Downey, C.W.; Shaw, J.T.; Tedrow, J.S. *Org. Lett.* ***2002***, *4*, 1127.
[1146]Crimmins, M.T.; McDougall, P.J. *Org. Lett.* ***2003***, *5*, 591.
[1147]Corey, E.J.; Choi, S. *Tetrahedron Lett.* ***2000***, *41*, 2769.

The condensation of an ester enolate and a ketone[1148] can be used as part of a Robinson annulation-like sequence (see **16-34**).

OS **I**, 252; **III**, 132; **V**, 80, 564; **70**, 256; **X**, 437; **81**, 157. Also see OS **IV**, 278, 478; **V**, 251.

16-37 The Henry Reaction[1149]

$$CH_3NO_2 + HCHO \xrightarrow{^-OH} HOCH_2CH_2NO_2$$

When aliphatic nitro compounds are used instead of aldehydes or ketones, no reduction occurs, and the reaction has been referred to as a Tollens' reaction (see **16-43**). However, the classical condensation of an aliphatic nitro compound with an aldehyde or ketone is usually called the *Henry reaction*[1150] or the *Kamlet reaction*, and is essentially a nitro aldol reaction. A variety of conditions have been reported, including the use of a silica catalyst,[1151] Mg–Al hydrotalcite,[1152] a tetraalkylammonium hydroxide,[1153] proazaphosphatranes,[1154] or an ionic liquid.[1155] A solvent free Henry reaction was reported in which a nitroalkane and an aldehyde were reacted on KOH powder.[1156] Potassium phosphate has been used with nitromethane and aryl aldehydes.[1157] The Henry reaction has been done using $ZnEt_2$ and 20% ethanolamine.[1158] A gel-entrapped base has been used to catalyze this reaction.[1159]

[1148]Posner, G.H.; Lu, S.; Asirvatham, E.; Silversmith, E.F.; Shulman, E.M. *J. Am. Chem. Soc.* ***1986***, *108*, 511. For an extension of this work to the coupling of four components, see Posner, G.H.; Webb, K.S.; Asirvatham, E.; Jew, S.; Degl'Innocenti, A. *J. Am. Chem. Soc.* ***1988***, *110*, 4754.

[1149]For a review of this reaction with respect to nitroalkanes (the *Henry reaction*, **16-37**), see Baer, H.H.; Urbas, L., in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, Wiley, NY, ***1970***, pp. 76–117. See also, Rosini, G.; Ballini, R.; Sorrenti, P. *Synthesis* ***1983***, 1014; Matsumoto, K. *Angew. Chem. Int. Ed.* ***1984***, *23*, 617; Eyer, M.; Seebach, D. *J. Am. Chem. Soc.* ***1985***, *107*, 3601. For reviews of the nitroalkenes that are the products of this reaction, see Barrett, A.G.M.; Graboski, G.G. *Chem. Rev.* ***1986***, *86*, 751; Kabalka, G.W.; Varma, R.S. *Org. Prep. Proced. Int.* ***1987***, *19*, 283.

[1150]Henry, L. *Compt. Rend.* ***1895***, *120*, 1265; Kamlet, J. *U.S. Patent* 2,151,171 ***1939*** [*Chem. Abstr., 33*: 5003' ***1939***]; Hass, H.B.; Riley, E.F. *Chem. Rev.* ***1943***, *32*, 373 (see p. 406); Lichtenthaler, F.W. *Angew. Chem. Int. Ed.* ***1964***, *3*, 211. For a review, see Luzzio, F.A. *Tetrahedron* ***2001***, *57*, 915.

[1151]Demicheli, G.; Maggi, R.; Mazzacani, A.; Righi, P.; Sartori, G.; Bigi, F. *Tetrahedron Lett.* ***2001***, *42*, 2401.

[1152]Bulbule, V.J.; Deshpande, V.H.; Velu, S.; Sudalai, A.; Sivasankar, S.; Sathe, V.T. *Tetrahedron* ***1999***, *55*, 9325.

[1153]Bulbule, V.J.; Jnaneshwara, G.K.; Deshmukh, R.R.; Borate, H.B.; Deshpande, V.H. *Synth. Commun.* ***2001***, *31*, 3623.

[1154]Kisanga, P.B.; Verkade, J.G. *J. Org. Chem.* ***1999***, *64*, 4298.

[1155]In TMG Lac, tetramethylguanidinium lactate: Jiang, T.; Gao, H.; Han, B.; Zhao, G.; Chang, Y.; Wu, W.; Gao, L.; Yang, G. *Tetrahedron Lett.* ***2004***, *45*, 2699.

[1156]Ballini, R.; Bosica, G.; Parrini, M. *Chem. Lett.* ***1999***, 1105.

[1157]Desai, U.V.; Pore, D.M.; Mane, R.B.; Solabannavar, S.B.; Wadgaonkar, P.P. *Synth. Commun.* ***2004***, *34*, 19.

[1158]Klein, G.; Pandiaraju, S.; Reiser, O. *Tetrahedron Lett.* ***2002***, *43*, 7503.

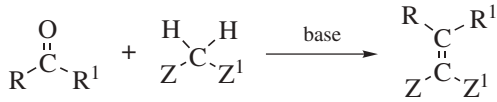
[1159]Bandgar, B.P.; Uppalla, L.S. *Synth. Commun.* ***2000***, *30*, 2071.

Catalytic enantioselective Henry reactions are known,[1160] such as the use of a chiral copper catalyst[1161] or a zinc catalyst.[1162] The Henry reaction of nitromethane an a chiral aldehyde under high pressure gives the β-nitro alcohol with excellent enantioselectivity.[1163]

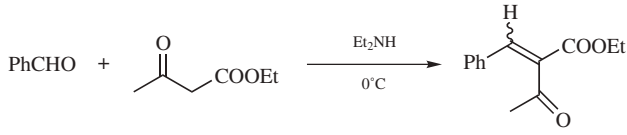
A variation of this reaction converts nitro compounds to nitronates $RCH{=}N^{+}(OTMS){-}O^{-}$, which react with aldehydes in the presence of a copper catalyst to give the β-nitro alcohol.[1164]

16-38 The Knoevenagel Reaction

Bis(ethoxycarbonyl)methylene-de-oxo-bisubstitution, and so on



The condensation of aldehydes or ketones, usually not containing an α hydrogen, with compounds of the form $Z{-}CH_2{-}Z'$ or $Z{-}CHR{-}Z'$ is called the *Knoevenagel reaction*.[1165] Both Z and Z′ may be CHO, COR, COOH, COOR, CN, NO_2, SOR, SO_2R, SO_2OR, or similar groups. Such compounds have a significantly higher enol content[1166] and the α-proton is much more acidic (Table 8.1 on p. 360). When Z = COOH, decarboxylation of the product often takes place *in situ*.[1167] If a strong enough base is used, the reaction can be performed on compounds possessing only a single Z (e.g., CH_3Z or RCH_2Z). Other active hydrogen compounds can also be employed, among them $CHCl_3$, 2-methylpyridines, terminal acetylenes, cyclopentadienes, and so on.; in fact any compound that contains a C—H bond the hydrogen of which can be removed by a base. As shown in the example, the reaction of β-keto esters and aldehydes to give **44** is promoted by diethylamine at 0°C. Nitroalkanes[1149] as well as β-keto sulfoxides[1168] undergo the reaction.



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[1160]Christensen, C.; Juhl, K.; Jørgensen, K.A. *Chem. Commun.* ***2001***, 2222; Christensen, C.; Juhl, K.; Hazell, R.G.; Jørgensen, K.A. *J. Org. Chem.* ***2002***, *67*, 4875.

[1161]Evans, D.A.; Seidel, D.; Rueping, M.; Lam, H.W.; Shaw, J.T.; Downey, C.W. *J. Am. Chem. Soc.* ***2003***, *125*, 12692.

[1162]Trost, B.M.; Yeh, V.S.C. *Angew. Chem. Int. Ed.* ***2002***, *41*, 861.

[1163]Misumi, Y.; Matsumoto, K. *Angew. Chem. Int. Ed.* ***2002***, *41*, 1031.

[1164]Risgaard, T.; Gothelf, K.V.; Jørgensen, K.A. *Org. Biomol. Chem.* ***2003***, *1*, 153.

[1165]For reviews, see Jones, G. *Org. React.* ***1967***, *15*, 204; Wilk, B.K. *Tetrahedron* ***1997***, *53*, 7097.

[1166]Rochlin, E.; Rappoport, Z. *J. Org. Chem.* ***2003***, *68*, 1715.

[1167]For a discussion of the mechanism when the reaction is accompanied by decarboxylation, see Tanaka, M.; Oota, O.; Hiramatsu, H.; Fujiwara, K. *Bull. Chem. Soc. Jpn.* ***1988***, *61*, 2473.

[1168]Kuwajima, I.; Iwasawa, H. *Tetrahedron Lett.* ***1974***, 107. See also, Huckin, S.N.; Weiler, L. *Can. J. Chem.* ***1974***, *52*, 2157.

As with **16-34**, these reactions have sometimes been performed with acid catalysts.[1169] Ionic liquid solvents have been used,[1170] and heating on quaternary ammonium salts without solvent leads to a Knoevenagel reaction.[1171] Other solvent-free reactions are known.[1172] Ultrasound has been used to promote the reaction,[1173] and it has also been done using microwave irradiation[1174] or on silica,[1175] with microwave irradiation. Another solid-state variation is done on moist LiBr,[1176] heating with sodium carbonate and molecular sieves 4 Å promotes the reaction,[1177] as do zeolites.[1178] High-pressure conditions have been used.[1179] Transition-metal compounds such as palladium complexes,[1180] SmI_2[1181] or $BiCl_3$[1182] have been used to promote the Knoevenagel reaction.

In the reaction with terminal acetylenes,[1183] sodium acetylides are the most common reagents (when they are used, the reaction is often called the *Nef reaction*), but lithium,[1184] magnesium, and other metallic acetylides have also been used. A particularly convenient reagent is lithium acetylide–ethylenediamine complex,[1185] a stable, free-flowing powder that is commercially available. Alternatively, the substrate may be treated with the alkyne itself in the presence of

[1169]For example, see Rappoport, Z.; Patai, S. *J. Chem. Soc.* ***1962***, 731.

[1170]In bmim Cl, 1-butyl-3-methylimidazolium chloride, with $AlCl_3$: Harjani, J.R.; Nara, S.J.; Salunkhe, M.M. *Tetrahedron Lett.* ***2002***, *43*, 1127. See Morrison, D.W.; Forbes, D.C.; Davis Jr., J.H. *Tetrahedron Lett.* ***2001***, *42*, 6053. In bmim BF_4, 1-butyl-3-methylimidazolium tetrafluoroborate: Su, C.; Chen, Z.-C.; Zheng, Q.G. *Synthesis* ***2003***, 555.

[1171]Bose, D.S.; Narsaiah, A.V. *J. Chem. Res. (S)* ***2001***, 36.

[1172]McCluskey, A.; Robinson, P.J.; Hill, T.; Scott, J.L.; Edwards, J.K. *Tetrahedron Lett.* ***2002***, *43*, 3117; Ren, Z.; Cao, W.; Tong, W. *Synth. Commun.* ***2002***, *32*, 3475; Mogilaiah, K.; Prashanthi, M.; Reddy, G.R.; Reddy, Ch.S.; Reddy, N.V. *Synth. Commun.* ***2003***, *33*, 2309; Zuo, W.-X.; Hua, R.; Qiu, X. *Synth. Commun.* ***2004***, *34*, 3219.

[1173]McNulty, J.; Steeve, J.A.; Wolf, S. *Tetrahedron Lett.* ***1998***, *39*, 8013; Li, J.-T.; Zang, H.-J.; Feng, Y.-Y.; Li, L.-J.; Li, T.-S. *Synth. Commun.* ***2001***, *31*, 653.

[1174]de la Cruz, P.; Díez-Barra, E.; Loupy, A.; Langa, F. *Tetrahedron Lett.* ***1996***, *37*, 1113; Mitra, A.K.; De, A.; Karchaudhuri, N. *Synth. Commun.* ***1999***, *29*, 2731; Balalaie, S.; Nemati, N. *Synth. Commun.* ***2000***, *30*, 869; Loupy, A.; Song, S.-J.; Sohn, S.-M.; Lee, Y.-M.; Kwon, T.W.; *J. Chem. Soc., Perkin Trans. 1* ***2001***, 1220; Yadav, J.S.; Reddy, B.V.S.; Basak, A.K.; Visali, B.; Narsaiah, A.V.; Nagaiah, K. *Eur. J. Org. Chem.* ***2004***, 546.

[1175]Kumar, H.M.S.; Reddy, B.V.S.; Reddy, P.T.; Srinivas, D.; Yadav, J.S. *Org. Prep. Proceed. Int.* ***2000***, *32*, 81; Peng, Y.; Song, G.; Qian, X. *J. Chem. Res. (S)* ***2001***, 188.

[1176]Prajapati, D.; Lekhok, K.C.; Sandhu, J.S.; Ghosh, A.C. *J. Chem. Soc. Perkin Trans. 1* ***1996***, 959.

[1177]Siebenhaar, B.; Casagrande, B.; Studer, M.; Blaser, H.-U. *Can. J. Chem.* ***2001***, *79*, 566.

[1178]Reddy, T.I.; Varma, R.S. *Tetrahedron Lett.* ***1997***, *38*, 1721.

[1179]Jenner, G. *Tetrahedron Lett.* ***2001***, *42*, 243.

[1180]You, J.; Verkade, J.G. *J. Org. Chem.* ***2003***, *68*, 8003.

[1181]Chandrasekhar, S.; Yu, J.; Falck, J.R.; Mioskowski, C. *Tetrahedron Lett.* ***1994***, *35*, 5441.

[1182]This catalyst was used in the reaction without solvent. See Prajapati, D.; Sandhu, J.S. *Chem. Lett.* ***1992***, 1945.

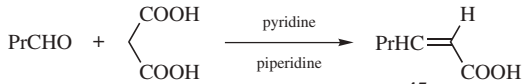
[1183]For reviews, see Ziegenbein, W., in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 207–241; Ried, W. *Newer Methods Prep. Org. Chem.* ***1968***, *4*, 95.

[1184]See Midland, M.M. *J. Org. Chem.* ***1975***, *40*, 2250, for the use of amine-free monolithium acetylide.

[1185]Beumel Jr., O.F.; Harris, R.F. *J. Org. Chem.* ***1963***, *28*, 2775.

a base, so that the acetylide is generated *in situ*. This procedure is called the *Favorskii reaction*, not to be confused with the Favorskii rearrangement (**18-7**).[1186]

With most of these reagents the alcohol is not isolated (only the alkene) *if* the alcohol has a hydrogen in the proper position.[1187] However, in some cases the alcohol is the major product. A β-keto allylic ester was shown to react with an aldehyde to give a β-hydroxy ketone, with loss of the allyl ester moiety, upon treatment with $YbCl_3$ and a palladium catalyst.[1188] With suitable reactants, the Knoevenagel reaction, like the aldol (**16-2**), has been carried out diastereoselectively[1189] and enantioselectively.[1190] When the reactant is of the form ZCH_2Z', aldehydes react much better than ketones and few successful reactions with ketones have been reported. However, it is possible to get good yields of alkene from the condensation of diethyl malonate, $CH_2(COOEt)_2$, with ketones, as well as with aldehydes, if the reaction is run with $TiCl_4$ and pyridine in THF.[1191] In reactions with ZCH_2Z', the catalyst is most often a secondary amine (piperidine is the most common, but see formation of **44**), though many other catalysts have been used. When the catalyst is pyridine (to which piperidine may or may not be added) the reaction is known as the *Doebner modification* of the Knoevenagel reaction and the product is usually the conjugated acid **45**. Alkoxides are also common catalysts. Microwave-induced Doebner condensation reactions are known.[1192]



45

A number of special applications of the Knoevenagel reaction follow:

1. The dilithio derivative of *N*-methanesulfinyl-*p*-toluidine[1193] (**46**) adds to aldehydes and ketones to give, after hydrolysis, the hydroxysulfinamides

[1186]For a discussion of the mechanism of the Favorskii addition reaction, see Kondrat'eva, L.A.; Potapova, I.M.; Grigina, I.N.; Glazunova, E.M.; Nikitin, V.I. *J. Org. Chem. USSR* ***1976***, *12*, 948.

[1187]For lists of reagents (with references) that condense with aldehydes and ketones to give alkene products, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 317–325, 341–350. For those that give the alcohol product, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1178–1179, 1540–1541, 1717–1724, 1727, 1732–1736, 1778–1780, 1801–1805.

[1188]Lou, S.; Westbrook J.A.; Schaus, S.E. *J. Am. Chem. Soc.* ***2004***, *126*, 11440.

[1189]See, for example, Trost, B.M.; Florez, J.; Jebaratnam, D.J. *J. Am. Chem. Soc.* ***1987***, *109*, 613; Mahler, U.; Devant, R.M.; Braun, M. *Chem. Ber.* ***1988***, *121*, 2035; Ronan, B.; Marchalin, S.; Samuel, O.; Kagan, H.B. *Tetrahedron Lett.* ***1988***, *29*, 6101; Barrett, A.G.M.; Robyr, C.; Spilling, C.D. *J. Org. Chem.* ***1989***, *54*, 1233; Pyne, S.G.; Boche, G. *J. Org. Chem.* ***1989***, *54*, 2663.

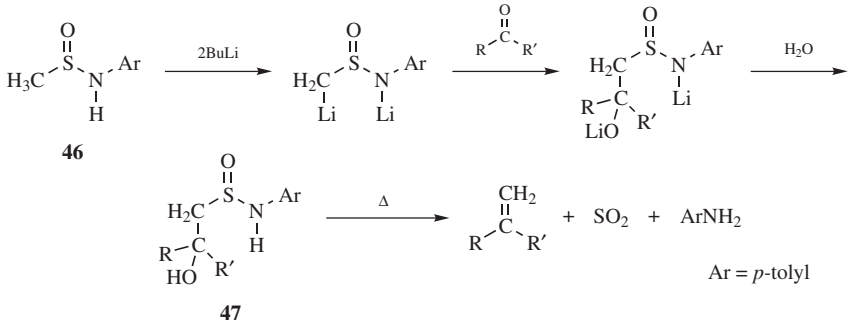
[1190]See, for example, Enders, D.; Lotter, H.; Maigrot, N.; Mazaleyrat, J.; Welvart, Z. *Nouv. J. Chim.*, ***1984***, *8*, 747; Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* ***1986***, *108*, 6405; Togni, A.; Pastor, S.D. *J. Org. Chem.* ***1990***, *55*, 1649; Sakuraba, H.; Ushiki, S. *Tetrahedron Lett.* ***1990***, *31*, 5349; Niwa, S.; Soai, K. *J. Chem. Soc. Perkin Trans. 1* ***1990***, 937.

[1191]Lehnert, W. *Tetrahedron* ***1973***, *29*, 635; *Synthesis* ***1974***, 667, and references cited therein.

[1192]Mitra, A.K.; De, A.; Karchaudhuri, N. *Synth. Commun.* ***1999***, *29*, 573; Pellón, R.F.; Mamposo, T.; González, E.; Calderón, O. *Synth. Commun.* ***2000***, *30*, 3769.

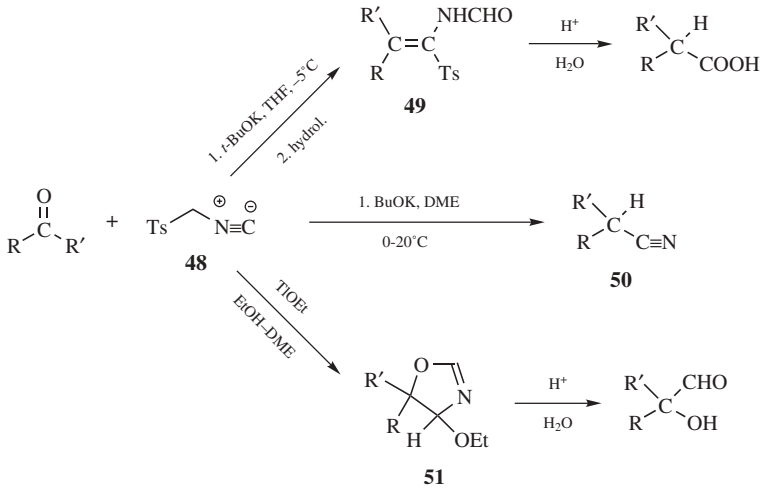
[1193]For a method of preparing **46**, see Bowlus, S.B.; Katzenellenbogen, J.A. *Synth. Commun.* ***1974***, *4*, 137.

47, which, upon heating, undergo stereospecifically syn eliminations to give alkenes.[1194] The reaction is thus a method for achieving the conversion $RR'CO \rightarrow RR'C{=}CH_2$ and represents an alternative to the Wittig reaction.[1195] Note that sulfones with an amide group at the α-position, $ArSO_2CH(R)N(R)C{=}O$, react with ketones via acyl addition in the presence of SmI_2.[1196]



46 **47**

2. The reaction of ketones with tosylmethylisocyanide (**48**) gives different products,[1197] depending on the reaction conditions.



48 **49** **50** **51**

[1194]Corey, E.J.; Durst, T. *J. Am. Chem. Soc.* ***1968***, *90*, 5548, 5553.

[1195]For similar reactions, see Jung, F.; Sharma, N.K.; Durst, T. *J. Am. Chem. Soc.* ***1973***, *95*, 3420; Kuwajima, I.; Uchida, M. *Tetrahedron Lett.* ***1972***, 649; Johnson, C.R.; Shanklin, J.R.; Kirchhoff, R.A. *J. Am. Chem. Soc.* ***1973***, *95*, 6462; Lau, P.W.K.; Chan, T.H. *Tetrahedron Lett.* ***1978***, 2383; Yamamoto, K.; Tomo, Y.; Suzuki, S. *Tetrahedron Lett.* ***1980***, *21*, 2861; Martin, S.F.; Phillips, G.W.; Puckette, T.A.; Colapret, J.A. *J. Am. Chem. Soc.* ***1980***, *102*, 5866; Arenz, T.; Vostell, M.; Frauenrath, H. *Synlett* ***1991***, 23.

[1196]Yoda, H.; Ujihara, Y.; Takabe, K. *Tetrahedron Lett.* ***2001***, *42*, 9225.

[1197]For reviews of α-metalated isocyanides, see Schöllkopf, U. *Pure Appl. Chem.* ***1979***, *51*, 1347; *Angew. Chem. Int. Ed.* ***1977***, *16*, 339; Hoppe, D. *Angew. Chem. Int. Ed.* ***1974***, *13*, 789.

When the reaction is run with potassium *tert*-butoxide in THF at −5°C, one obtains (after hydrolysis) the normal Knoevenagel product **49**, except that the isocyano group has been hydrated (**16-97**).[1198] With the same base but with 1,2-dimethoxyethane (DME) as solvent the product is the nitrile **50**.[1199] When the ketone is treated with **48** and thallium(I) ethoxide in a 4:1 mixture of absolute ethanol and DME at room temperature, the product is a 4-ethoxy-2-oxazoline **51**.[1200] Since **50** can be hydrolyzed[1201] to a carboxylic acid[1198] and **51** to an α-hydroxy aldehyde,[1200] this versatile reaction provides a means for achieving the conversion of RCOR′ to RCHR′COOH, RCHR′CN, or RCR′(OH)CHO. The conversions to RCHR′COOH and to RCHR′CN[1202] have also been carried out with certain aldehydes (R′ = H).

3. Aldehydes and ketones RCOR′ react with α-methoxyvinyllithium, $CH_2{=}C(Li)OMe$, to give hydroxy enol ethers, $RR'C(OH)C(OMe){=}CH_2$, which are easily hydrolyzed to acyloins, RR′C(OH)COMe.[1203] In this reaction, the $CH_2{=}C(Li)OMe$ is a synthon for the unavailable $H_3C{-}\overset{\ominus}{C}{=}O$,[1204] and is termed an *acyl anion equivalent*. The reagent also reacts with esters RCOOR′ to give $RC(OH)(COMe{=}CH_2)_2$. A synthon for the Ph—C=O ion is $PhC(CN)OSiMe_3$, which adds to aldehydes and ketones RCOR′ to give, after hydrolysis, the α-hydroxy ketones, RR′C(OH)*C(OH)COPh*.[1205]

4. Lithiated allylic carbamates (**52**) (prepared as shown) react with aldehydes or ketones (R^6COR^7), in a reaction accompanied by an allylic rearrangement, to give (after hydrolysis) γ-hydroxy aldehydes or ketones.[1206] The reaction is called *the homoaldol reaction*, since the product is a homolog of the product of **16-34**. The reaction has been performed enantioselectively.[1207]

[1198]Schöllkopf, U.; Schröder, U.; Blume, E. *Liebigs Ann. Chem.* ***1972***, *766*, 130; Schöllkopf, U.; Schröder, U. *Angew. Chem. Int. Ed.* ***1972***, *11*, 311.

[1199]Oldenziel, O.H.; van Leusen, D.; van Leusen, A.M. *J. Org. Chem.* ***1977***, *42*, 3114.

[1200]Oldenziel, O.H.; van Leusen, A.M. *Tetrahedron Lett.* ***1974***, 163, 167. For conversions to α,β-unsaturated ketones and diketones, see, respectively, Moskal, J.; van Leusen, A.M. *Tetrahedron Lett.* ***1984***, *25*, 2585; van Leusen, A.M.; Oosterwijk, R.; van Echten, E.; van Leusen, D. *Recl. Trav. Chim. Pays-Bas* ***1985***, *104*, 50.

[1201]Compound **49** can also be converted to a nitrile; see **17-30**.

[1202]van Leusen, A.M.; Oomkes, P.G. *Synth. Commun.* ***1980***, *10*, 399.

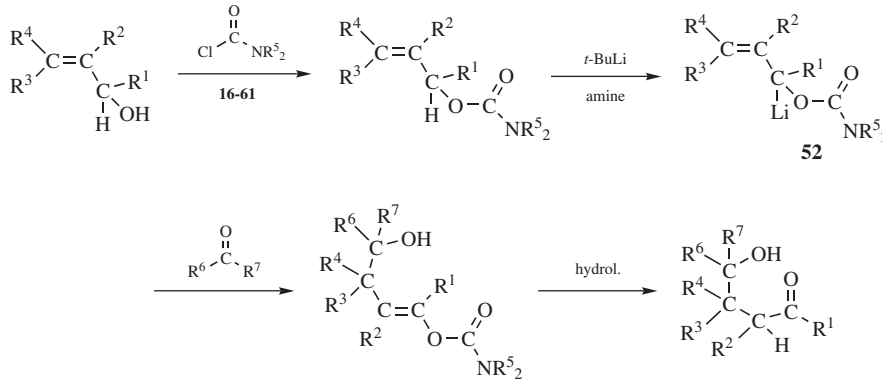
[1203]Baldwin, J.E.; Höfle, G.A.; Lever Jr., O.W. *J. Am. Chem. Soc.* ***1974***, *96*, 7125. For a similar reaction, see Tanaka, K.; Nakai, T.; Ishikawa, N. *Tetrahedron Lett.* ***1978***, 4809.

[1204]For a synthon for the $^{\ominus}$COCOOEt ion, see Reetz, M.T.; Heimbach, H.; Schwellnus, K. *Tetrahedron Lett.* ***1984***, *25*, 511.

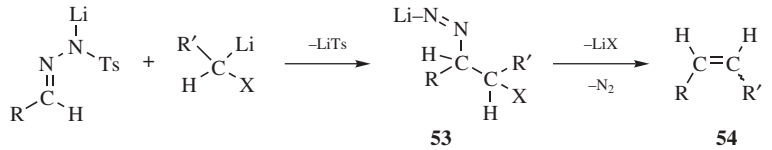
[1205]Hünig, S.; Wehner, G. *Synthesis* ***1975***, 391.

[1206]For a review, see Hoppe, D. *Angew. Chem. Int. Ed.* ***1984***, *23*, 932.

[1207]Krämer, T.; Hoppe, D. *Tetrahedron Lett.* ***1987***, *28*, 5149.



5. The lithium salt of an active hydrogen compound adds to the lithium salt of the tosylhydrazone of an aldehyde to give product **53**. If X = CN, SPh, or SO_2R, **53** spontaneously loses N_2 and LiX to give the alkene **54**. The entire process is done in one reaction vessel: The active hydrogen compound is mixed with the tosylhydrazone and the mixture is treated with $(i\text{Pr})_2\text{NLi}$ to form both salts at once.[1208] This process is another alternative to the Wittig reaction for forming double bonds.



OS **I**, 181, 290, 413; **II**, 202; **III**, 39, 165, 317, 320, 377, 385, 399, 416, 425, 456, 479, 513, 586, 591, 597, 715, 783; **IV**, 93, 210, 221, 234, 293, 327, 387, 392, 408, 441, 463, 471, 549, 573, 730, 731, 777; **V**, 130, 381, 572, 585, 627, 833, 1088, 1128; **VI**, 41, 95, 442, 598, 683; **VII**, 50, 108, 142, 276, 381, 386, 456; **VIII**, 258, 265, 309, 353, 391, 420; **X**, 271. Also see, OS **III**, 395; **V**, 450.

16-39 The Perkin Reaction

α-Carboxyalkylidene-de-oxo-bisubstitution

The condensation of aromatic aldehydes with anhydrides is called the *Perkin reaction*.[1209] When the anhydride has two α hydrogens (as shown), dehydration

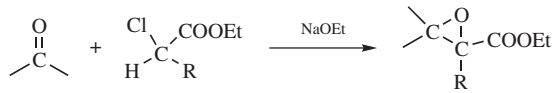
[1208]Vedejs, E.; Dolphin, J.M.; Stolle, W.T. *J. Am. Chem. Soc.* ***1979***, *101*, 249.
[1209]For a review, see Johnson, J.R. *Org. React.* ***1942***, *1*, 210.

always occurs; the β-hydroxy acid salt is never isolated. In some cases, anhydrides of the form $(R_2CHCO)_2O$ have been used, and then the hydroxy compound is the product since dehydration cannot take place. The base in the Perkin reaction is nearly always the salt of the acid corresponding to the anhydride. Although the Na and K salts have been most frequently used, higher yields and shorter reaction times have been reported for the Cs salt.[1210] Besides aromatic aldehydes, their vinylogs ArCH=CHCHO also give the reaction. Otherwise, the reaction is not suitable for aliphatic aldehydes.[1211]

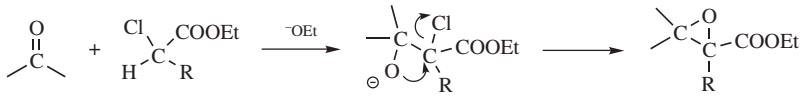
OS **I**, 398; **II**, 61, 229; **III**, 426.

16-40 Darzens Glycidic Ester Condensation

(2 + 1)*OC*,*CC-cyclo*-α-Alkoxycarbonylmethylene-addition



Aldehydes and ketones condense with α-halo esters in the presence of bases to give α,β-epoxy esters, called *glycidic esters*. This is called *the Darzens condensation*.[1212] The reaction consists of an initial Knoevenagel-type reaction (**16-38**), followed by an internal S_N2 reaction (**10-9**):[1213]



Although the intermediate halo alkoxide is generally not isolated,[1214] it has been done, not only with α-fluoro esters (since fluorine is such a poor leaving group in nucleophilic substitutions), but also with α-chloro esters.[1215] This is only one of several types of evidence that rule out a carbene intermediate.[1216] Sodium ethoxide is often used as the base, though other bases, including sodium amide, are sometimes used. Aromatic aldehydes and ketones give good yields, but aliphatic aldehydes react poorly. However, the reaction can be made to give good yields

[1210]Koepp, E.; Vögtle, F. *Synthesis* ***1987***, 177.

[1211]Crawford, M.; Little, W.T. *J. Chem. Soc.* ***1959***, 722.

[1212]For a review, see Berti, G. *Top. Stereochem.* ***1973***, *7*, 93, pp. 210–218. Also see Bakó, P.; Szöllõsy, Á; Bombicz, P.; Töke, L. *Synlett* ***1997***, 291.

[1213]For discussions of the mechanism of the reaction, and especially of the stereochemistry, see Roux-Schmitt, M.; Seyden-Penne, J.; Wolfe, S. *Tetrahedron* ***1972***, *28*, 4965; Bansal, R.K.; Sethi, K. *Bull. Chem. Soc. Jpn.* ***1980***, *53*, 1197.

[1214]The transition state for this reaction has been examined. See Yliniemelä, A.; Brunow, G.; Flügge, J.; Teleman, O. *J. Org. Chem.* ***1996***, *61*, 6723.

[1215]Ballester, M.; Pérez-Blanco, D. *J. Org. Chem.* ***1958***, *23*, 652; Martynov, V.F.; Titov, M.I. *J. Gen. Chem. USSR* ***1963***, *33*, 1350; ***1964***, *34*, 2139; Elkik, E.; Francesch, C. *Bull. Soc. Chim. Fr.* ***1973***, 1277, 1281.

[1216]Another, based on the stereochemistry of the products, is described by Zimmerman, H.E.; Ahramjian, L. *J. Am. Chem. Soc.* ***1960***, *82*, 5459.

(~80%) with simple aliphatic aldehydes, as well as with aromatic aldehydes and ketones by treatment of the α-halo ester with the base lithium bis(trimethylsilyl) amide, $LiN(SiMe_3)_2$, in THF at −78°C (to form the conjugate base of the ester) and addition of the aldehyde or ketone to this solution.[1217] If a preformed dianion of an α-halo carboxylic acid $Cl-\overset{\ominus}{C}R-COO^{\ominus}$ is used instead, α,β-epoxy acids are produced directly.[1218] The Darzens reaction has also been carried out on α-halo ketones, α-halo nitriles,[1219] α-halo sulfoxides[1220] and sulfones,[1221] α-halo *N,N*-disubstituted amides,[1222] α-halo ketimines,[1223] and even on allylic[1224] and benzylic halides. Phase-transfer catalysis has been used.[1225] Note that the reaction of a β-bromo-α-oxo ester and a Grignard reagent leads to the glycidic ester.[1226] Acid-catalyzed Darzens reactions have also been reported.[1227] (see also, **16-46**).

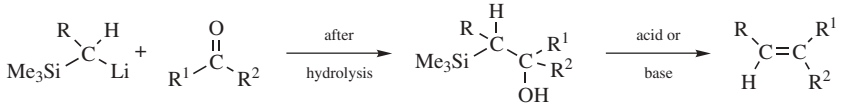
The Darzens reaction has been performed enantioselectively, by coupling optically active α-bromo-β-hydroxy esters with aldehydes.[1228] Chiral phase-transfer agents have been used to give epoxy ketones with modest enantioselectivity.[1229] Chiral additives have proven to be effective.[1230]

Glycidic esters can easily be converted to aldehydes (**12-40**). The reaction has been extended to the formation of analogous aziridines by treatment of an imine with an α-halo ester or an α-halo *N,N*-disubstituted amide and *t*-BuOK in the solvent 1,2-dimethoxyethane.[1231] However, yields were not high.

OS **III**, 727; **IV**, 459, 649.

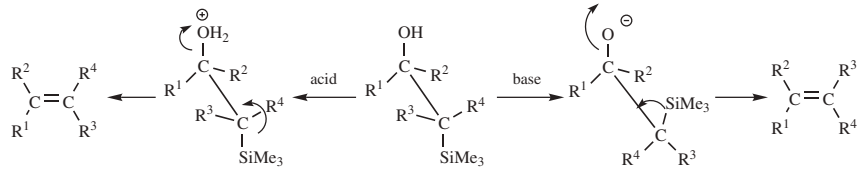
16-41 The Peterson Alkenylation Reaction

Alkylidene-de-oxo-bisubstitution



[1217]Borch, R.F. *Tetrahedron Lett.* ***1972***, 3761.
[1218]Johnson, C.R.; Bade, T.R. *J. Org. Chem.* ***1982***, *47*, 1205.
[1219]See White, D.R.; Wu, D.K. *J. Chem. Soc., Chem. Commun.* ***1974***, 988.
[1220]Satoh, T.; Sugimoto, A.; Itoh, M.; Yamakawa, K. *Tetrahedron Lett.* ***1989***, *30*, 1083.
[1221]Arai, S.; Ishida, T.; Shioiri, T. *Tetrahedron Lett.* ***1998***, *39*, 8299.
[1222]Tung, C.C.; Speziale, A.J.; Frazier, H.W. *J. Org. Chem.* ***1963***, *28*, 1514.
[1223]Mauzé, B. *J. Organomet. Chem.* ***1979***, *170*, 265.
[1224]Sulmon, P.; De Kimpe, N.; Schamp, N.; Declercq, J.; Tinant, B. *J. Org. Chem.* ***1988***, *53*, 4457.
[1225]See Jończyk, A.; Kwast, A.; Makosza, M. *J. Chem. Soc., Chem. Commun.* ***1977***, 902; Gladiali, S.; Soccolini, F. *Synth. Commun.* ***1982***, *12*, 355; Arai, S.; Suzuki, Y.; Tokumaru, K.; Shioiri, T. *Tetrahedron Lett.* ***2002***, *43*, 833. See Starks, C.M.; Liotta, C. *Phase Transfer Catalysis*, Academic Press, NY, ***1978***, pp. 197–198.
[1226]Jung, M.E.; Mengel, W.; Newton, T.W. *Synth. Commun.* ***1999***, *29*, 3659.
[1227]Sipos, G.; Schöbel, G.; Sirokmán, F. *J. Chem. Soc. Perkin Trans. 2* ***1975***, 805.
[1228]Corey, E.J.; Choi, S. *Tetrahedron Lett.* ***1991***, *32*, 2857. For a review, see Ohkata, K.; Kimura, J.; Shinohara, Y.; Takagi, R.; Hiraga, Y. *Chem. Commun.* ***1996***, 2411.
[1229]Arai, S.; Shirai, Y.; Ishida, T.; Shioiri, T. *Tetrahedron* ***1999***, *55*, 6375.
[1230]Aggarwal, V.K.; Hynd, G.; Picoul, W.; Vasse, J.-L. *J. Am. Chem. Soc.* ***2002***, *124*, 9964.
[1231]Deyrup, J.A. *J. Org. Chem.* ***1969***, *34*, 2724.

In the *Peterson alkenylation reaction*[1232, 1233] the lithio (or sometimes magnesio) derivative of a trialkylsilane adds to an aldehyde or ketone to give a β-hydroxysilane, which spontaneously eliminates water, or can be made to do so by treatment with acid or base, to produce an alkene. This reaction is still another alternative to the Wittig reaction (**16-44**), and is sometimes called the *silyl-Wittig reaction*.[1234] The R group can also be a COOR group, in which case the product is an α,β-unsaturated ester,[1235] or an SO_2Ph group, in which case the product is a vinylic sulfone.[1236] The stereochemistry of the product can often be controlled by whether an acid or a base is used to achieve elimination. The role of Si—O interactions has also been examined.[1237] Use of a base generally gives syn elimination (E^i mechanism, see p. 1507), while an acid usually results in anti elimination (E2 mechanism, see p. 1478).[1238] Samarium(II) iodide in HMPA has also been used for elimination of the hydroxy sulfone.[1239] α-Alkoxy benzotriazoyl sulfones ($ROCH_2SO_2Bt$, where Bt = benzothiazole, reacts with lithium hexamethyldisilazide and an aldehyde to give a vinyl ether.[1240]



[1232]Peterson, D.J. *J. Org. Chem.* ***1968***, *33*, 780. For reviews, see Ager, D.J. *Org. React.* ***1990***, *38*, 1; *Synthesis* ***1984***, 384; Colvin, E.W. *Silicon Reagents in Organic Synthesis*, Academic Press, NY, ***1988***, pp. 63–75; Weber, W.P. *Silicon Reagents for Organic Synthesis*, Springer, NY, ***1983***, pp. 58–78; Magnus, P. *Aldrichimica Acta* ***1980***, *13*, 43; Chan, T. *Acc. Chem. Res.* ***1977***, *10*, 442. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 337–341.

[1233]For reviews of these compounds, see Poirier, J. *Org. Prep. Proced. Int.* ***1988***, *20*, 319; Brownbridge, P. *Synthesis* ***1983***, 1–28, 85; Rasmussen, J.K. *Synthesis* ***1977***, 91. For monographs on silicon reagents in organic synthesis see Colvin, E.W. *Silicon Reagents in Organic Synthesis*, Academic Press, NY, ***1988***. For reviews, see Colvin, E.W., in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 4, Wiley, NY, pp. 539–621; Ager, D.J. *Chem. Soc. Rev.* ***1982***, *11*, 493; Colvin, E.W. *Chem. Soc. Rev.* ***1978***, *7*, 15, pp. 43–50.

[1234]For discussions of the mechanism, see Bassindale, A.R.; Ellis, R.J.; Lau, J.C.; Taylor, P.G. *J. Chem. Soc. Perkin Trans. 2* ***1986***, 593; Hudrlik, P.F.; Agwaramgbo, E.L.O.; Hudrlik, A.M. *J. Org. Chem.* ***1989***, *54*, 5613.

[1235]Hartzell, S.L.; Sullivan, D.F.; Rathke, M.W. *Tetrahedron Lett.* ***1974***, 1403; Shimoji, K.; Taguchi, H.; Oshima, K.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* ***1974***, *96*, 1620; Chan, T.H.; Moreland, M. *Tetrahedron Lett.* ***1978***, 515; Strekowski, L.; Visnick, M.; Battiste, M.A. *Tetrahedron Lett.* ***1984***, *25*, 5603.

[1236]Craig, D.; Ley, S.V.; Simpkins, N.S.; Whitham, G.H.; Prior, M.J. *J. Chem. Soc. Perkin Trans. 1* ***1985***, 1949.

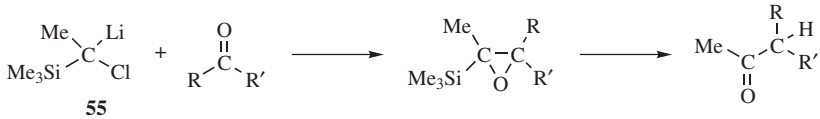
[1237]Bassindale, A.R.; Ellis, R.J.; Taylor, P.G. *J. Chem. Res. (S)* ***1996***, 34.

[1238]See Colvin, E.W. *Silicon Reagents in Organic Synthesis*, Academic Press, NY, ***1988***, pp. 65–69.

[1239]Markò, I.E.; Murphy, F.; Kumps, L.; Ates, A.; Touillaux, R.; Craig, D.; Carballares, S.; Dolan, S. *Tetrahedron* ***2001***, *57*, 2609.

[1240]Surprenant, S.; Chan, W.Y.; Berthelette, C. *Org. Lett.* ***2003***, *5*, 4851.

When aldehydes or ketones are treated with reagents of the form **55**, the product is an epoxy silane (**16-46**), which can be hydrolyzed to a methyl ketone.[1241] For aldehydes, this is a method for converting RCHO to a methyl ketone RCH_2COMe.



55

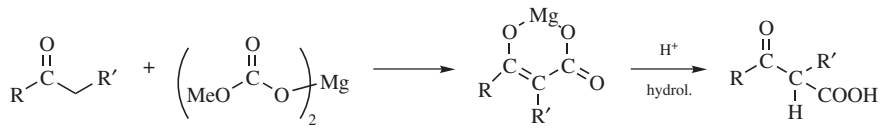
The reagents $Me_3SiCHRM$ (M = Li or Mg) are often prepared from $Me_3SiCHRCl$[1242] (by **12-38** or **12-39**), but they have also been made by **12-22** and by other procedures.[1243]

A new version of the reaction has been developed, reacting $Me_3SiCH_2CO_2Et$ with an aldehyde and a catalytic amount of CsF in DMSO.[1244] A seleno-amide derivative has been used in a similar manner.[1245]

There are no references in *Organic Syntheses*, but see OS **VIII**, 602, for a related reaction.

16-42 The Addition of Active Hydrogen Compounds to CO_2 and CS_2

α-Acylalkyl-de-methoxy-substitution (Overall reaction)



56 **57**

Ketones of the form $RCOCH_3$ and $RCOCH_2R'$ can be carboxylated indirectly by treatment with magnesium methyl carbonate **56**.[1246] Because formation of the chelate **57** provides the driving force of the reaction, carboxylation cannot be achieved at a disubstituted α position. The reaction has also been performed on CH_3NO_2 and compounds of the form RCH_2NO_2[1247] and on certain lactones.[1248] Direct carboxylation has been reported in a number of instances. Ketones have

[1241]Cooke, F.; Roy, G.; Magnus, P. *Organometallics* ***1982***, *1*, 893.
[1242]For a review of these reagents, see Anderson, R. *Synthesis* ***1985***, 717.
[1243]See, for example, Ager, D.J. *J. Chem. Soc. Perkin Trans. 1* ***1986***, 183; Barrett, A.G.M.; Flygare, J.A. *J. Org. Chem.* ***1991***, *56*, 638.
[1244]Bellassoued, M.; Ozanne, N. *J. Org. Chem.* ***1995***, *60*, 6582.
[1245]Murai, T.; Fujishima, A.; Iwamoto, C.; Kato, S. *J. Org. Chem.* ***2003***, *68*, 7979.
[1246]Stiles, M. *J. Am. Chem. Soc.* ***1959***, *81*, 2598; *Ann. N.Y. Acad. Sci.* ***1960***, *88*, 332; Crombie, L.; Hemesley, P.; Pattenden, G. *Tetrahedron Lett.* ***1968***, 3021.
[1247]Finkbeiner, H.L.; Stiles, M. *J. Am. Chem. Soc.* ***1963***, *85*, 616; Finkbeiner, H.L.; Wagner, G.W. *J. Org. Chem.* ***1963***, *28*, 215.
[1248]Martin, J.; Watts, P.C.; Johnson, F. *Chem. Commun.* ***1970***, 27.

been carboxylated in the α position to give β-keto acids.[1249] The base here was lithium 4-methyl-2,16-di-*tert*-butylphenoxide.

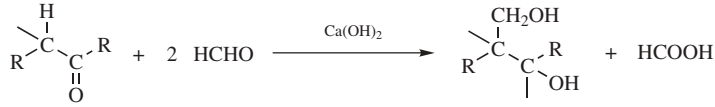
Ketones $RCOCH_2R'$ (as well as other active hydrogen compounds) undergo base-catalyzed addition to CS_2[1250] to give a dianion intermediate $RCOC^-R'CSS^{2-}$, which can be dialkylated with a halide R^2X to produce α-dithiomethylene ketones, $RCOCR'{=}C(SR^2)_2$.[1251] Compounds of the form ZCH_2Z' also react with bases and CS_2 to give analogous dianions.[1252]

Although reactions with N=O derivatives do not formally fall into this category of reactions, it is somewhat related. Nitroso compounds react with activated nitriles in the presence of LiBr and microwave irradiation to give a cyano imine, $ArN{=}C(CN)Ar$.[1253] This transformation has been called the *Ehrlich–Sachs reaction*.[1254]

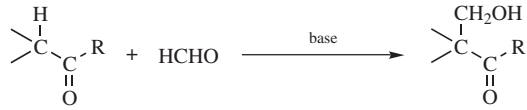
OS **VII**, 476. See also, OS **VIII**, 578.

16-43 Tollens' Reaction

O-Hydro-*C*(β-hydroxyalkyl)-addition



In the *Tollens' reaction* an aldehyde or ketone containing an α hydrogen is treated with formaldehyde in the presence of $Ca(OH)_2$ or a similar base. The first step is a mixed aldol reaction (**16-34**).



The reaction can be stopped at this point, but more often a second equivalent of formaldehyde is permitted to reduce the newly formed aldol to a 1,3-diol, in a crossed Cannizzaro reaction (**19-81**). If the aldehyde or ketone has several α hydrogens, they can all be replaced. An important use of the reaction is to prepare pentaerythritol from acetaldehyde:

$$CH_3CHO + 4\,HCHO \longrightarrow C(CH_2OH)_4 + HCOOH$$

[1249]Tirpak, R.E.; Olsen, R.S.; Rathke, M.W. *J. Org. Chem.* ***1985***, *50*, 4877. For an enantioselective version, see Hogeveen, H.; Menge, W.M.P.B. *Tetrahedron Lett.* ***1986***, *27*, 2767.

[1250]For reviews of the reactions of CS_2 with carbon nucleophiles, see Dunn, A.D.; Rudorf, W. *Carbon Disulphide in Organic Chemistry*, Ellis Horwood, Chichester, ***1989***, pp. 120–225; Yokoyama, M.; Imamoto, T. *Synthesis* ***1984***, 797, pp. 797–804.

[1251]See, for example, Corey, E.J.; Chen, R.H.K. *Tetrahedron Lett.* ***1973***, 3817.

[1252]Jensen, L.; Dalgaard, L.; Lawesson, S. *Tetrahedron* ***1974***, *30*, 2413; Konen, D.A.; Pfeffer, P.E.; Silbert, L.S. *Tetrahedron* ***1976***, *32*, 2507, and references cited therein.

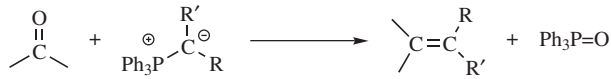
[1253]Laskar, D.D.; Prajapati, D.; Sandhu, J.S. *Synth. Commun.* ***2001***, *31*, 1427.

[1254]Ehrlich, P.; Sachs, F. *Chem. Ber.* ***1899***, *32*, 2341

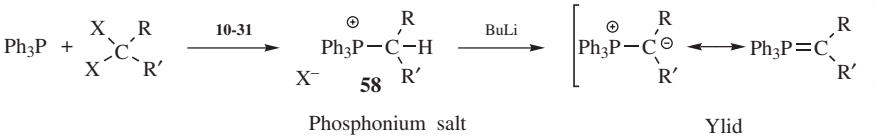
OS **I**, 425; **IV**, 907; **V**, 833.

16-44 The Wittig Reaction

Alkylidene-de-oxo-bisubstitution



In the *Wittig reaction* an aldehyde or ketone is treated with a *phosphorus ylid* (also spelled ylide and called a *phosphorane*) to give an alkene.[1255] The conversion of a carbonyl compound to an alkene with a phosphorus ylid is called the *Wittig reaction*. Phosphorus ylids are usually prepared by treatment of a phosphonium salt with a base,[1256] and phosphonium salts are usually prepared from a triaryl phosphine and an alkyl halide (**10-31**):



The reaction of triphenylphosphine and an alkyl halides is facilitated by the use of microwave irradiation.[1257] Indeed, the Wittig reaction itself is assisted by microwave irradiation.[1258] Phosphonium salts are also prepared by addition of phosphines to Michael alkenes (like **15-8**) and in other ways. The phosphonium salts are most often converted to the ylids by treatment with a strong base such as

[1255]For a general treatise, see Cadogan, J.I.G. *Organophosphorus Reagents in Organic Synthesis*, Academic Press, NY, ***1979***. For a monograph on the Wittig reaction, see Johnson, A.W. *Ylid Chemistry*, Academic Press, NY, ***1966***. For reviews, see Maryanoff, B.E.; Reitz, A.B. *Chem. Rev.* ***1989***, *89*, 863; Bestmann, H.J.; Vostrowsky, O. *Top. Curr. Chem.* ***1983***, *109*, 85; Pommer, H.; Thieme, P.C. *Top. Curr. Chem.* ***1983***, *109*, 165; Pommer, H. *Angew. Chem. Int. Ed.* ***1977***, *16*, 423; Maercker, A. *Org. React.* ***1965***, *14*, 270; House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 682–709; Lowe, P.A. *Chem. Ind. (London)* ***1970***, 1070; Bergelson, L.D.; Shemyakin, M.M., in Patai, S. *The Chemistry of Carboxylic Acids and Esters*, Wiley, NY, ***1969***, pp. 295–340; *Newer Methods Prep. Org. Chem.* ***1968***, *5*, 154. For related reviews, see Tyuleneva, V.V.; Rokhlin, E.M.; Knunyants, I.L. *Russ. Chem. Rev.* ***1981***, *50*, 280; Starks, C.M.; Liotta, C. *Phase Transfer Catalysis*, Academic Press, NY, ***1978***, pp. 288–297; Weber, W.P.; Gokel, G.W. *Phase Transfer Catalysis in Organic Synthesis*, Springer, NY, ***1977***; pp. 234–241; Zbiral, E. *Synthesis* ***1974***, 775; Bestmann, H.J. *Bull. Soc. Chim. Fr.* ***1971***, 1619; *Angew. Chem. Int. Ed.* ***1965***, *4*, 583, 645–660, 830–838; *Newer Methods Prep. Org. Chem.* ***1968***, *5*, 1; Horner, L. *Fortschr. Chem. Forsch.*, ***1966***, *7*, 1. For a historical background, see Wittig, G. *Pure Appl. Chem.* ***1964***, *9*, 245. For a list of reagents and references for the Wittig and related reactions, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 327–337.

[1256]When phosphonium *fluorides* are used, no base is necessary, as these react directly with the substrate to give the alkene: Schiemenz, G.P.; Becker, J.; Stöckigt, J. *Chem. Ber.* ***1970***, *103*, 2077.

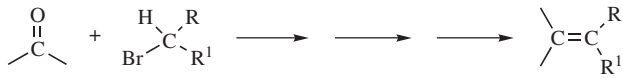
[1257]Kiddle, J.J. *Tetrahedron Lett.* ***2000***, *41*, 1339.

[1258]Frattini, S.; Quai, M.; Cereda, E. *Tetrahedron Lett.* ***2001***, *42*, 6827.; Wu, J.; Wu, H.; Wei, S.; Dai, W.-M. *Tetrahedron Lett.* ***2004***, *45*, 4401.

butyllithium, sodium amide,[1259] sodium hydride, or a sodium alkoxide, though weaker bases can be used if the salt is acidic enough. Unusual bases such as 1,5,7-triazabicyclo [4.4.0]dec-5-ene have been used to promote the Wittig reaction.[1260] In some cases, and excess of fluoride ion is sufficient.[1261] For $(Ph_3P^+)_2CH_2$, sodium carbonate is a strong enough base.[1262] When the base used does not contain lithium, the ylid is said to be prepared under "salt-free" conditions[1263] because the lithium halide (where the halide counterion comes from the phosphonium salt) is absent.

When the phosphorus ylid reacts with the aldehyde or ketone to form an alkene, a phosphine oxide is also formed. When triphenylphosphine is used to give $Ph_3P{=}CRR'$, for example, the by-product is triphenylphosphine oxide, Ph_3PO, which is sometimes difficult to separate from the other reaction products. Ylids are usually prepared from triphenylphosphine, but other triarylphosphines,[1264] trialkylphosphines,[1265] and triphenylarsine[1266] have also been used. Tellurium ylids have been prepared *in situ* from α-halo esters and $BrTeBu_2OTeBu_2Br$ and react with aldehydes to give conjugated esters.[1267] Polymer-bound aryldiphenylphosphino compounds[1268] have been used in reactions with alkyl halides to complete a Wittig reaction. Phosphines that have an α-hydrogen should be avoided, so that reaction with the chosen alkyl halide will lead to a phosphonium salt (**58**) with the α-proton at the desired position. This limitation is essential if a specific ylid is to be formed from the alkyl halide precursor. The Wittig reaction has been carried out with polymer-supported ylids.[1269] It has also been done on silica gel.[1270]

If we view the Wittig reaction from an alkyl halide starting material (alkyl halide phosphonium salt → phosphorus ylid → alkene), the halogen-bearing carbon of an alkyl halide must contain at least one hydrogen as in **59** (for deprotonation at the phosphonium salt stage).



59

[1259]For a convenient method of doing this that results in high yields, see Schlosser, M.; Schaub, B. *Chimia* ***1982***, *36*, 396.

[1260]Simoni, D.; Rossi, M.; Rondanin, R.; Mazzali, A.; Baruchello, R.; Malagutti, C.; Roberti, M.; Invidiata, F.P. *Org. Lett.* ***2000***, *2*, 3765.

[1261]Kobayashi, T.; Eda, T.; Tamura, O.; Ishibashi, H. *J. Org. Chem.* ***2002***, *67*, 3156.

[1262]Ramirez, F.; Pilot, J.F.; Desai, N.B.; Smith, C.P.; Hansen, B.; McKelvie, N. *J. Am. Chem. Soc.* ***1967***, *89*, 6273.

[1263]Bestmann, H.J. *Angew. Chem. Int. Ed.* ***1965***, *4*, 586.

[1264]Schiemenz, G.P.; Thobe, J. *Chem. Ber.* ***1966***, *99*, 2663.

[1265]For example, see Johnson, A.W.; LaCount, R.B. *Tetrahedron* ***1960***, *9*, 130; Bestmann, H.J.; Kratzer, O. *Chem. Ber.* ***1962***, *95*, 1894.

[1266]An arsenic ylid has been used in a catalytic version of the Wittig reaction; that is, the R_3AsO product is constantly regenerated to produce more arsenic ylid: Shi, L.; Wang, W.; Wang, Y.; Huang, Y. *J. Org. Chem.* ***1989***, *54*, 2027; Huang, Z.-Z.; Huang, X.; Huang, Y.-Z. *Tetrahedron Lett.* ***1995***, *36*, 425.

[1267]Huang, Z.-Z.; Tang, Y. *J. Org. Chem.* ***2002***, *67*, 5320.

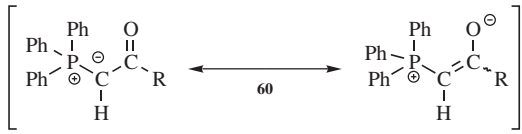
[1268]Betancort, J.M.; Barbas III, C.F. *Org. Lett.* ***2001***, *3*, 3737.

[1269]Bernard, M.; Ford, W.T.; Nelson, E.C. *J. Org. Chem.* ***1983***, *48*, 3164.

[1270]Patil, V.J.; Mävers, U. *Tetrahedron Lett.* ***1996***, *37*, 1281.

The reaction is very general.[1271] The aldehyde or ketone may be aliphatic, alicyclic, or aromatic (including diaryl ketones). Wittig reactions in which the ylid and/or the carbonyl substrate contain double or triple bonds; it may contain various functional groups, such as OH, OR, NR_2, aromatic nitro or halo, acetal, amide,[1272] or even ester groups.[1273] Note, however, that a Wittig reaction has been reported in which the carbonyl group of an ester was converted to a vinyl ether.[1274] An important advantage of the Wittig reaction is that the *position* of the new double bond is always certain, in contrast to the result in most of the base-catalyzed condensations (**16-34**–**16-43**). Ylids have been shown to react with lactones, however, to form ω-alkenyl alcohols.[1275] β-Lactams have also been converted to alkenyl-azetidine derivatives using phosphorus ylids.[1276] Double or triple bonds *conjugated* with the carbonyl also do not interfere, the attack being at the C=O carbon. The carbonyl partner can be generated *in situ*, in the presence of an ylid; the reaction of an alcohol with a mixture of an oxidizing agent and an ylid generates an alkene. Oxidizing agents used in this manner include $BaMnO_4$,[1277] MnO_2,[1278] and $PhI(OAc)_2$.[1279] Polyhalomethanes, such as CBr_3F, react with triphenylphosphine in the presence of diethylzinc and an aldehyde or ketone to give the *gem*-dihaloalkene, RCH(R′)=CF(Br).[1280]

The phosphorus ylid may also contain double or triple bonds and certain functional groups. Simple ylids (R, R′ = hydrogen or alkyl) are highly reactive, reacting with oxygen, water, hydrohalic acids, and alcohols, as well as carbonyl compounds and carboxylic esters, so the reaction must be run under conditions where these materials are absent. When an electron-withdrawing group, for example, COR, CN, COOR, CHO, is present in the α position, the ylids are much more stable, because the charge on the carbon is delocalized by resonance as in **60**.



[1271]For a discussion of a cooperative ortho effect, see Dunne, E.C.; Coyne, É.J.; Crowley, P.B.; Gilheany, D.G. *Tetrahedron Lett.* ***2002***, *43*, 2449.

[1272]Smith, M.B.; Kwon, T.W. *Synth. Commun.* ***1992***, *22*, 2865. For the reaction of an acyl imidazole ylid, see Matsunaga, S.; Kinoshita, T.; Okada, S.; Harada, S.; Shibasaki, M. *J. Am. Chem. Soc.* ***2004***, *126*, 7559.

[1273]For an example, see Harcken, C.; Martin, S.F. *Org. Lett.* ***2001***, *3*, 3591; Yu, X.; Huang, X. *Synlett* ***2002***, 1895. Although phosphorus ylids also react with esters, that reaction is too slow to interfere: Greenwald, R.; Chaykovsky, M.; Corey, E.J. *J. Org. Chem.* ***1963***, *28*, 1128.

[1274]Tsunoda, T.; Takagi, H.; Takaba, D.; Kaku, H.; Itô, S. *Tetrahedron Lett.* ***2000***, *41*, 235.

[1275]Brunel, Y.; Rousseau, G. *Tetrahedron Lett.* ***1996***, *37*, 3853.

[1276]Baldwin, J.E.; Edwards, A.J.; Farthing, C.N.; Russell, A.T. *Synlett* ***1993***, 49.

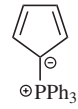
[1277]Shuto, S.; Niizuma, S.; Matsuda, A. *J. Org. Chem.* ***1998***, *63*, 4489.

[1278]Reid, M.; Rowe, D.J.; Taylor, R.J.K. *Chem. Commun.* ***2003***, 2284; Blackburn, L.; Pei, C.; Taylor, R.J.K. *Synlett* ***2002***, 215; Raw, S.A.; Reid, M.; Roman, E.; Taylor, R.J.K. *Synlett* ***2004***, 819.

[1279]Zhang, P.-F.; Chen, Z.-C. *Synth. Commun.* ***2001***, *31*, 1619.

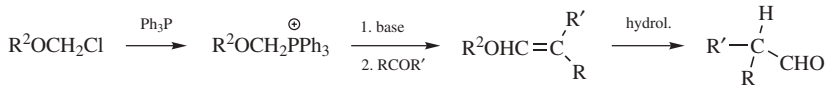
[1280]Lei, X.; Dutheuil, G.; Pannecoucke, X.; Quirion, J.-C. *Org. Lett.* ***2004***, *6*, 2101.

Such ylids react readily with aldehydes, but slowly or not at all with ketones.[1281] In extreme cases (e.g., **61**), the

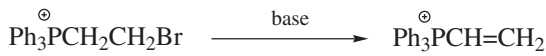


61

ylid does not react with ketones *or* aldehydes. Besides these groups, the ylid may contain one or two α halogens[1282] or an α OR or OAr group. In the latter case, the product is an enol ether, which can be hydrolyzed



(**10-6**) to an aldehyde,[1283] so that this reaction is a means of achieving the conversion $RCOR' \rightarrow RR'CHCHO$.[1284] However, the ylid may not contain an α nitro group. If the phosphonium salt contains a potential leaving group, such as Br or OMe, in the β position, treatment with a base gives elimination, instead of the ylid:



However, a β COO^- group may be present, and the product is a β,γ-unsaturated acid:[1285] This is the only convenient way to make these compounds, since elimination by any other route gives the thermodynamically more stable α,β-unsaturated isomers. This is an illustration of the utility of the Wittig method for the specific location of a double bond. Another illustration is the conversion of cyclohexanones to alkenes containing exocyclic double bonds, for example,[1286]

[1281]For successful reactions of stabilized ylids with ketones, under high pressure, see Isaacs, N.S.; El-Din, G.N. *Tetrahedron Lett.* ***1987***, *28*, 2191. See also, Dauben, W.G.; Takasugi, J.J. *Tetrahedron Lett.* ***1987***, *28*, 4377.

[1282]Seyferth, D.; Heeren, J.K.; Singh, G.; Grim, S.O.; Hughes, W.B. *J. Organomet. Chem.* ***1966***, *5*, 267; Schlosser, M.; Zimmermann, M. *Synthesis* ***1969***, 75; Burton, D.J.; Greenlimb, P.E. *J. Fluorine Chem.* ***1974***, *3*, 447; Smithers, R.H. *J. Org. Chem.* ***1978***, *43*, 2833; Miyano, S.; Izumi, Y.; Fujii, K.; Ohno, Y.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* ***1979***, *52*, 1197; Stork, G.; Zhao, K. *Tetrahedron Lett.* ***1989***, *30*, 2173.

[1283]For references to the use of the Wittig reaction to give enol ethers or enol thioethers, which are then hydrolyzed, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1441–1444, 1457–1458.

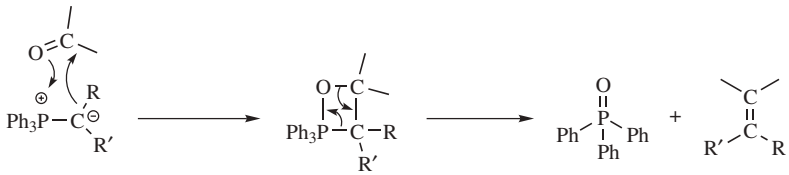
[1284]For other methods of achieving this conversion via Wittig-type reactions, see Ceruti, M.; Degani, I.; Fochi, R. *Synthesis* ***1987***, 79; Moskal, J.; van Leusen, A.M. *Recl. Trav. Chim. Pays-Bas* ***1987***, *106*, 137; Doad, G.J.S. *J. Chem. Res. (S)* ***1987***, 370.

[1285]Corey, E.J.; McCormick, J.R.D.; Swensen, W.E. *J. Am. Chem. Soc.* ***1964***, *86*, 1884.

[1286]Wittig, G.; Schöllkopf, U. *Chem. Ber.* ***1954***, *87*, 1318.

Still another example is the easy formation of anti-Bredt bicycloalkenones[1287] (see p. 229). As indicated above, α,α′-dihalophosphoranes can be used to prepare 1,1-dihaloalkenes. Another way to prepare such compounds[1288] is to treat the carbonyl compound with a mixture of CX_4 (X = Cl, Br, or I) and triphenylphosphine, either with or without the addition of zinc dust (which allows less Ph_3P to be used).[1289] Aryl aldehydes react with these dihalophosphoranes to give aryl alkynes after treatment of the initially formed vinyl halide with potassium *tert*-butoxide.[1290] Formamides have been converted to ynamines by reaction with a mixture of PPh_3/CCl_4 followed by *n*-butyllithium.[1291] The carbonyl compound can be generated *in situ*, in the presence of the phosphorane. A cyclopropylcarbonyl alcohol was converted to a β-cyclopropyl-α,β-unsaturated ester by reaction with MnO_2 in the presence of $Ph_3P{=}CHCO_2Me$.[1292]

The mechanism[1293] of the key step of the Wittig reaction is as follows:[1294]



Oxaphosphetane

The energetics of ylid formation and their reaction is solution has been studied.[1295] For many years it was assumed that a diionic compound, called a *betaine*, is an intermediate on the pathway from the starting compounds

[1287]Bestmann, H.J.; Schade, G. *Tetrahedron Lett.* ***1982***, *23*, 3543.

[1288]For a list of references to the preparation of haloalkenes by Wittig reactions, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 725–727.

[1289]See, for example, Rabinowitz, R.; Marcus, R. *J. Am. Chem. Soc.* ***1962***, *84*, 1312; Ramirez, F.; Desai, N.B.; McKelvie, N. *J. Am. Chem. Soc.* ***1962***, *84*, 1745; Corey, E.J.; Fuchs, P.L. *Tetrahedron Lett.* ***1972***, 3769; Posner, G.H.; Loomis, G.L.; Sawaya, H.S. *Tetrahedron Lett.* ***1975***, 1373; Suda, M.; Fukushima, A. *Tetrahedron Lett.* ***1981***, *22*, 759; Gaviña, F.; Luis, S.V.; Ferrer, P.; Costero, A.M.; Marco, J.A. *J. Chem. Soc., Chem. Commun.* ***1985***, 296; Li, P.; Alper, H. *J. Org. Chem.* ***1986***, *51*, 4354.

[1290]Michel, P.; Gennet, D.; Rassat, A. *Tetrahedron Lett.* ***1999***, *40*, 8575. See Michael, P.; Rassat, A. *Tetrahedron Lett.* ***1999***, *40*, 8579.

[1291]Brückner, D. *Synlett* ***2000***, 1402.

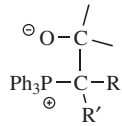
[1292]Blackburn, L.; Wei, X.; Taylor, R.J.K. *Chem. Commun.* ***1999***, 1337.

[1293]For a review of the mechanism, see Cockerill, A.F.; Harrison, R.G., in Patai, S. *The Chemistry of Functional Groups: Supplement A*, pt. 1, Wiley, NY, ***1977***, pp. 232–240. For a thorough discussion, see Vedejs, E.; Marth, C.F. *J. Am. Chem. Soc.* ***1988***, *110*, 3948.

[1294]It has been contended that another mechanism, involving single electron transfer, may be taking place in some cases: Olah, G.A.; Krishnamurthy, V.V. *J. Am. Chem. Soc.* ***1982***, *104*, 3987; Yamataka, H.; Nagareda, K.; Hanafusa, T.; Nagase, S. *Tetrahedron Lett.* ***1989***, *30*, 7187. A diradical mechanism has also been proposed for certain cases: Ward, Jr., W.J.; McEwen, W.E. *J. Org. Chem.* ***1990***, *55*, 493.

[1295]Arnett, E.M.; Wernett, P.C. *J. Org. Chem.* ***1993***, *58*, 301.

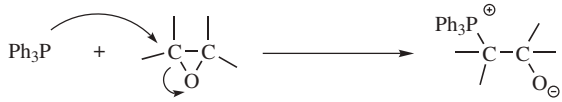
to the oxaphosphetane, and in fact it may be so, but there is little evidence for it.[1296]



Betaine

"Betaine" precipitates have been isolated in certain Wittig reactions,[1297] but these are betaine–lithium halide adducts, and might just as well have been formed from the oxaphosphetane as from a true betaine.[1298] However, there is one report of an observed betaine lithium salt during the course of a Wittig reaction.[1299] An X-ray structure was determined for a gauche betaine from a thio-Wittig reaction.[1300] In contrast, there is much evidence for the presence of the oxaphosphetane intermediates, at least with unstable ylids. For example, ^{31}P NMR spectra taken of the reaction mixtures at low temperatures[1301] are compatible with an oxaphosphetane structure that persists for some time but not with a tetra-coordinated phosphorus species. Since a betaine, an ylid, and a phosphine oxide all have tetracoordinated phosphorus, these species could not be causing the spectra, leading to the conclusion that an oxaphosphetane intermediate is present in the solution. In certain cases oxaphosphetanes have been isolated.[1302] It has even been possible to detect cis and trans isomers of the intermediate oxaphosphetanes by NMR spectroscopy.[1303] According to this mechanism, an optically active phosphonium salt $RR'R^2P^+CHR^2$ should retain its configuration all the way through the reaction, and it should be preserved in the phosphine oxide $RR'R^2PO$. This has been shown to be the case.[1304]

The proposed betaine intermediates can be formed, in a completely different manner, by nucleophilic substitution by a phosphine on an epoxide (**10-35**):



[1296]See Vedejs, E.; Marth, C.F. *J. Am. Chem. Soc.* ***1990***, *112*, 3905.

[1297]Wittig, G.; Weigmann, H.; Schlosser, M. *Chem. Ber.* ***1961***, *94*, 676; Schlosser, M.; Christmann, K.F. *Liebigs Ann. Chem.* ***1967***, *708*, 1.

[1298]Maryanoff, B.E.; Reitz, A.B. *Chem. Rev.* ***1989***, *89*, 863, see p. 865.

[1299]Neumann, R.A.; Berger, S. *Eur. J. Org. Chem.* ***1998***, 1085.

[1300]Puke, C.; Erker, G.; Wibbeling, B.; Fröhlich, R. *Eur. J. Org. Chem.* ***1999***, 1831.

[1301]Vedejs, E.; Meier, G.P.; Snoble, K.A.J. *J. Am. Chem. Soc.* ***1981***, *103*, 2823. See also, Nesmayanov, N.A.; Binshtok, E.V.; Reutov, O.A. *Doklad. Chem.* ***1973***, *210*, 499.

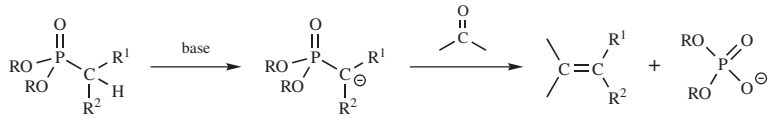
[1302]Birum, G.H.; Matthews, C.N. *Chem. Commun.* ***1967***, 137; Mazhar-Ul-Haque; Caughlan, C.N.; Ramirez, F.; Pilot, J.F.; Smith, C.P. *J. Am. Chem. Soc.* ***1971***, *93*, 5229.

[1303]Maryanoff, B.E.; Reitz, A.B.; Mutter, M.S.; Inners, R.R.; Almond Jr., H.R.; Whittle, R.R.; Olofson, R.A. *J. Am. Chem. Soc.* ***1986***, *108*, 7664. See also, Pískala, A.; Rehan, A.H.; Schlosser, M. *Coll. Czech. Chem. Commun.* ***1983***, *48*, 3539.

[1304]McEwen, W.E.; Kumli, K.F.; Bladé-Font, A.; Zanger, M.; VanderWerf, C.A. *J. Am. Chem. Soc.* ***1964***, *86*, 2378.

Betaines formed in this way can then be converted to the alkene, and this is one reason why betaine intermediates were long accepted in the Wittig reaction.

The Wittig reaction has also been carried out with phosphorus ylids other than phosphoranes, the most important being prepared from phosphonates, such as **62**.[1305]



62

This method, sometimes called the *Horner–Emmons*, *Wadsworth–Emmons*, or *Wittig–Horner reaction*,[1306] has several advantages over the use of phosphoranes, including selectivity.[1307] These ylids are more reactive than the corresponding phosphoranes, and when R^1 or R^2 is an electron-withdrawing group, these compounds often react with ketones that are inert to phosphoranes. High pressure has been used to facilitate this reaction.[1308] In addition, the phosphorus product is a phosphate ester and hence soluble in water, unlike Ph_3PO, which makes it easy to separate it from the alkene product. Phosphonates are also cheaper than phosphonium salts and can easily be prepared by the *Arbuzov reaction*:[1309]

Phosphonates have also been prepared from alcohols and $(ArO)_2P(=O)Cl$, NEt_3 and a $TiCl_4$ catalyst.[1310] The reaction of $(RO)_2P(=O)H$ and aryl iodides with a CuI catalyst leads to aryl phosphonates.[1311] Polymer-bound phosphonate esters have been used for olefination.[1312] Dienes are produced when allylic phosphonate esters react with aldehydes.[1313]

[1305]Horner, L.; Hoffmann, H.; Wippel, H.G.; Klahre, G. *Chem. Ber.* ***1959***, *92*, 2499; Wadsworth, Jr., W.S.; Emmons, W.D. *J. Am. Chem. Soc.* ***1961***, *83*, 1733.

[1306]For reviews, see Wadsworth, Jr., W.S. *Org. React.* ***1977***, *25*, 73; Stec, W.J. *Acc. Chem. Res.* ***1983***, *16*, 411; Walker, B.J., in Cadogan, J.I.G. *Organophosphorous Reagents in Organic Synthesis*, Academic Press, NY, ***1979***, pp. 156–205; Dombrovskii, A.V.; Dombrovskii, V.A. *Russ. Chem. Rev.* ***1966***, *35*, 733; Boutagy, J.; Thomas, R. *Chem. Rev.* ***1974***, *74*, 87. For a convenient method of carrying out this reaction, see Seguineau, P.; Villieras, J. *Tetrahedron Lett.* ***1988***, *29*, 477, and other papers in this series.

[1307]Motoyoshiya, J.; Kasaura, T.; Kokin, K.; Yokoya, S.-i.; Takaguchi, Y.; Narita, S.; Aoyama, H. *Tetrahedron* ***2001***, *57*, 1715.

[1308]Has-Becker, S.; Bodmann, K.; Kreuder, R.; Santoni, G.; Rein, T.; Reiser, O. *Synlett* ***2001***, 1395.

[1309]Also known as the *Michaelis-Arbuzov rearrangement*. For reviews, see Petrov, A.A.; Dogadina, A.V.; Ionin, B.I.; Garibina, V.A.; Leonov, A.A. *Russ. Chem. Rev.* ***1983***, *52*, 1030; Bhattacharya, A.K.; Thyagarajan, G. *Chem. Rev.* ***1981***, *81*, 415. For related reviews, see Shokol, V.A.; Kozhushko, B.N. *Russ. Chem. Rev.* ***1985***, *53*, 98; Brill, T.B.; Landon, S.J. *Chem. Rev.* ***1984***, *84*, 577. See also, Kaboudin, B.; Balakrishna, M.S. *Synth. Commun.* ***2001***, *31*, 2773.

[1310]Jones, S.; Selitsianos, D. *Org. Lett.* ***2002***, *4*, 3671.

[1311]Gelman, D.; Jiang, L.; Buchwald, S.L. *Org. Lett.* ***2003***, *5*, 2315.

[1312]Barrett, A.G.M.; Cramp, S.M.; Roberts, R.S.; Zecri, F.J. *Org. Lett.* ***1999***, *1*, 579.

[1313]Wang, Y.; West, F.G. *Synthesis* ***2002***, 99.

Stereoselective alkenylation reactions have been achieved using chiral additives[1314] or auxiliaries.[1315] Ylids formed from phosphine oxides,

$$\begin{matrix} Ar_2P-CHRR' \\ \| \\ O \end{matrix}$$

phosphonic acid bisamides, $(R^2_2N)_2POCHRR'$,[1316] and alkyl phosphonothionates, $(MeO)_2PSCHRR'$,[1317] share some of these advantages. Reagents, such as $Ph_2POCH_2NR'_2$, react with aldehydes or ketones (R_2COR^3) to give good yields of enamines ($R^2R^3C{=}CHNR$).[1318] (*Z*)-Selective reagents are also known,[1319] including the use of a di(2,2,2-trifluoroethoxy)phosphonate with KHMDS and 18-crown-6.[1320] An interesting intramolecular version of the Horner–Emmons reaction leads to alkynes.[1321] The reaction of a functionalized aldehyde (R—CHO) with $(MeO)_2POCHN_2$, leads to the alkyne (R—C≡CH).[1322]

Some Wittig reactions give the (*Z*)-alkene; some the (*E*), and others give mixtures, and the question of which factors determine the stereoselectivity has been much studied.[1323] It is generally found that ylids containing stabilizing groups or formed from trialkylphosphines give (*E*)-alkenes. However, ylids formed from triarylphosphines and not containing stabilizing groups often give (*Z*) or a mixture of (*Z*) and (*E*)-alkenes.[1324] One explanation for this[1193] is that the reaction of the ylid with the carbonyl compound is a [2 + 2]-cycloaddition, which in order to be concerted must adopt the $[_\pi2_s + _\pi2_a]$ pathway. As we have seen earlier (p. 1225), this pathway leads to the formation of the more sterically crowded product, in this case the *Z* alkene. If this explanation is correct, it is not easy to explain the predominant formation of (*E*)

[1314]Mizuno, M.; Fujii, K.; Tomioka, K. *Angew. Chem. Int. Ed.* ***1998***, *37*, 515. Also see, Arai, S.; Hamaguchi, S.; Shioiri, T. *Tetrahedron Lett.* ***1998***, *39*, 2997. For a review of asymmetric Wittig-type reactions see Rein, T.; Pedersen, T.M. *Synthesis* ***2002***, 579.

[1315]Abiko, A.; Masamune, S. *Tetrahedron Lett.* ***1996***, *37*, 1077.

[1316]Corey, E.J.; Kwiatkowski, G.T. *J. Am. Chem. Soc.* ***1968***, *90*, 6816; Corey, E.J.; Cane, D.E. *J. Org. Chem.* ***1969***, *34*, 3053. For a chiral derivative, see Hanessian, S.; Beaudoin, S. *Tetrahedron Lett.* ***1992***, *33*, 7655, 7659.

[1317]Corey, E.J.; Kwiatkowski, G.T. *J. Am. Chem. Soc.* ***1966***, *88*, 5654.

[1318]Broekhof, N.L.J.M.; van der Gen, A. *Recl. Trav. Chim. Pays-Bas* ***1984***, *103*, 305; Broekhof, N.L.J.M.; van Elburg, P.; Hoff, D.J.; van der Gen, A. *Recl. Trav. Chim. Pays-Bas* ***1984***, *103*, 317.

[1319]Ando, K. *Tetrahedron Lett.* ***1995***, *36*, 4105.

[1320]Yu, W.; Su, M.; Jin, Z. *Tetrahedron Lett.* ***1999***, *40*, 6725.

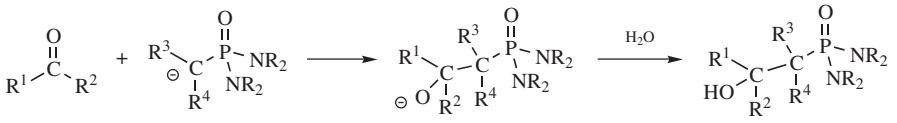
[1321]Nangia, A.; Prasuna, G.; Rao, P.B. *Tetrahedron Lett.* ***1994***, *35*, 3755; Couture, A.; Deniau, E.; Gimbert, Y.; Grandclaudon, P. *J. Chem. Soc. Perkin Trans. 1* ***1993***, 2463.

[1322]Hauske, J.R.; Dorff, P.; Julin, S.; Martinelli, G.; Bussolari, J. *Tetrahedron Lett.* ***1992***, *33*, 3715.

[1323]For reviews of the stereochemistry of the Wittig reactions, see Maryanoff, B.E.; Reitz, A.B. Chem. Rev. ***1989***, *89*, 863; Gosney, I.; Rowley, A.G., in Cadogan, J.I.G. *Organophosphorous Reagents in Organic Synthesis*, Academic Press, NY, ***1979***, pp. 17–153; Reucroft, J.; Sammes, P.G. *Q. Rev. Chem. Soc.* ***1971***, *25*, 135, see pp. 137–148, 169; Schlosser, M. *Top. Stereochem.* ***1970***, *5*, 1. Also see Takeuchi, K.; Paschal, J.W.; Loncharich, R.J. *J. Org. Chem.* ***1995***, *60*, 156.

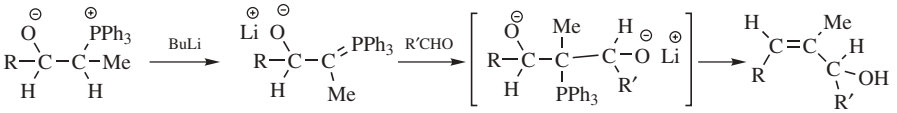
[1324]For cases where such an ylid gave (*E*)-alkenes, see Maryanoff, B.E.; Reitz, A.B.; Duhl-Emswiler, B.A. *J. Am. Chem. Soc.* ***1985***, *107*, 217; Le Bigot, Y.; El Gharbi, R.; Delmas, M.; Gaset, A. *Tetrahedron* ***1986***, *42*, 3813. For guidance in how to obtain the maximum yields of the *Z* product, see Schlosser, M.; Schaub, B.; de Oliveira-Neto, J.; Jeganathan, S. *Chimia* ***1986***, *40*, 244.

products from stable ylids, but (*E*) compounds are of course generally thermodynamically more stable than the (*Z*) isomers, and the stereochemistry seems to depend on many factors.



63 **64**

The (*E*/*Z*) ratio of the product can often be changed by a change in solvent or by the addition of salts.[1325] Another way of controlling the stereochemistry of the product is by use of the aforementioned phosphonic acid bisamides. In this case, the betaine (**63**) does form and when treated with water gives the β-hydroxyphosphonic acid bisamides **64**, which can be crystallized and then cleaved to $R^1R^2C{=}CR^3R^4$ by refluxing in benzene or toluene in the presence of silica gel.[1316] **64** are generally formed as mixtures of diastereomers, and these mixtures can be separated by recrystallization. Cleavage of the two diastereomers gives the two isomeric alkenes. Optically active phosphonic acid bisamides have been used to give optically active alkenes.[1326] Another method of controlling the stereochemistry of the alkene [to obtain either the (*Z*) or (*E*) isomer] starting with a phosphine oxide (Ph_2POCH_2R), has been reported.[1327]



65 R = *n*-C_6H_{13} **66** **67** **68**

In reactions where the betaine–lithium halide intermediate is present, it is possible to extend the chain further if a hydrogen is present α to the phosphorus. For example, reaction of ethylidnetriphenylphosphorane with heptanal at −78°C gave **65**, which with butyllithium gave the ylid **66**. Treatment of this with an aldehyde R′CHO gave the intermediate **67**, which after workup gave **68**.[1328] This reaction gives the unsaturated alcohols **68** stereoselectively. **66** also reacts with other electrophiles. For example, treatment of **66** with *n*-chlorosuccinimide or $PhICl_2$ gives the vinylic chloride RCH=CMeCl stereoselectively: NCS giving the cis and $PhICl_2$

[1325]See, for example, Reitz, A.B.; Nortey, S.O.; Jordan, Jr., A.D.; Mutter, M.S.; Maryanoff, B.E. *J. Org. Chem.* ***1986***, *51*, 3302.

[1326]Hanessian, S.; Delorme, D.; Beaudoin, S.; Leblanc, Y. *J. Am. Chem. Soc.* ***1984***, *106*, 5754; Rein, T.; Reiser, O. *Acta Chem. Scand. B*, ***1996***, *50*, 369. For a review of asymmetric ylid reactions, see Li, A.-H.; Dai, L.-X.; Aggarwal, V.K. *Chem. Rev.* ***1997***, *97*, 2341.

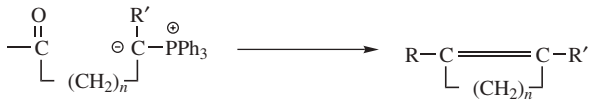
[1327]Ayrey, P.M.; Warren, S. *Tetrahedron Lett.* ***1989***, *30*, 4581.

[1328]Corey, E.J.; Yamamoto, H. *J. Am. Chem. Soc.* ***1970***, *92*, 226; Schlosser, M.; Coffinet, D. *Synthesis* ***1972***, 575; Corey, E.J.; Ulrich, P.; Venkateswarlu, A. *Tetrahedron Lett.* ***1977***, 3231; Schlosser, M.; Tuong, H.B.; Respondek, J.; Schaub, B. *Chimia* ***1983***, *37*, 10.

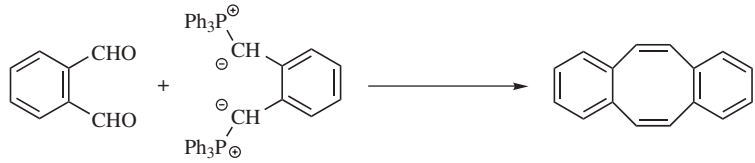
the trans isomer.[1329] The use of Br_2 and $FClO_3$ (see **12-4** for the explosive nature of this reagent) gives the corresponding bromides and fluorides, respectively.[1330] Reactions of **66** with electrophiles have been called *scoopy* reactions (α *s*ubstitution plus *c*arbonyl alkeneylation via β-*o*xido *p*hosphorus *ylid*s).[1331]

The reaction of a phosphonate ester, DBU, NaI, and HMPA with an aldehyde leads to a conjugated ester with excellent (*Z*)-selectivity.[1332] A (*Z*)-selective reaction was reported using a trifluoroethyl phosphonate in a reaction with an aldehyde and potassium *tert*-butoxide.[1333]

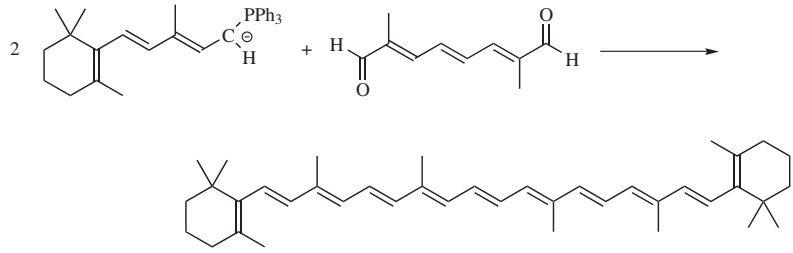
The Wittig reaction has been carried out intramolecularly, to prepare rings containing from 5 to 16 carbons,[1334] both by single ring closure



and double ring closure.[1335]



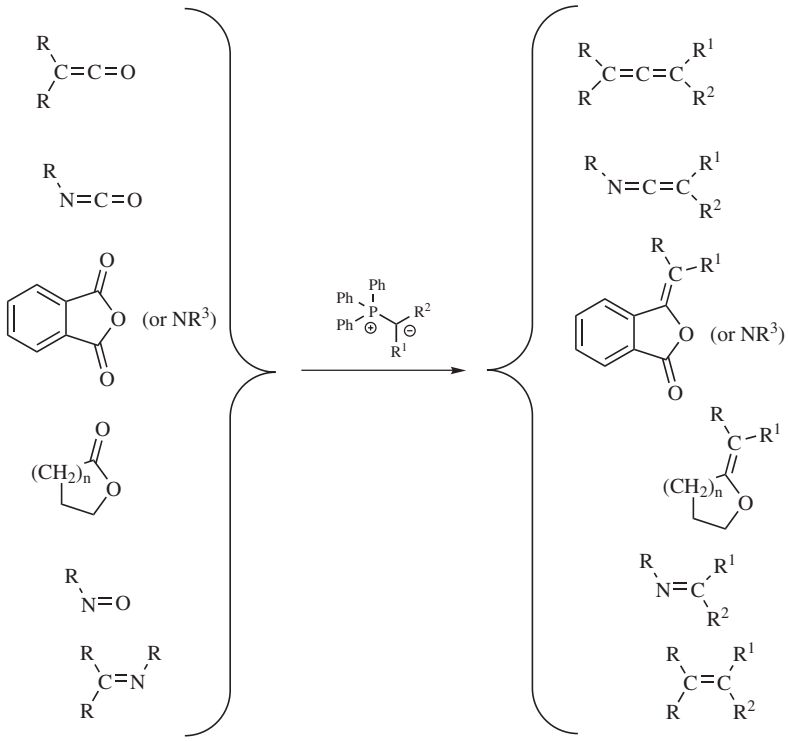
The Wittig reaction has proved very useful in the synthesis of natural products, some of which are quite difficult to prepare in other ways.[1336] One example out of many is the synthesis of β-carotene:[1337]



β-Carotene

[1329]Schlosser, M.; Christmann, K. *Synthesis* ***1969***, 38; Corey, E.J.; Shulman, J.I.; Yamamoto, H. *Tetrahedron Lett.* ***1970***, 447.
[1330]Schlosser, M.; Christmann, K.-F. *Synthesis* ***1969***, 38.
[1331]Schlosser, M. *Top. Stereochem.* ***1970***, *5*, 1, p. 22.
[1332]Ando, K.; Oishi, T.; Hirama, M.; Ohno, H.; Ibuka, T. *J. Org. Chem.* ***2000***, *65*, 4745.
[1333]Touchard, F.P. *Tetrahedron Lett.* ***2004***, *45*, 5519.
[1334]For a review, see Becker, K.B. *Tetrahedron* ***1980***, *36*, 1717.
[1335]For a review of these double-ring closures, see Vollhardt, K.P.C. *Synthesis* ***1975***, 765.
[1336]For a review of applications of the Wittig reaction to the synthesis of natural products, see Bestmann, H.J.; Vostrowsky, O. *Top. Curr. Chem.* ***1983***, *109*, 85.
[1337]Wittig, G.; Pommer, H. German patent ***1956***, 954,247, [*Chem. Abstr.* ***1959***, *53*, 2279].

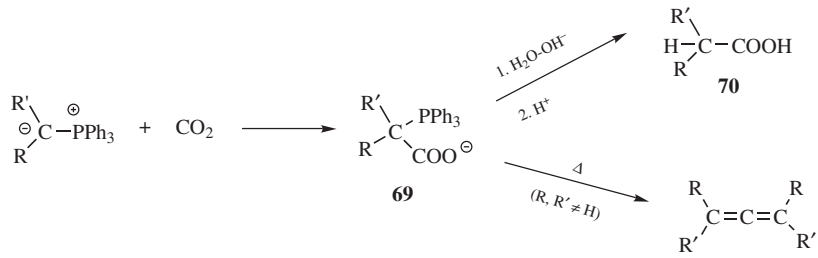
Phosphorus ylids also react in a similar manner with the C=O bonds of ketenes,[1338] isocyanates,[1339] certain anhydrides[1340] lactones,[1341] and imides,[1342] the N=O of nitroso groups, and the C=N of imines,[1343] for example,



Phosphorus ylids react with carbon dioxide to give the isolable salts **69**,[1344] which can be hydrolyzed to the carboxylic acids **70** (thus achieving the conversion

[1338]For example, see Aksnes, G.; Frøyen, P. *Acta Chem. Scand.* ***1968***, *22*, 2347.
[1339]For example, see Frøyen, P. *Acta Chem. Scand. Ser. B* ***1974***, *28*, 586.
[1340]See, for example, Abell, A.D.; Massy-Westropp, R.A. *Aust. J. Chem.* ***1982***, *35*, 2077; Kayser, M.M.; Breau, L. *Can. J. Chem.* ***1989***, *67*, 1401. For a study of the mechanism, see Abell, A.D.; Clark, B.M.; Robinson, W.T. *Aust. J. Chem.* ***1988***, *41*, 1243.
[1341]With microwave irradiation, see Sabitha, G.; Reddy, M.M.; Srinivas, D.; Yadov, J.S. *Tetrahedron Lett.* ***1999***, *40*, 165.
[1342]For a review of the reactions with anhydrides and imides (and carboxylic esters, thiol esters, and amides), see Murphy, P.J.; Brennan, J. *Chem. Soc. Rev.* ***1988***, *17*, 1. For a review with respect to imides, see Flitsch, W.; Schindler, S.R. *Synthesis* ***1975***, 685.
[1343]Bestmann, H.J.; Seng, F. *Tetrahedron* ***1965***, *21*, 1373.
[1344]Bestmann, H.J.; Denzel, T.; Salbaum, H. *Tetrahedron Lett.* ***1974***, 1275.

RR′CHX → RR′CHCOOH) or (if neither R nor R′ is hydrogen) dimerized to allenes.



Although phosphorus ylids are most commonly used to alkenylation reactions, nitrogen ylids can occasionally be used. As an example, the reaction of *N*-benzyl-*N*-phenylpiperidinium bromide with base generated a N-ylid, which reacted with benzaldehyde to form styrene.[1345] The structure has been determined for an intermediate in an aza-Wittig reaction.[1346]

OS **V**, 361, 390, 499, 509, 547, 751, 949, 985; **VI**, 358; **VII**, 164, 232; **VIII**, 265, 451; **75**, 139, **OS IX**, 39, 230.

16-45 Tebbe, Petasis and Alternative Alkenylations

Methylene-de-oxo-bisubstitution

A useful alternative to phosphorus ylids are the titanium reagents, such as, **71**, prepared from dicyclopentadienyltitanium dichloride and trimethylaluminum.[1347] Treatment of a carbonyl compound with the titanium cyclopentadienide complex **71** (*Tebbe's reagent*) in toluene–THF containing a small amount of pyridine[1348] leads to the alkene. Dimethyltitanocene (Me_2TiCp_2), called the *Petasis reagent*, is a convenient and highly useful alternative to **71**.[1349] The mechanism of Petasis olefination has been examined.[1350] Tebbe's reagent and the Petasis reagent give good results with ketones.[1351] An important feature of these new reagents is that

[1345]Lawrence, N.J.; Beynek, H. *Synlett* ***1998***, 497.
[1346]Kano, N.; Hua, X.J.; Kawa, S.; Kawashima, T. *Tetrahedron Lett.* ***2000***, *41*, 5237.
[1347]For a method of generating this reagent *in situ*, see Cannizzo, L.F.; Grubbs, R.H. *J. Org. Chem.* ***1985***, *50*, 2386.
[1348]Tebbe, F.N.; Parshall, G.W.; Reddy, G.S. *J. Am. Chem. Soc.* ***1978***, *100*, 3611; Pine, S.H.; Pettit, R.J.; Geib, G.D.; Cruz, S.G.; Gallego, C.H.; Tijerina, T.; Pine, R.D. *J. Org. Chem.* ***1985***, *50*, 1212. See also, Clawson, L.; Buchwald, S.L.; Grubbs, R.H. *Tetrahedron Lett.* ***1984***, *25*, 5733; Clift, S.M.; Schwartz, J. *J. Am. Chem. Soc.* ***1984***, *106*, 8300.
[1349]Petasis N.A.; Bzowej, E.I. *J. Am. Chem. Soc.* ***1990***, *112*, 6392.
[1350]Meurer, E.C.; Santos, L.S.; Pilli, R.A.; Eberlin, M.N. *Org. Lett.* ***2003***, *5*, 1391.
[1351]Pine, S.H.; Shen, G.S.; Hoang, H. *Synthesis* ***1991***, 165.

carboxylic esters and lactones[1352] can be converted in good yields to the corresponding enol ethers. The enol ether can be hydrolyzed to a ketone (**10-6**), so this is also an indirect method for making the conversion $RCOOR' \rightarrow RCOCH_3$ (see also, **16-82**). Conjugated esters are converted to alkoxy-dienes with this reagent.[1353] Lactams, including β-lactams, are converted with alkylidene cycloamines (alkylidene azetidines from β-lactams, which are easily hydrolyzed to β-amino ketones).[1354]

Besides stability and ease of preparation, another advantage of the Petasis reagent is that structural analogs can be prepared, including $Cp_2Ti(C_3H_5)_2$[1355] (C_3H_5 = cyclopropyl), $CpTi(CH_2SiMe_3)_3$,[1356] and $Cp_2TiMe(CH{=}CH_2)$.[1357] In another variation, 2 equivalents of $Cp_2Ti[P(OEt)_3]_2$ reacted with a ketone in the presence of 1,1-diphenylthiocyclobutane to give the alkenylcyclobutane derivative.[1358] An alternative titanium reagent was prepared using $TiCl_4$, magnesium metal and dichloromethane, reacting with both ketones[1359] and esters[1360] to give alkenes or vinyl ethers, respectively. Alkenes are generated form ketones and alkyl iodides in the presence of a catalytic amount of $Cp_2Ti[POEt)_3]_2$.[1361]

α,α-Dibromosulfones ($ArSO_2SHBr_2$) react with ketones in the presence of Sm/SmI_2 and a $CrCl_3$ catalyst gives to corresponding vinyl sulfone.[1362] Imides are converted to alkylidene lactams when treated with an alkyl halide, 2.5 equivalents of SmI_2 and a NiI_2 catalyst.[1363]

Carboxylic esters undergo the conversion $C{=}O \rightarrow C{=}CHR$ (R = primary or secondary alkyl) when treated with $RCHBr_2$, Zn,[1364] and $TiCl_4$ in the presence of *N,N,N′,N′*-tetramethylethylenediamine.[1365] Metal carbene complexes[1366] $R_2C{=}ML_n$ (L = ligand), where M is a transition metal, such as Zr, W, or Ta, have also been

[1352]See Martínez, I.; Andrews, A.E.; Emch, J.D.; Ndakala, A.J.; Wang, J.; Howell, A.R.; Rheingold, A.L.; Figuero, J.S. *Org. Lett.* ***2003***, *5*, 399; Dollinger, L.M.; Ndakala, A.J.; Hashemzadeh, M.; Wang, G.; Wang, Y.; Martínez, K.; Arcari, J.T.; Galluzzo, D.J.; Howell, A.R.; Rheingold, A.L. Figuero. J.S.; *J. Org. Chem.* ***1999***, *64*, 7074.

[1353]Petasis N.A.; Lu, S.-P. *Tetrahedron Lett.* ***1995***, *36*, 2393.

[1354]Tehrani, K.A.; De Kimpe, N. *Tetrahedron Lett.* ***2000***, *41*, 1975. See Martínez, I.; Howell, A.R. *Tetrahedron Lett.* ***2000***, *41*, 5607.

[1355]Petasis N.A.; Browej, E.I. *Tetrahedron Lett.* ***1993***, *34*, 943.

[1356]Petasis N.A.; Akritopoulou, I. *Synlett* ***1992***, 665.

[1357]Petasis N.A.; Hu, Y.-H. *J. Org. Chem.* ***1997***, *62*, 782. Also see, Petasis N.A.; Straszewski, J.P.; Fu, D.-K. *Tetrahedron Lett.* ***1995***, *36*, 3619; Rahim, Md.A.; Taguchi, H.; Watanabe, M.; Fujiwara, T.; Takeda, T. *Tetrahedron Lett.* ***1998***, *39*, 2153; Petasis N.A.; Browej, E.I. *J. Org. Chem.* ***1992***, *57*, 1327.

[1358]Fujiwara, T.; Iwasaki, N.; Takeda, T. *Chem. Lett.* ***1998***, 741. For an example using a *gem*-dichloride, see Takeda, T.; Sasaki, R.; Fujiwara, T. *J. Org. Chem.* ***1998***, *63*, 7286.

[1359]Yan, T.H.; Tsai, C.-C.; Chien, C.-T.; Cho, C.-C. Huang, P.-C. *Org. Lett.* ***2004***, *6*, 4961.

[1360]Yan, T.-H.; Chien, C.-T.; Tsai, C.-C.; Lin, K.-W.; Wu, Y.-H. *Org. Lett.* ***2004***, *6*, 4965.

[1361]Takeda, T.; Shimane, K.; Ito, K.; Saeki, N.; Tsubouchi, A. *Chem. Communn.* ***2002***, 1974.

[1362]Liu, Y.; Wu, H.; Zhang, Y. *Synth. Commun.* ***2001***, *31*, 47.

[1363]Farcas, S.; Namy, J.-L. *Tetrahedron Lett.* ***2001***, *42*, 879.

[1364]Ishino, Y.; Mihara, M.; Nishihama, S.; Nishiguchi, I. *Bull. Chem. Soc. Jpn.* ***1998***, *71*, 2669.

[1365]Okazoe, T.; Takai, K.; Oshima, K.; Utimoto, K. *J. Org. Chem.* ***1987***, *52*, 4410. For the reaction with $CH_2(ZnI)_2$ with $TiCl_2$, see Matsubra, S.; Ukai, K.; Mizuno, T.; Utimoto, K. *Chem. Lett.* ***1999***, 825. This procedure is also successful for silyl esters, to give silyl enol ethers: Takai, K.; Kataoka, Y.; Okazoe, T.; Utimoto, K. *Tetrahedron Lett.* ***1988***, *29*, 1065.

[1366]For a review of the synthesis of such complexes, see Aguero, A.; Osborn, J.A. *New J. Chem.* ***1988***, *12*, 111.

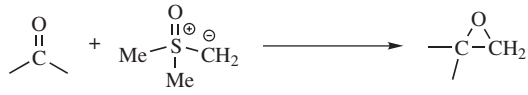
used to convert the C=O of carboxylic esters and lactones to CR_2.[1367] It is likely that the complex $Cp_2Ti=CH_2$ is an intermediate in the reaction with Tebbe's reagent.

There are a few other methods for converting ketones or aldehydes to alkenes. When a ketone is treated with $CH_3CHBr_2/Sm/SmI_2$, with a catalytic amount of $CrCl_3$, for example, the alkene is formed.[1368] α-Halo esters also react with $CrCl_2$ in the presence of a ketone to give vinyl halides.[1369] In another reaction, an aldehydes reacted with EtCHBr(OAc) in the presence of $Zn/CrCl_3$ to give the alkene.[1370] α-Diazo esters react with ketones in the presence of an iron catalyst to give the corresponding alkene.[1371] α-Diazo silylalkanes react similarly in the presence of a rhodium catalyst.[1372] Benzylic alcohols also react with α-diazo silylalknes in the presence of a rhodium catalyst, to give alkenes after pretreatment with oxygen and a palladium catalyst.[1373] The react of aryl aldehydes and $MeC(CO_2Et)_3$ with a catalytic amount of phenol leads to the corresponding conjugated ethyl ester ($ArCH=CHCO_2Et$).[1374]

OS **VIII**, 512, **IX**, 404; **X**, 355.

16-46 The Formation of Epoxides from Aldehydes and Ketones

(1 + 2)*OC*,*CC*-*cyclo*-Methylene-addition



72

Aldehydes and ketones can be converted to epoxides[1375] in good yields with the sulfur ylids dimethyloxosulfonium methylid (**72**) and dimethylsulfonium

[1367]See, for example, Schrock, R.R. *J. Am. Chem. Soc.* ***1976***, *98*, 5399; Aguero, A.; Kress, J.; Osborn, J.A. *J. Chem. Soc., Chem. Commun.* ***1986***, 531; Hartner, Jr., F.W.; Schwartz, J.; Clift, S.M. *J. Am. Chem. Soc.* ***1990***, *105*, 640.

[1368]Matsubara, S.; Horiuchi, M.; Takai, K.; Utimoto, K. *Chem. Lett.* ***1995***, 259.

[1369]Barma, D.K.; Kundu, A.; Zhang, H.; Mioskowski, C.; Falck, J.R. *J. Am. Chem. Soc.* ***2003***, *125*, 3218.

[1370]Knecht, M.; Boland, W. *Synlett* ***1993***, 837.

[1371]Chen, Y.; Huang, L.; Zhang, X.P. *Org. Lett.* ***2003***, *5*, 2493; Mirafzal, G.A.; Cheng, G.; Woo, L.K. *J. Am. Chem. Soc.* ***2002***, *124*, 176; Aggarwal, V.K.; Fulton, J.R.; Sheldon, C.G.; de Vincente, J. *J. Am. Chem. Soc.* ***2003***, *125*, 6034.

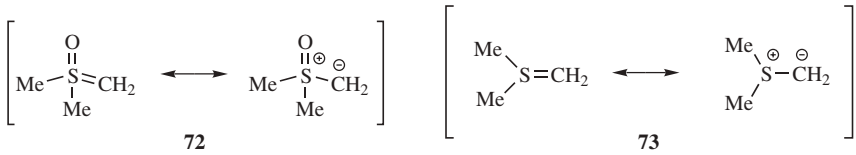
[1372]Lebel, H.; Guay, D.; Paquet, V.; Huard, K. *Org. Lett.* ***2004***, *6*, 3047. For a synthesis of dienes from conjugated aldehydes, see Lebel, H.; Paquet, V. *J. Am. Chem. Soc.* ***2004***, *126*, 320.

[1373]Lebel, H.; Paquet, V. *J. Am. Chem. Soc.* ***2004***, *126*, 11152.

[1374]Kumar, H.M.S.; Rao, M.S.; Joyasawal, S.; Yadav, J.S. *Tetrahedron Lett.* ***2003***, *44*, 4287.

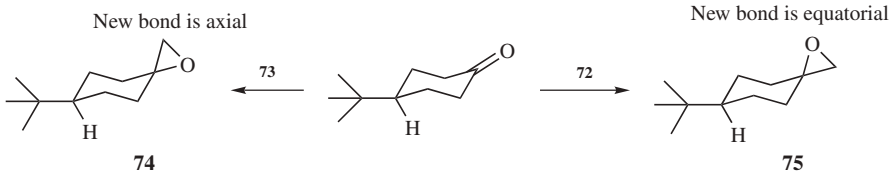
[1375]For reviews, see Block, E. *Reactions of Organosulfur Compounds*, Academic Press, NY, ***1978***, pp. 101–105; Berti, G. *Top. Stereochem.* ***1973***, *7*, 93, 218–232. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 944–951.

methylid (**73**).[1376] For most purposes, **72** is the



72 **73**

reagent of choice, because **73** is much less stable and ordinarily must be used as soon as it is formed, while **72** can be stored several days at room temperature. When diastereomeric epoxides can be formed, **73** usually attacks from the more hindered and **72** from the less-hindered side. Thus, 4-*tert*-butylcyclohexanone, treated with **72** gave exclusively **75** while **73** gave mostly **74**.[1377] Another difference in behavior between the



74 **75**

two reagents is that with α,β-unsaturated ketones, **72** gives only cyclopropanes (reaction **15-64**), while **73** gives oxirane formation. Other sulfur ylids have been used in an analogous manner, to transfer CHR or CR_2.[1378] High yields have been achieved by the use of sulfonium ylids anchored to insoluble polymers under phase-transfer conditions.[1379] A solvent-free version of this reaction has been developed using powdered K *tert*-butoxide and $Me_3S^+I^-$.[1380] Note that treatment of epoxides with 2 equivalents of $Me_2S{=}CH_2$ leads to allylic alcohols.[1381] Other sulfur ylids convert aldehydes to epoxides, including the one generated *in situ* from $RR'S^+CH_2COO^-$.[1382] Chiral sulfur ylids[1383] have been prepared, giving

[1376]For reviews, see House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 709–733; Durst, T. *Adv. Org. Chem.* ***1969***, *6*, 285, see pp. 321–330. For a monograph on sulfur ylids, see Trost, B.M.; Melvin, Jr., L.S. *Sulfur Ylids*; Academic Press, NY, ***1975***.

[1377]Corey, E.J.; Chaykovsky, M. *J. Am. Chem. Soc.* ***1965***, *87*, 1353.

[1378]Adams, J.; Hoffman, Jr., L.; Trost, B.M. *J. Org. Chem.* ***1970***, *35*, 1600; Yoshimine, M.; Hatch, M.J. *J. Am. Chem. Soc.* ***1967***, *89*, 5831; Braun, H.; Huber, G.; Kresze, G. *Tetrahedron Lett.* ***1973***, 4033; Corey, E.J.; Jautelat, M.; Oppolzer, W. *Tetrahedron Lett.* ***1967***, 2325.

[1379]Farrall, M.J.; Durst, T.; Fréchet, J.M.J. *Tetrahedron Lett.* ***1979***, 203.

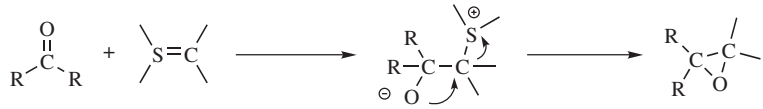
[1380]Toda, F.; Kanemoto, K. *Heterocycles* ***1997***, *46*, 185.

[1381]Harnett, J.J.; Alcaraz, L.; Mioskowski, C.; Martel, J.P.; Le Gall, T.; Shin, D.-S.; Falck, J.R. *Tetrahedron Lett.* ***1994***, *35*, 2009; Alcaraz, L.; Harnett, J.J.; Mioskowski, C.; Martel, J.P.; Le Gall, T.; Shin, D.-S.; Falck, J.R. *Tetrahedron Lett.* ***1994***, *35*, 5449. Also see, Alcaraz, L.; Harnett, J.J.; Mioskowski, C.; Martel, J.P. Le Gall, T.; Shin, D.-S.; Falck, J.R. *Tetrahedron Lett.* ***1994***, *35*, 5453 for generation of alkenes from $Me_2S{=}CH_2$ and alkyl halides or mesylates.

[1382]Forbes, D.C.; Standen, M.C.; Lewis, D.L. *Org. Lett.* ***2003***, *5*, 2283.

[1383]See Aggarwal, V.K.; Angelaud, R.; Bihan, D.; Blackburn, P.; Fieldhouse, R.; Fonguerna, S.J.; Ford, G.D.; Hynd, G.; Jones, E.; Jones, R.V.H.; Jubault, P.; Palmer, M.J.; Ratcliffe, P.D.; Adams, H. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 2604.

the epoxide with good asymmetric induction.[1384] Chiral selenium ylids have been used in a similar manner.[1385]

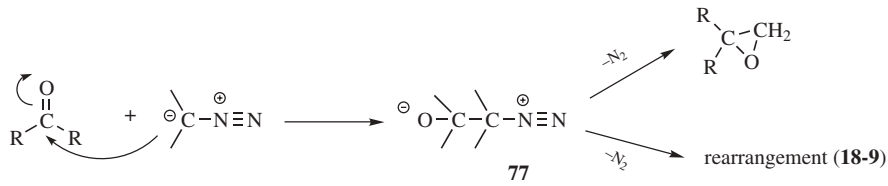


76

The generally accepted mechanism for the reaction between sulfur ylids and aldehydes or ketone is formation of **76**, with displacement of the Me_2S leaving group by the alkoxide.[1386] This mechanism is similar to that of the reaction of sulfur ylids with C=C double bonds (**15-64**).[1387] The stereochemical difference in the behavior of **72** and **73** has been attributed to formation of the betaine **76** being reversible for **72**, but not for the less stable **73**, so that the more-hindered product is the result of kinetic control and the less-hindered of thermodynamic control.[1388]

Phosphorus ylids do not give this reaction, but give **16-44** instead.

Aldehydes and ketones can also be converted to epoxides by treatment with a diazoalkane,[1389] most commonly diazomethane, but an important side reaction is the formation of an aldehyde or ketone with one more carbon than the starting compound (reaction **18-9**). The reaction can be carried out with many aldehydes, ketones, and quinones, usually with a rhodium catalyst.[1390] A mechanism that accounts for both products is



77

Compound **77** or nitrogen-containing derivatives of it have sometimes been isolated.

An alternative route to epoxides from ketones uses α-chloro sulfones and potassium *tert*-butoxide to give α,β-epoxy sulfones.[1391] A similar reaction was reported

[1384]Baird, C.P.; Taylor, P.C. *J. Chem. Soc. Perkin Trans. 1* ***1998***, 3399; Domingo, V.M.; Castañer, J. *J. Chem. Soc., Chem. Commun.* ***1995***, 893; Hayakawa, R.; Shimizu, M. *Synlett* ***1999***, 1328; Zanardi, J.; Leriverend, C.; Aubert, D.; Julienne, K.; Metzner, P. *J. Org. Chem.* ***2001***, *66*, 5620; Saito, T.; Akiba, D.; Sakairi, M.; Kanazawa, S. *Tetrahedron Lett.* ***2001***, *42*, 57; Winn, C.L.; Bellenie, B.R.; Goodman, J.M. *Tetrahedron Lett.* ***2002***, *43*, 5427.

[1385]See Takada, H.; Metzner, P.; Philouze, C. *Chem. Commun.* ***2001***, 2350.

[1386]See Aggarwal, V.K.; Harvery, J.N.; Richardson, J. *J. Am. Chem. Soc.* ***2002***, *124*, 5747.

[1387]See, for example, Townsend, J.M.; Sharpless, K.B. *Tetrahedron Lett.* ***1972***, 3313; Johnson, C.R.; Schroeck, C.W.; Shanklin, J.R. *J. Am. Chem. Soc.* ***1973***, *95*, 7424.

[1388]Johnson, C.R.; Schroeck, C.W.; Shanklin, J.R. *J. Am. Chem. Soc.* ***1973***, *95*, 7424.

[1389]For a review, see Gutsche, C.D. *Org. React.* ***1954***, *8*, 364.

[1390]See Davies, H.M.L.; De Meese, J. *Tetrahedron Lett.* ***2001***, *42*, 6803.

[1391]Mąkosza, M.; Urbańska, N.; Chesnokov, A.A. *Tetrahedron Lett.* ***2003***, *44*, 1473.

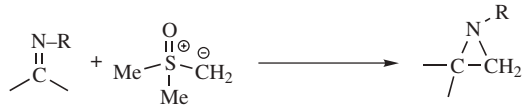
using KOH and 10% of a chiral phase-transfer agent, giving moderate enantioselectivity in the epoxy sulfone product.[1392]

Dihalocarbenes and carbenoids, which readily add to C=C bonds (**15-64**), do not generally add to the C=O bonds of ordinary aldehydes and ketones.[1393] See also, **16-91**.

OS **V**, 358, 755.

16-47 The Formation of Aziridines from Imines

(1 + 2)*NC*,*CC-cyclo*-Methylene-addition



72

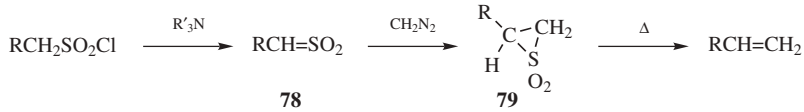
Just as sulfur ylids react with the carbonyl of an aldehyde or ketone to give an epoxide, tellurium ylids react with imines to give an aziridine. The reaction of an allylic tellurium salt, $RCH{=}CHCH_2Te^+Bu_2\ Br^-$, with lithium hexamethyldisilazide in HMPA/toluene leads to the tellurium ylid via deprotonation. In the presence of an imine, the ylid add to the imine and subsequent displacement of Bu_2Te generates an aziridine with a pendant vinyl group.[1394]

16-48 The Formation of Episulfides and Episulfones[1395]

Epoxides can be converted directly to episulfides by treatment with NH_4SCN and ceric ammonium nitrate.[1396] Diazoalkanes, treated with sulfur, give episulfides.[1397] It is likely that $R_2C{=}S$ is an intermediate, which is attacked by another molecule of diazoalkane, in a process similar to that shown in **16-46**. Thioketones *do* react with diazoalkanes to give episulfides.[1398] Thioketones have also been converted to episulfides with sulfur ylids.[1377] Carbenes, such as the dichlorocarbene from $CHCl_3$ and base, react with thioketones to give an

[1392]Arai, S.; Shioiri, T. *Tetrahedron* ***2002***, *58*, 1407.
[1393]For exceptions, see Greuter, H.; Winkler, T.; Bellus, D. *Helv. Chim. Acta* ***1979***, *62*, 1275; Sadhu, K.M.; Matteson, D.S. *Tetrahedron Lett.* ***1986***, *27*, 795; Araki, S.; Butsugan, Y. *J. Chem. Soc., Chem. Commun.* ***1989***, 1286.
[1394]Liao, W.-W.; Deng, X.-M.; Tang, Y. *Chem. Commun.* ***2004***, 1516.
[1395]For a review, see Muller, L.L.; Hamer, J. *1,2-Cycloaddition Reactions*, Wiley, NY, ***1967***, pp. 57–86.
[1396]Iranpoor, N.; Kazemi, F. *Synthesis* ***1996***, 821.
[1397]Schönberg, A.; Frese, E. *Chem. Ber.* ***1962***, *95*, 2810.
[1398]For example, see Beiner, J.M.; Lecadet, D.; Paquer, D.; Thuillier, A. *Bull. Soc. Chim. Fr.* ***1973***, 1983.

α,α-dichloro episufide.[1399]



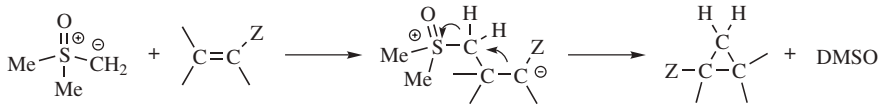
78 **79**

Alkanesulfonyl chlorides, when treated with diazomethane in the presence of a base (usually a tertiary amine), give episulfones (**79**).[1400] The base removes HCl from the sulfonyl halide to produce the highly reactive sulfene (**78**) (**17-14**), which then adds CH_2. The episulfone can then be heated to give off SO_2 (**17-20**), making the entire process a method for achieving the conversion $RCH_2SO_2Cl \rightarrow RCH{=}CH_2$.[1401]

OS **V**, 231, 877.

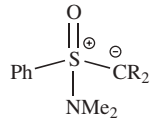
16-49 Cyclopropanation of Conjugated Carbonyl Compounds

Double-bond compounds that undergo the Michael reaction (**15-24**) can be converted to cyclopropane derivatives with sulfur ylids.[1402] Among the most common of these is dimethyloxosulfonium methylid



72

72,[1403] which is widely used to transfer CH_2 to activated double bonds, but other sulfur ylids



80

[1399]Mlosteń, G.; Romański, J.; Swiątek, A.; Hemgartner, H. *Helv. Chim. Acta* ***1999***, *82*, 946.
[1400]Opitz, G.; Fischer, K. *Angew. Chem. Int. Ed.* ***1965***, *4*, 70.
[1401]For a review of this process, see Fischer, N.S. *Synthesis* ***1970***, 393.
[1402]For a monograph on sulfur ylids, see Trost, B.M.; Melvin Jr., L.S. *Sulfur Ylids*, Academic Press, NY, ***1975***. For reviews, see Fava, A., in Bernardi, F.; Csizmadia, I.G.; Mangini, A. *Organic Sulfur Chemistry*, Elsevier, NY, ***1985***, pp. 299–354; Belkin, Yu.V.; Polezhaeva, N.A. *Russ. Chem. Rev.* ***1981***, *50*, 481; Block, E., in Stirling, C.J.M. *The Chemistry of the Sulphonium Group*, pt. 2, Wiley, NY, ***1981***, pp. 680–702; Block, E. *Reactions of Organosulfur Compounds*, Academic Press, NY, ***1978***, pp. 91–127. See also, Mamai, A.; Madalengoitia, J.S. *Tetrahedron Lett.* ***2000***, *41*, 9009.
[1403]Truce, W.E.; Badiger, V.V. *J. Org. Chem.* ***1964***, *29*, 3277; Corey, E.J.; Chaykovsky, M. *J. Am. Chem. Soc.* ***1965***, *87*, 1353; Agami, C.; Prevost, C. *Bull. Soc. Chim. Fr.* ***1967***, 2299. For a review of this reagent, see Gololobov, Yu.G.; Nesmeyanov, A.N.; Lysenko, V.P.; Boldeskul, I.E. *Tetrahedron* ***1987***, *43*, 2609.

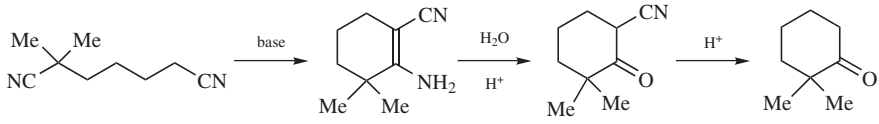
have also been used. A combination of DMSO and KOH in an ionic liquid converts conjugated ketones to α,β-cyclopropyl ketones.[1404] Both CHR and CR_2 can be added in a similar manner with certain nitrogen-containing compounds. For example, ylids,[1405] such as **80**, add various groups to activated double bonds.[1406] Sulfur ylids react with allylic alcohols in the presence of MnO_2 and molecular sieve 4 Å to give the cyclopropyl aldehyde.[1407] Similar reactions have been performed with phosphorus ylids,[1408] with pyridinium ylids,[1409] and with the compounds $(PhS)_3CLi$ and $Me_3Si(PhS)_2CLi$.[1410] The reactions with ylids such as these involve of course nucleophilic acyl addition.

Other reagents can be used to convert an aldehyde or ketone to a cyclopropane derivative. Conjugated ketones react with $Cp_2Zr(CH_2{-}CH_2)$ and PMe_3 to give a vinyl cyclopropane derivative after treatment with aqueous sulfuric acid.[1411]

16-50 The Thorpe Reaction

N-Hydro-*C*-(α-cyanoalkyl)-addition

In the *Thorpe reaction*, the α carbon of one nitrile molecule is added to the CN carbon of another, so this reaction is analogous to the aldol reaction (**16-34**). The C=NH bond is, of course, hydrolyzable (**16-2**), so β-keto nitriles can be prepared in this manner. The Thorpe reaction can be done intramolecularly, in which case it is



81

[1404]In bmim PF_6, 1-butyl-3-methylimidazolium hexafluorophosphate: Chandrasekhar, S.; Jagadeshwar, N.V.; Reddy, K.V. *Tetrahedron Lett.* ***2003***, *44*, 3629.

[1405]For a review of sulfoximides ($R_2S(O)NR_2$) and ylids derived from them, see Kennewell, P.D.; Taylor, J.B. *Chem. Soc. Rev.* ***1980***, *9*, 477.

[1406]For reviews, see Johnson, C.R. *Aldrichimica Acta* ***1985***, *18*, 1; *Acc. Chem. Res.* ***1973***, *6*, 341; Kennewell, P.D.; Taylor, J.B. *Chem. Soc. Rev.* ***1975***, *4*, 189; Trost, B.M. *Acc. Chem. Res.* ***1974***, *7*, 85.

[1407]Oswald, M.F.; Raw, S.A.; Taylor, R.J.K. *Org. Lett.* ***2004***, *6*, 3997.

[1408]Bestmann, H.J.; Seng, F. *Angew. Chem. Int. Ed.* ***1962***, *1*, 116; Grieco, P.A.; Finkelhor, R.S. *Tetrahedron Lett.* ***1972***, 3781.

[1409]Shestopalov, A.M.; Sharanin, Yu.A.; Litvinov, V.P.; Nefedov, O.M. *J. Org. Chem. USSR* ***1989***, *25*, 1000.

[1410]Cohen, T.; Myers, M. *J. Org. Chem.* ***1988***, *53*, 457.

[1411]Bertus, P.; Gandon, V.; Szymoniak, J. *Chem. Commun.* ***2000***, 171.

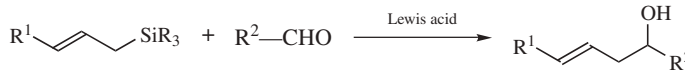
called the *Thorpe-Ziegler reaction*.[1412] This is a useful method for closing large rings. Yields are high for five- to eight-membered rings, fall off to about zero for rings of nine to thirteen members, but are high again for fourteen-membered and larger rings, if high-dilution techniques are employed. The product in the Thorpe–Ziegler reaction is not the imine, but the tautomeric enamine, for example, **81**; if desired this can be hydrolyzed to an α-cyano ketone (**16-2**), which can in turn be hydrolyzed and decarboxylated (**16-4**, **12-40**). Other active-hydrogen compounds can also be added to nitriles.[1413]

OS **VI**, 932.

H. Other Carbon or Silicon Nucleophiles

16-51 Addition of Silanes

***O*-Hydro-*C*-alkyl-addition**



Allylic silanes react with aldehydes, in the presence of Lewis acids, to give a homoallylic alcohol.[1414] In the case of benzylic silanes, this addition reaction has been induced with $Mg(ClO_4)_2$ under photochemical conditions.[1415] Cyclopropylcarbinyl silanes add to acetals in the presence of TMSOTf to give a homoallylic alcohol.[1416] Allyltrichlorosilane adds an allyl group to an aldehyde in the presence of a cyclic urea and AgOTf.[1417] The addition of chiral additives leads to the alcohol with good asymmetric induction.[1418] In a related reaction, allylic silanes react with acyl halides to produce the corresponding carbonyl derivative. The reaction of phenyl chloroformate, allyltrimethylsilane and $AlCl_3$, for example, gave phenyl but-3-enoate.[1419]

Allylic silanes also add to imines, in the presence of $TiCl_4$, to give amines.[1420]

[1412]For a monograph, see Taylor, E.C.; McKillop, A. *The Chemistry of Cyclic Enaminonitriles and ortho-Amino Nitriles*, Wiley, NY, ***1970***. For a review, see Schaefer, J.P.; Bloomfield, J.J. *Org. React.* ***1967***, *15*, 1.

[1413]See, for example, Josey, A.D. *J. Org. Chem.* ***1964***, *29*, 707; Barluenga, J.; Fustero, S.; Rubio, V.; Gotor, V. *Synthesis* ***1977***, 780; Hiyama, T.; Kobayashi, K. *Tetrahedron Lett.* ***1982***, *23*, 1597; Gewald, K.; Bellmann, P.; Jänsch, H. *Liebigs Ann. Chem.* ***1984***, 1702; Page, P.C.B.; van Niel, M.B.; Westwood, D. *J. Chem. Soc. Perkin Trans. 1* ***1988***, 269.

[1414]Panek, J.S.; Liu, P. *Tetrahedron Lett.* ***1997***, *38*, 5127.

[1415]Fukuzumi, S.; Okamoto, T.; Otera, J. *J. Am. Chem. Soc.* ***1994***, *116*, 5503.

[1416]Braddock, D.C.; Badine, D.M.; Gottschalk, T. *Synlett* ***2001***, 1909.

[1417]Chataigner, I.; Piarulli, U.; Gennari, C. *Tetrahedron Lett.* ***1999***, *40*, 3633.

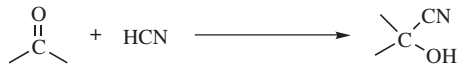
[1418]Ishihara, K.; Mouri, M.; Gao, Q.; Maruyama, T.; Furuta, K.; Yamamoto, H. *J. Am. Chem. Soc.* ***1993***, *115*, 11490.

[1419]Mayr, H.; Gabriel, A.O.; Schumacher, R. *Liebigs Ann. Chem.* ***1995***, 1583.

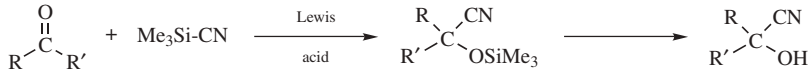
[1420]Kercher, T.; Livinghouse, T. *J. Am. Chem. Soc.* ***1996***, *118*, 4200.

16-52 The Formation of Cyanohydrins

***O*-Hydro-*C*-cyano-addition**



The addition of HCN to aldehydes or ketones produces cyanohydrins.[1421] This is an equilibrium reaction, and for aldehydes and aliphatic ketones the equilibrium lies to the right; therefore the reaction is quite feasible, except with sterically hindered ketones such as diisopropyl ketone. However, ketones ArCOR give poor yields, and the reaction cannot be carried out with ArCOAr since the equilibrium lies too far to the left. With aromatic aldehydes the benzoin condensation (**16-55**) competes. With α,β-unsaturated aldehydes and ketones, 1,4-addition competes (**15-38**). The reaction has been carried out enantioselectively: optically active cyanohydrins were prepared with the aid of optically active catalysts.[1422] Hydrogen cyanide adds to aldehydes in the presence of a lyase to give the cyanohydrin with good enantioselectivity.[1423] Cyanohydrins have been formed using a lyase in an ionic liquid.[1424]



82

Ketones of low reactivity, such as ArCOR, can be converted to cyanohydrins by treatment with diethylaluminum cyanide (Et_2AlCN) (see OS **VI**, 307) or, indirectly, with cyanotrimethylsilane (Me_3SiCN)[1425] in the presence of a Lewis acid or base,[1426]

[1421]For reviews, see Friedrich, K., in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C*, pt. 2, Wiley, NY, ***1983***, pp. 1345–1390; Friedrich, K.; Wallenfels, K., in Rappoport, Z. *The Chemistry of the Cyano Group*, Wiley, NY, ***1970***, pp. 72–77.

[1422]See Minamikawa, H.; Hayakawa, S.; Yamada, T.; Iwasawa, N.; Narasaka, K. *Bull. Chem. Soc. Jpn.* ***1988***, *61*, 4379; Jackson, W.R.; Jayatilake, G.S.; Matthews, B.R.; Wilshire, C. *Aust. J. Chem.* ***1988***, *41*, 203; Garner, C.M.; Fernández, J.M.; Gladysz, J.A. *Tetrahedron Lett.* ***1989***, *30*, 3931; Mori, A.; Ikeda, Y.; Kinoshita, K.; Inoue, S. *Chem. Lett.* ***1989***, 2119; Kobayashi, S.; Tsuchiya, Y.; Mukaiyama, T. *Chem. Lett.* ***1991***, 541; Gröger, H.; Capan, E.; Barthuber, A.; Vorlop, K.-D. *Org. Lett.* ***2001***, *3*, 1969, and references cited therein. For a review, see Brune, J.-M.; Holmes, I.P. *Angew. Chem. Int. Ed.* ***2004***, *43*, 2752.

[1423]Gerrits, P.J.; Marcus, J.; Birikaki, L.; van der Gen, A. *Tetrahedron Asymmetry* ***2001***, *12*, 971.

[1424]In bmim BF_4, 1-butyl-3-methylimidazolium tetrafluoroborate: Gaisberger, R.P.; Fechter, M.H.; Griengl, H. *Tetrahedron Asymmetry* ***2004***, *15*, 2959.

[1425]For reviews of Me_3SiCN and related compounds, see Rasmussen, J.K.; Heilmann, S.M.; Krepski, L. *Adv. Silicon Chem.* ***1991***, *1*, 65; Groutas, W.C.; Felker, D. *Synthesis* ***1980***, 861. For procedures using Me_3SiCl and ^-CN instead of Me_3SiCN, see Yoneda, R.; Santo, K.; Harusawa, S.; Kurihara, T. *Synthesis* ***1986***, 1054; Sukata, K. *Bull. Chem. Soc. Jpn.* ***1987***, *60*, 3820.

[1426]Kobayashi, S.; Tsuchiya, Y.; Mukaiyama, T. *Chem. Lett.* ***1991***, 537; Belokon', Y.; Flego, M.; Ikonnikov, N.; Moscalenko, M.; North, M.; Orizu, C.; Tararov, V.; Tasinazzo, M. *J. Chem. Soc. Perkin Trans. 1* ***1997***, 1293; Wada, M.; Takahashi, T.; Domae, T.; Fukuma, T.; Miyoshi, N.; Smith, K. *Tetrahedron Asymmetry*, ***1997***, *8*, 3939; Kanai, M.; Hamashima, Y.; Shibasaki, M. *Tetrahedron Lett.* ***2000***, *41*, 2405. The reaction works in some cases without a Lewis acid, see Manju, K.; Trehan, S. *J. Chem. Soc. Perkin Trans. 1* ***1995***, 2383.

followed by hydrolysis of the resulting *O*-trimethylsilyl cyanohydrin **82**. Solvent-free conditions have been reported using TMSCN, an aldehydes and potassium carbonate.[1427] Amine *N*-oxides catalyze the reaction[1428] as does tetrabutylammonium cyanide.[1429] Lithium perchlorate in ether facilitates this reaction.[1430] With $MgBr_2$ as a catalyst, the reaction proceeds to good syn selectivity. [1431] Other useful catalysts include platinum complexes,[1432] $Ti(OiPr)_4$,[1433] and $InBr_3$.[1434] When $TiCl_4$ is used, the reaction between Me_3SiCN and aromatic aldehydes or ketones gives α-chloro nitriles (ClCRR′—CN).[1435] The use of chiral additives in this latter reaction leads to cyanohydrins with good asymmetric induction.[1436] Sulfoximine–titanium reagents have been used in enantioselective trimethylsilyl cyanations of aldehydes.[1437] Chiral transition-metal catalysts have been used to give *O*-trialkylsilyl cyanohydrins with good enantioselectivity, including titanium complexes[1438] as well as complexes of other metals.[1439] A vanadium catalysts has been used in an ionic liquid.[1440] Note that the reaction of an aldehyde and TMSCN in the presence of aniline and a $BiCl_3$ catalyst leads to an α-cyano amine.[1441] α-Cyano amines are also formed by the reaction of an aldehyde with $(Et_2N)_2BCN$.[1442]

[1427]He, B.; Li, Y.; Feng, X.; Zhang, G. *Synlett* ***2004***, 1776.

[1428]Shen, Y.; Feng, X.; Li, Y.; Zhang, G.; Jiang, Y. *Tetrahedron* ***2003***, *59*, 5667. See Bakendale, I.R.; Ley, S.V.; Sneddon, H.F. *Synlett* ***2002***, 775; Shen, Y.; Feng, X.; Li, Y.; Zhang, G.; Jiang, Y. *Eur. J. Org. Chem.* ***2004***, 129.

[1429]Amurrio, I.; Córdoba, R.; Csákÿ, A.G.; Plumet, J. *Tetrahedron* ***2004***, *60*, 10521.

[1430]Jenner, G. *Tetrahedron Lett.* ***1999***, *40*, 491.

[1431]Ward, D.E.; Hrapchak, M.J.; Sales, M. *Org. Lett.* ***2000***, *2*, 57.

[1432]Fossey, J.S.; Richards, C.J. *Tetrahedron Lett.* ***2003***, *44*, 8773.

[1433]Huang, W.; Song, Y.; Bai, C.; Cao, G.; Zheng, Z. *Tetrahedron Lett.* ***2004***, *45*, 4763; He, B.; Chen, F.-X.; Li, Y.; Feng, X.; Zhang, G. *Tetrahedron Lett.* ***2004***, *45*, 5465.

[1434]Bandini, M.; Cozzi, P.G.; Melchiorre, P.; Umani-Ronchi, A. *Tetrahedron Lett* ***2001***, *42*, 3041.

[1435]Kiyooka, S.; Fujiyama, R.; Kawaguchi, K. *Chem. Lett.* ***1984***, 1979.

[1436]Tararov, V.I.; Hibbs, D.E.; Hursthouse, M.B.; Ikonnikov, N.S.; Malik, K.M.A.; North, M.; Orizu, C.; Belokon, Y.N. *Chem. Commun.* ***1998***, 387; Bolm, C.; Müller, P. *Tetrahedron Lett.* ***1995***, *36*, 1625; Ryu, D.H.; Corey, E.J. *J. Am. Chem. Soc.* ***2004***, *126*, 8106.

[1437]Bolm, C.; Müller, P.; Harms, K. *Acta Chem. Scand. B*, ***1996***, *50*, 305.

[1438]Hamashima, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem.Soc.* ***2000***, *122*, 7412; Belokon, Y.N.; Green, B.; Ikonnikov, N.S.; North, M.; Parsons, T.; Tararov, V.I. *Tetrahedron* ***2001***, *57*, 771 and references cited therein; Liang, S.; Bu, X.R. *J. Org. Chem.* ***2002***, *67*, 2702; Li, Y.; He, B.; Qin, B.; Feng, X.; Zhang, G. *J. Org. Chem.* ***2004***, *69*, 7910; Chen, F.-X.; Qin, B.; Feng, X.; Zhang, G.; Jiang, Y. *Tetrahedron* ***2004***, *60*, 10449; Uang, B.-J.; Fu, I.-P.; Hwang, C.-D.; Chang, C.-W.; Yang, C.-T.; Hwang, D.-R. *Tetrahedron* ***2004***, *60*, 10479; Gama, A.; Flores-López, L.-Z.; Aguirre, G.; Parra-Hake, M.; Somanathan, R.; Walsh, P.J. *Tetrahedron Asymmetry* ***2002***, *13*, 149.

[1439]Transition metals used include **Yb**: Aspinall, H.C.; Greeves, N.; Smith, P.M. *Tetrahedron Lett.* ***1999***, *40*, 1763. **Al**: Hamashima, Y.; Sawada, D.; Nogami, H.; Kanai, M.; Shibasaki, M. *Tetrahedron* ***2001***, *57*, 805; Deng, H.; Isler, M.P.; Snapper, M.L.; Hoveyda, A.H. *Angew. Chem. Int. Ed.* ***2002***, *41*, 1009. **Sc**: Karimi, B.; Ma'Mani, L. *Org. Lett.* ***2004***, *6*, 4813.

[1440]In bmim PF_6, 1-butyl-3-methylimidazolium hexafluorophosphate: Baleizão, C.; Gigante, B.; Garcia, H.; Corma, A. *Tetrahedron Lett.* ***2003***, *44*, 6813.

[1441]De, S.K.; Gibbs, R.A. *Tetrahedron Lett.* ***2004***, *45*, 7407.

[1442]Suginome, M.; Yamamoto, A.; Ito, Y. *Chem. Commun.* ***2002***, 1392.

Ketones can be converted to cyanohydrin *O*-carbonates, $R_2C(CN)OCO_2R'$, by reaction with $EtO_2C{-}CN$. In the presence of a Cinchona alkaloid, the product is formed with good enantioselectivity.[1443] Potassium cyanide and acetic anhydride reacts with an aldehyde in the presence of a chiral titanium catalyst to give an α-acetoxy nitrile.[1444]

Rather than direct reaction with an aldehyde or ketone, the bisulfite addition product is often treated with cyanide. The addition is nucleophilic and the actual nucleophile is ^-CN, so the reaction rate is increased by the addition of base.[1445] This was demonstrated by Lapworth in 1903, and consequently this was one of the first organic mechanisms to be known.[1446] This method is especially useful for aromatic aldehydes, since it avoids competition from the benzoin condensation. If desired, it is possible to hydrolyze the cyanohydrin *in situ* to the corresponding α-hydroxy acid. This reaction is important in the *Kiliani–Fischer* method of extending the carbon chain of a sugar.

A particularly useful variation of this reaction uses cyanide rather than HCN. α-Amino nitriles[1447] can be prepared in one step by the treatment of an aldehyde or ketone with NaCN and NH_4Cl. This is called the *Strecker synthesis*;[1448] and it is a special case of the Mannich reaction (**16-19**). Since the CN is easily hydrolyzed to the acid, this is a convenient method for the preparation of α-amino acids. The reaction has also been carried out with $NH_3 + HCN$ and with NH_4CN. Salts of primary and secondary amines can be used instead of NH_4^+ to obtain *N*-substituted and *N,N*-disubstituted α-amino nitriles. Unlike **16-52**, the Strecker synthesis is useful for aromatic as well as aliphatic ketones. As in **16-52**, the Me_3SiCN method has been used; **76** is converted to the product with ammonia or an amine.[1449] The effect of pressure on the Strecker synthesis has been studied.[1450]

OS **I**, 336; **II**, 7, 29, 387; **III**, 436; **IV**, 58, 506; **VI**, 307; **VII**, 20, 381, 517, 521. For the reverse reaction, see OS **III**, 101. For the Strecker synthesis, see OS **I**, 21, 355; **III**, 66, 84, 88, 275; **IV**, 274; **V**, 437; **VI**, 334.

[1443]Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* ***2001***, *123*, 6195.

[1444]Belokon, Y.N.; Gutnov, A.V.; Moskalenko, M.A.; Yashkina, L.V.; Lesovoy, D.E.; Ikonnikov, N.S.; Larichev, V.S.; North, M. *Chem. Commun.* ***2002***, 244; Kawasaki, Y.; Fujii, A.; Nakano, Y.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* ***1999***, *64*, 4214.

[1445]For a review, see Ogata, Y.; Kawasaki, A., in Zabicky, J. *The Chemistry of the Carbonyl Group*, Vol. 2, Wiley, NY, ***1970***, pp. 21–32. See also, Okano, V.; do Amaral, L.; Cordes, E.H. *J. Am. Chem. Soc.* ***1976***, *98*, 4201; Ching, W.; Kallen, R.G. *J. Am. Chem. Soc.* ***1978***, *100*, 6119.

[1446]Lapworth, A. *J. Chem. Soc.* ***1903***, *83*, 998.

[1447]For a review of α-amino nitriles, see Shafran, Yu.M.; Bakulev, V.A.; Mokrushin, V.S. *Russ. Chem. Rev.* ***1989***, *58*, 148.

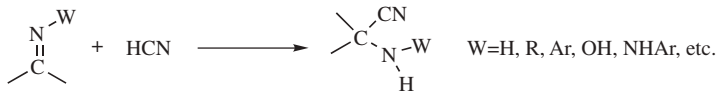
[1448]For a review of asymmetric Strecker syntheses, see Williams, R.M. *Synthesis of Optically Active α-Amino Acids*, Pergamon, Elmsford, NY, ***1989***, pp. 208–229; Yet, L. *Angew. Chem. Int. Ed.* ***2001***, *40*, 875; Gröger, H. *Chem. Rev.* ***2003***, *103*, 2795.

[1449]See Mai, K.; Patil, G. *Tetrahedron Lett.* ***1984***, *25*, 4583; *Synth. Commun.* ***1985***, *15*, 157.

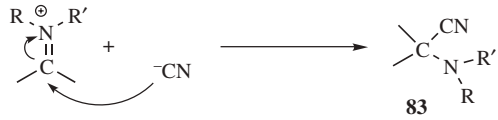
[1450]Jenner, G.; Salem, R.B.; Kim, J.C.; Matsumoto, K. *Tetrahedron Lett.* ***2003***, *44*, 447.

16-53 The Addition of HCN to C=N and C≡N Bonds

N-Hydro-*C*-cyano-addition



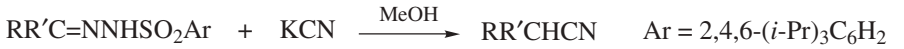
HCN adds to imines, Schiff bases, hydrazones, oximes, and similar compounds. Cyanide can be added to iminium ions to give α-cyano amines (**83**).



83

As in **16-50**, the addition to imines has been carried out enantioselectively.[1451] Chiral ammonium salts have been used with HCN.[1452] TMSCN reacts with *N*-tosyl imines in the presence of BF_3•OEt_2 to give the α-cyano *N*-tosyl amine.[1453] In the presence of a chiral zirconium[1454] or aluminum[1455] catalyst, Bu_3SnCN react with imines to give α-cyanoamines enantioselectively. The reaction of an imine and TMSCN gives the cyano amine with good enantioselectivity using a chiral scandium catalyst.[1456] Titanium catalysts have been used in the presence of a chiral Schiff base.[1457] Treatment of an imine with a chiral 1,4,6- triazabicyclo[3.3.0]oct-4-ene and then HCN give the α-cyano amine with good enantioselectivity.[1458]

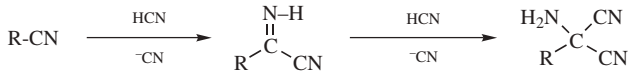
The addition of KCN to triisopropylbenzenesulfonyl hydrazones **84** provides an indirect method for achieving the conversion RR′CO → RR′CHCN.[1459] The reaction is successful for hydrazones of aliphatic aldehydes and ketones.



84

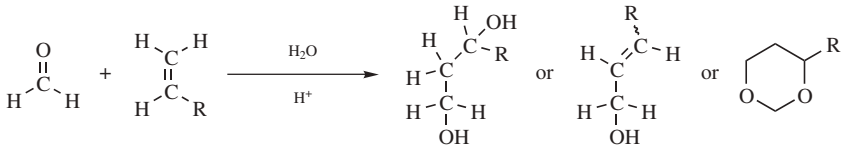
[1451]Saito, K.; Harada, K. *Tetrahedron Lett.* ***1989***, *30*, 4535.
[1452]Huang, J.; Corey, E.J. *Org. Lett.* ***2004***, *6*, 5027.
[1453]Prasad, B.A.B.; Bisai, A.; Singh, V.K. *Tetrahedron Lett.* ***2004***, *45*, 9565.
[1454]Ishitani, H.; Komiyama, S.; Hasegawa, Y.; Kobayashi, S. *J. Am. Chem. Soc.* ***2000***, *122*, 762.
[1455]Nakamura, S.; Sato, N.; Sugimoto, M.; Toru, T. *Tetrahedron Asymmetry* ***2004***, *15*, 1513.
[1456]Chavarot, M.; Byrne, J.J.; Chavant, P.Y.; Vallée, Y. *Tetrahedron Asymmetry* ***2001***, *12*, 1147.
[1457]Krueger, C.A.; Kuntz, K.W.; Dzierba, C.D.; Wirschun, W.G.; Gleason, J.D.; Snapper, M.L.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***1999***, *121*, 4284.
[1458]Corey, E.J.; Grogan, M.J. *Org. Lett.* ***1999***, *1*, 157.
[1459]Jiricny, J.; Orere, D.M.; Reese, C.B. *J. Chem. Soc. Perkin Trans. 1* ***1980***, 1487. For other methods of achieving this conversion, see Ziegler, F.E.; Wender, P.A. *J. Org. Chem.* ***1977***, *42*, 2001; Cacchi, S.; Caglioti, L.; Paolucci, G. *Synthesis* ***1975***, 120; Yoneda, R.; Harusawa, S.; Kurihara, T. *Tetrahedron Lett.* ***1989***, *30*, 3681; Okimoto, M.; Chiba, T. *J. Org. Chem.* ***1990***, *55*, 1070.

HCN can also be added to the C≡N bond to give iminonitriles or α-aminomalononitriles.[1460]

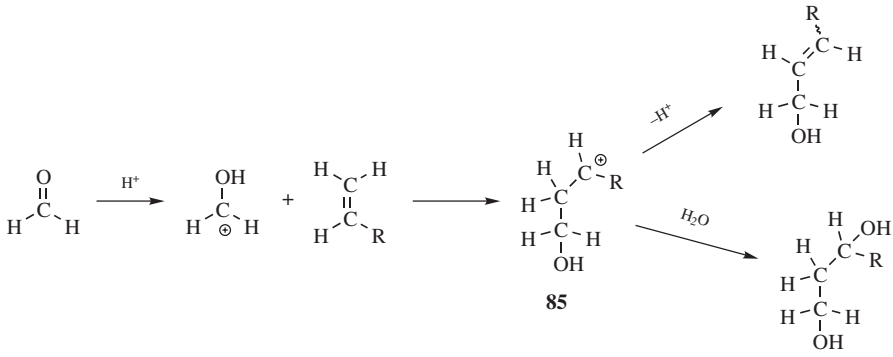


OS **V**, 344. See also, OS **V**, 269.

16-54 The Prins Reaction



The addition of an alkene to formaldehyde in the presence of an acid[1461] catalyst is called the *Prins reaction*.[1462] Three main products are possible; which one predominates depends on the alkene and the conditions. When the product is the 1,3-diol or the dioxane,[1463] the reaction involves addition to the C=C as well as to the C=O. The mechanism is one of electrophilic attack on both double bonds. The acid first protonates the C=O, and the resulting carbocation is attacked by the C=C to give **85**.



The cation product **85** can undergo loss of H^+ to give the alkene or add water to give the diol.[1464] It has been proposed that **85** is stabilized by neighboring-group

[1460]For an example, see Ferris, J.P.; Sanchez, R.A. *Org. Synth.* ***V***, 344.

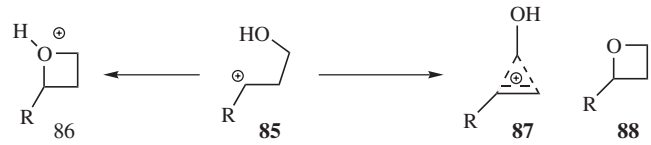
[1461]The Prins reaction has also been carried out with basic catalysts: Griengl, H.; Sieber, W. *Monatsh. Chem.* ***1973***, *104*, 1008, 1027.

[1462]For reviews, see Adams, D.R.; Bhatnagar, S.P. *Synthesis* ***1977***, 661; Isagulyants, V.I.; Khaimova, T.G.; Melikyan, V.R.; Pokrovskaya, S.V. *Russ. Chem. Rev.* ***1968***, *37*, 17. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, p. 248.

[1463]The reaction to produce dioxanes has also been carried out with equimolar mixtures of formaldehyde and another aldehyde RCHO. The R appears in the dioxane on the carbon between the two oxygens: Safarov, M.G.; Nigmatullin, N.G.; Ibatullin, U.G.; Rafikov, S.R. *Doklad. Chem.* ***1977***, *236*, 507.

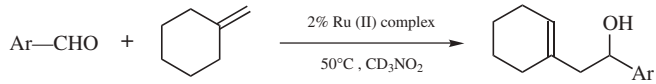
[1464]Hellin, M.; Davidson, M.; Coussemant, F. *Bull. Soc. Chim. Fr.* ***1966***, 1890, 3217.

attraction, with either the oxygen[1465] or a carbon[1466] stabilizing the charge (**86** and



87, respectively). This stabilization is postulated to explain the fact that with 2-butenes[1467] and with cyclohexenes the addition is anti. A backside attack of H_2O on the three- or four-membered ring would account for it. Other products are obtained too, which can be explained on the basis of **86** or **87**.[1465,1466] Additional evidence for the intermediacy of **86** is the finding that oxetanes (**88**) subjected to the reaction conditions (which would protonate **88** to give **86**) give essentially the same product ratios as the corresponding alkenes.[1468] An argument against the intermediacy of **86** and **87** is that not all alkenes show the anti-stereoselectivity mentioned above. Indeed, the stereochemical results are often quite complex, with syn, anti, and nonstereoselective addition reported, depending on the nature of the reactants and the reaction conditions.[1469] Since addition to the C=C bond is electrophilic, the reactivity of the alkene increases with alkyl substitution and Markovnikov's rule is followed. The dioxane product may arise from a reaction between the 1,3-diol and formaldehyde[1470] (**16-5**) or between **86** and formaldehyde.

Lewis acids, such as $SnCl_4$, also catalyze the reaction, in which case the species that adds to the alkenes is $H_2C^+—O^-—SnCl_4$.[1471] Montmorillonite K10 clay containing zinc (IV) has been used to promote the reaction.[1472] The reaction can also be catalyzed by peroxides, in which case the mechanism is probably a free-radical one. Other transition metal complexes can be used to form homoallylic alcohols. A typical example is the reaction of methylenecyclohexane with an aryl aldehyde to give **89**.[1473]



89

[1465]Blomquist, A.T.; Wolinsky, J. *J. Am. Chem. Soc.* ***1957***, *79*, 6025; Schowen, K.B.; Smissman, E.E.; Schowen, R.L. *J. Org. Chem.* ***1968***, *33*, 1873.

[1466]Dolby, L.J.; Lieske, C.N.; Rosencrantz, D.R.; Schwarz, M.J. *J. Am. Chem. Soc.* ***1963***, *85*, 47; Dolby, L.J.; Schwarz, M.J. *J. Org. Chem.* ***1963***, *28*, 1456; Safarov, M.G.; Isagulyants, V.I.; Nigmatullin, N.G. *J. Org. Chem. USSR* ***1974***, *10*, 1378.

[1467]Fremaux, B.; Davidson, M.; Hellin, M.; Coussemant, F. *Bull. Soc. Chim. Fr.* ***1967***, 4250.

[1468]Meresz, O.; Leung, K.P.; Denes, A.S. *Tetrahedron Lett.* ***1972***, 2797.

[1469]For example, see LeBel, N.A.; Liesemer, R.N.; Mehmedbasich, E. *J. Org. Chem.* ***1963***, *28*, 615; Portoghese, P.S.; Smissman, E.E. *J. Org. Chem.* ***1962***, *27*, 719; Wilkins, C.L.; Marianelli, R.S. *Tetrahedron* ***1970***, *26*, 4131; Karpaty, M.; Hellin, M.; Davidson, M.; Coussemant, F. *Bull. Soc. Chim. Fr.* ***1971***, 1736; Coryn, M.; Anteunis, M. *Bull. Soc. Chim. Belg.* ***1974***, *83*, 83.

[1470]Hellin, M.; Davidson, M; Coussemant, F *Bull. Soc. Chim. Fr.* ***1966***, 1890, 3217; Isagulyants, V.I.; Isagulyants, G.V.; Khairudinov, I.R.; Rakhmankulov, D.L. *Bull. Acad. Sci. USSR. Div. Chem. Sci.*, ***1973***, *22*, 1810; Sharf, V.Z.; Kheifets, V.I.; Freidlin, V.I. *Bull. Acad. Sci. USSR Div. Chem. Sci.*, ***1974***, *23*, 1681.

[1471]Yang, D.H.; Yang, N.C.; Ross, C.B. *J. Am. Chem. Soc.* ***1959***, *81*, 133.

[1472]Tateiwa, J.-i.; Kimura, A.; Takasuka, M.; Uemura, S. *J. Chem. Soc. Perkin Trans. 1* ***1997***, 2169.

[1473]Ellis, W.W.; Odenkirk, W.; Bosnich, B. *Chem. Commun.* ***1998***, 1311.

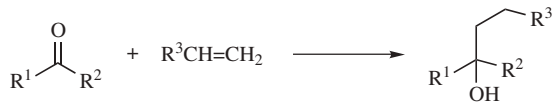
Samarium iodide promotes this addition reaction.[1474] In a related reaction, simple alkene units add to esters in the presence of sodium and liquid ammonia to give an alcohol.[1475] Structural variations in the alkene lead to different products. Homoallylic alcohols react with aldehydes in the presence of Montmorillonite KSF clay to give 4-hydroxytetrahydropyrans.[1476] A variation of this reaction converts an aryl aldehyde and a homoallylic alcohol to a 4-chlorotetrahydropyran in the presence of $InCl_3$.[1477] Homoallylic alcohols, protected as —O(CHMeOAc) react with BF_3•OEt_2 and acetic acid to give 4-acetoxytetrahydropyrans or with $SnBr_4$ to give 4-bromotetrahydropyrans.[1478] Homoallylic alcohols with a vinyl silane moiety react with $InCl_3$ and an aldehyde to give a dihydropyran.[1479]

A closely related reaction has been performed with activated aldehydes or ketones; without a catalyst such as chloral and acetoacetic ester, but with heat.[1480] The product in these cases is a β-hydroxy alkene, and the mechanism is pericyclic:[1481]

This reaction is reversible and suitable β-hydroxy alkenes can be cleaved by heat (**17-32**). There is evidence that the cleavage reaction occurs by a cyclic mechanism (p. 1551), and, by the principle of microscopic reversibility, the addition mechanism should be cyclic too.[1482] Note that this reaction is an oxygen analog of the ene synthesis (**15-23**). This reaction can also be done with unactivated aldehydes[1483] and ketones[1484] if Lewis-acid catalysts such as dimethylaluminum chloride (Me_2AlCl) or ethylaluminum dichloride ($EtAlCl_2$) are used.[1485] Lewis acid catalysts

[1474]Sarkar, T.K.; Nandy, S.K. *Tetrahedron Lett.* ***1996***, *37*, 5195.
[1475]Cossy, J.; Gille, B.; Bellosta, V. *J. Org. Chem.* ***1998***, *63*, 3141.
[1476]Yadav, J.S.; Reddy, B.V.S.; Kumar, G.M.; Murthy, Ch.V.S.R. *Tetrahedron Lett.* ***2001***, *42*, 89.
[1477]Yang, J.; Viswanathan, G.S.; Li, C.-J. *Tetrahedron Lett.* ***1999***, *40*, 1627.
[1478]Jaber, J.J.; Mitsui, K.; Rychnovsky, S.D. *J. Org. Chem.* ***2001***, *66*, 4679.
[1479]Dobbs, A.P.; Martinović, S. *Tetrahedron Lett.* ***2002***, *43*, 7055.
[1480]Arnold, R.T.; Veeravagu, P. *J. Am. Chem. Soc.* ***1960***, *82*, 5411; Klimova, E.I.; Abramov, A.I.; Antonova, N.D.; Arbuzov, Yu.A. *J. Org. Chem. USSR* ***1969***, *5*, 1308; Klimova, E.I.; Antonova, N.D.; Arbuzov, Yu.A. *J. Org. Chem. USSR* ***1969***, *5*, 1312, 1315.
[1481]See, for example, Achmatowicz, Jr., O.; Szymoniak, J. *J. Org. Chem.* ***1980***, *45*, 1228; Ben Salem, R.; Jenner, G. *Tetrahedron Lett.* ***1986***, *27*, 1575. There is evidence that the mechanism is somewhat more complicated than shown here: Kwart, H.; Brechbiel, M. *J. Org. Chem.* ***1982***, *47*, 3353.
[1482]For other evidence, see Achmatowicz Jr., O.; Szymoniak, J. *J. Org. Chem.* ***1980***, *45*, 1228; Ben Salem, R.; Jenner, G. *Tetrahedron Lett.* ***1986***, *27*, 1575; Papadopoulos, M.; Jenner, G. *Tetrahedron Lett.* ***1981***, *22*, 2773.
[1483]Snider, B.B. *Acc. Chem. Res.* ***1980***, *13*, 426; Cartaya-Marin, C.P.; Jackson, A.C.; Snider, B.B. *J. Org. Chem.* ***1984***, *49*, 2443.
[1484]Jackson, A.C.; Goldman, B.E.; Snider, B.B. *J. Org. Chem.* ***1984***, *49*, 3988.
[1485]For discussions of the mechanism with Lewis acid catalysts, see Stephenson, L.M.; Orfanopoulos, M. *J. Org. Chem.* ***1981***, *46*, 2200; Kwart, H.; Brechbiel, M. *J. Org. Chem.* ***1982***, *47*, 5409; Song, Z.; Beak, P. *J. Org. Chem.* ***1990***, *112*, 8126.

also increase rates with activated aldehydes.[1486] The use of optically active catalysts has given optically active products with high ee.[1487]



90

In a related reaction, alkenes can be added to aldehydes and ketones to give reduced alcohols **90**. This has been accomplished by several methods,[1488] including treatment with SmI_2[1489] or Zn and Me_3SiCl,[1490] and by electrochemical[1491] and photochemical[1492] methods. Most of these methods have been used for intramolecular addition and most or all involve free-radical intermediates.

OS **IV**, 786. See also, OS **VII**, 102.

16-55 The Benzoin Condensation

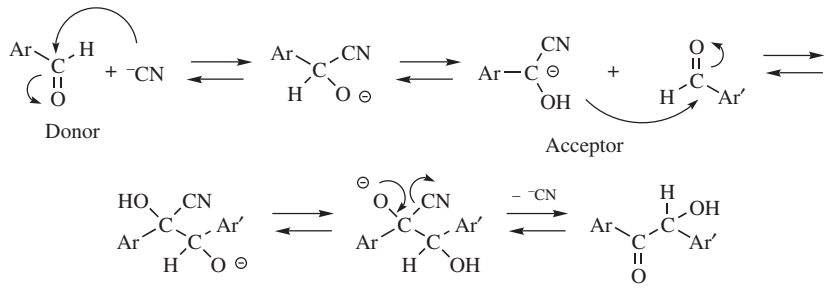
Benzoin aldehyde condensation

91

When certain aldehydes are treated with cyanide ion, *benzoins* (**91**) are produced in a reaction called the *benzoin condensation*. The condensation can be regarded as involving the addition of one molecule of aldehyde to the C=O group of another. The reaction only occurs with aromatic aldehydes, but not all of them,[1493] and for glyoxals RCOCHO. The two molecules of aldehyde obviously perform different functions. The one that no longer has a C–H bond in the product is called the *donor*, because it has "donated" its hydrogen to the oxygen of the other molecule, the *acceptor*. Some aldehydes can perform only one of these functions, and hence cannot be self-condensed, though they can often be condensed with a different aldehyde. For example, *p*-dimethylaminobenzaldehyde is not an acceptor but only a donor. Thus it cannot condense with itself, but it can condense with benzaldehyde, which can perform both functions, but is a better acceptor than it is a donor.

[1486]Benner, J.P.; Gill, G.B.; Parrott, S.J.; Wallace, B. *J. Chem. Soc. Perkin Trans. 1* ***1984***, 291, 315, 331.
[1487]Maruoka, K.; Hoshino, Y.; Shirasaka, T.; Yamamoto, H. *Tetrahedron Lett.* ***1988***, *29*, 3967; Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* ***1990***, *112*, 3949.
[1488]For references, see Ujikawa, O.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* ***1989***, *30*, 2837; Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1178–1179.
[1489]Ujikawa, O.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* ***1989***, *30*, 2837.
[1490]Corey, E.J.; Pyne, S.G. *Tetrahedron Lett.* ***1983***, *24*, 2821.
[1491]See Shono, T.; Kashimura, S.; Mori, Y.; Hayashi, T.; Soejima, T.; Yamaguchi, Y. *J. Org. Chem.* ***1989***, *54*, 6001.
[1492]See Belotti, D.; Cossy, J.; Pete, J.P.; Portella, C. *J. Org. Chem.* ***1986***, *51*, 4196.
[1493]For a review, see Ide, W.S.; Buck, J.S. *Org. React.* ***1948***, *4*, 269.

The following is the accepted mechanism[1494] for this reversible reaction, which was originally proposed by Lapworth in 1903:[1495]



The key step, the loss of the aldehydic proton, can take place because the acidity of this C—H bond is increased by the electron-withdrawing power of the CN group. Thus, cyanide is a highly specific catalyst for this reaction, because, almost uniquely, it can perform three functions: (*1*) It acts as a nucleophile; (*2*) its electron-withdrawing ability permits loss of the aldehydic proton; and (*3*) having done this, it then acts as a leaving group. Certain thiazolium salts can also catalyze the reaction.[1496] In this case, aliphatic aldehydes can also be used[1497] (the products are called *acyloins*), and mixtures of aliphatic and aromatic aldehydes give mixed α-hydroxy ketones.[1498] The reaction has also been carried out without cyanide, by using the benzoylated cyanohydrin as one of the components in a phase-transfer catalyzed process. By this means, products can be obtained from aldehydes that normally fail to self-condense.[1499] The condensation has also been done with excellent enantioselectivity using benzoylformate decarboxylase.[1500] Using aryl silyl ketones, $ArC(=O)SiMe_2Ph$, and aldehydes with a lanthanum catalyst, a 'mixed' benzoin condensation has been accomplished.[1501]

OS **I**, 94; **VII**, 95.

[1494]For a discussion, See Kuebrich, J.P.; Schowen, R.L.; Wang, M.; Lupes, M.E. *J. Am. Chem. Soc.* ***1971***, *93*, 1214.

[1495]Lapworth, A. *J. Chem. Soc.* ***1903***, *83*, 995; ***1904***, *85*, 1206.

[1496]See Ugai, T.; Tanaka, S.; Dokawa, S. *J. Pharm. Soc. Jpn.* ***1943***, *63*, 296 [*Chem. Abstr. 45*, 5148]; Breslow, R. *J. Am. Chem. Soc.* ***1958***, *80*, 3719; Breslow, R.; Kool, E. *Tetrahedron Lett.* ***1988***, *29*, 1635; Castells, J.; López-Calahorra, F.; Domingo, L. *J. Org. Chem.* ***1988***, *53*, 4433; Diederich, F.; Lutter, H. *J. Am. Chem. Soc.* ***1989***, *111*, 8438. For another catalyst, see Lappert, M.F.; Maskell, R.K. *J. Chem. Soc., Chem. Commun.* ***1982***, 580.

[1497]Stetter, H.; Rämsch, R.Y.; Kuhlmann, H. *Synthesis* ***1976***, 733; Stetter, H.; Kuhlmann, H. *Org. Synth.* ***VII***, 95; Matsumoto, T.; Ohishi, M.; Inoue, S. *J. Org. Chem.* ***1985***, *50*, 603.

[1498]Stetter, H.; Dämbkes, G. *Synthesis* ***1977***, 403.

[1499]Rozwadowska, M.D. *Tetrahedron* ***1985***, *41*, 3135.

[1500]Demir, A.S.; Dünnwald, T.; Iding, H.; Pohl, M.; Müller, M. *Tetrahedron Asymmetry* ***1999***, *10*, 4769.

[1501]Bausch, C.C.; Johnson, J.S. *J. Org. Chem.* ***2004***, *69*, 4283.

16-56 Addition of Radicals to C=O, C=S, C=N Compounds

Radical cyclization is not limited to reaction with a C=C unit (see **15-29** and **15-30**), and reactions with both C=N and C=O moieties are known. Reaction of $MeON{=}CH(CH_2)_3CHO$ with Bu_3SnH and AIBN, for example, led to *trans*-2-(methoxyamino)cyclopentanol in good yield.[1502] Conjugated ketones add to aldehyde via the β-carbon under radical conditions (2 equivalents of Bu_3SnH and 0.1 equivalent of CuCl) to give a β-hydroxy ketone.[1503] Addition of radical to the C=N unit of R–C=N–SPh[1504] or R–C=N–OBz[1505] led to cyclic imines. Radical addition to simple imines leads to aminocycloalkenes.[1506] Radical also add to the carbonyl unit of phenylthio esters to give cyclic ketones.[1507]

N,N-Dimethylaniline reacts with aldehydes under photochemical conditions to give acyl addition via the carbon atom of one of the methyl groups.[1508] The reaction of $PhNMe_2$ and benzaldehyde, for example, gave $PhN(Me)CH_2CH(OH)Ph$ upon photolysis.

ACYL SUBSTITUTION REACTIONS

A. O, N, and S Nucleophiles

16-57 Hydrolysis of Acyl Halides

Hydroxy-de-halogenation

$$RCOCl + H_2O \longrightarrow RCOOH$$

Acyl halides are so reactive that hydrolysis is easily carried out.[1509] In fact, most simple acyl halides must be stored under anhydrous conditions lest they react with water in the air. Consequently, water is usually a strong enough nucleophile for the reaction, though in difficult cases hydroxide ion may be required. The reaction is seldom synthetically useful, because acyl halides are normally prepared from acids. The reactivity order is $F < Cl < Br < I$.[1510] If a carboxylic acid is used as the nucleophile, an exchange may take place (see **16-79**). The mechanism[1510] of hydrolysis can be either S_N1 or tetrahedral, the former occurring in highly polar solvents

[1502]Tormo, J.; Hays, D.S.; Fu, G.C. *J. Org. Chem.* ***1998***, *63*, 201.
[1503]Ooi, T.; Doda, K.; Sakai, D.; Maruoka, K. *Tetrahedron Lett.* ***1999***, *40*, 2133.
[1504]Boivin, J.; Fouquet, E.; Zard, S.Z. *Tetrahedron* ***1994***, *50*, 1745.
[1505]Boivin, J.; Schiano, A.-M.; Zard, S.Z. *Tetrahedron Lett.* ***1994***, *35*, 249.
[1506]Bowman, W.R.; Stephenson, P.T.; Terrett, N.K.; Young, A.R. *Tetrahedron Lett.* ***1994***, *35*, 6369.
[1507]Kim, S.; Jon, S.Y. *Chem. Commun.* ***1996***, 1335.
[1508]Kim, S.S.; Mah, Y.J.; Kim, A.R. *Tetrahedron Lett.* ***2001***, *42*, 8315.
[1509]See Bentley, T.W.; Shim, C.S. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 1659 for a discussion on the solvolysis of acyl chlorides.
[1510]For a review, see Talbot, R.J.E., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 10; Elsevier, NY, ***1972***, pp. 226–257. For a review of the mechanisms of reactions of acyl halides with water, alcohols, and amines, see Kivinen, A., in Patai, S. *The Chemistry of Acyl Halides*, Wiley, NY, ***1972***, pp. 177–230.

and in the absence of strong nucleophiles.[1511] There is also evidence for the S_N2 mechanism in some cases.[1512]

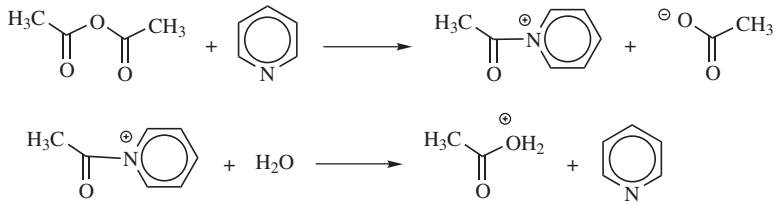
Hydrolysis of acyl halides is not usually catalyzed by acids, except for acyl fluorides, where hydrogen bonding can assist in the removal of F.[1513] There are several methods available for the hydrolysis of acyl fluorides.[1514]

OS **II**, 74.

16-58 Hydrolysis of Anhydrides

Hydroxy-de-acyloxy-substitution

Anhydrides are somewhat more difficult to hydrolyze than acyl halides, but here too water is usually a strong enough nucleophile. The mechanism is usually tetrahedral.[1515] Only under acid catalysis does the S_N1 mechanism occur and seldom even then.[1516] Anhydride hydrolysis can also be catalyzed by bases. Of course, hydroxide ion attacks more readily than water, but other bases can also catalyze the reaction. This phenomenon, called *nucleophilic catalysis* (p. 1258), is actually the result of two successive tetrahedral mechanisms. For example, pyridine catalyzes the hydrolysis of acetic anhydride in this manner.[1517]



Many other nucleophiles similarly catalyze the reaction.

OS **I**, 408; **II**, 140, 368, 382; **IV**, 766; **V**, 8, 813.

[1511]Bender, M.L.; Chen, M.C. *J. Am. Chem. Soc.* ***1963***, *85*, 30. See also, Song, B.D.; Jencks, W.P. *J. Am. Chem. Soc.* ***1989***, *111*, 8470; Bentley, T.W.; Koo, I.S.; Norman, S.J. *J. Org. Chem.* ***1991***, *56*, 1604.

[1512]Bentley, T.W.; Carter, G.E.; Harris, H.C.*J. Chem. Soc. Perkin Trans. 2* ***1985***, 983; Guthrie, J.P.; Pike, D.C. *Can. J. Chem.* ***1987***, *65*, 1951. See also, Lee, I.; Sung, D.D.; Uhm, T.S.; Ryu, Z.H. *J. Chem. Soc. Perkin Trans. 2* ***1989***, 1697.

[1513]Bevan, C.W.L.; Hudson, R.F. *J. Chem. Soc.* ***1953***, 2187; Satchell, D.P.N. *J. Chem. Soc.* ***1963***, 555.

[1514]Motie, R.E.; Satchell, D.P.N.; Wassef, W.N. *J. Chem. Soc. Perkin Trans. 2* ***1992***, 859; ***1993***, 1087.

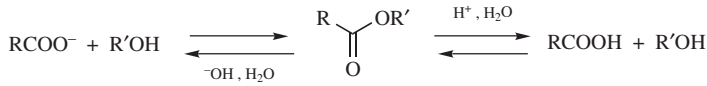
[1515]The kinetics of the acid hydrolysis has been determined. See Satchell, D.P.N.; Wassef, W.N.; Bhatti, Z.A. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 2373.

[1516]Satchell, D.P.N. *Q. Rev. Chem. Soc.* ***1963***, *17*, 160, 172–173. For a review of the mechanism, see Talbot, R.J.E., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 10, Elsevier, NY, ***1972***, pp. 280–287.

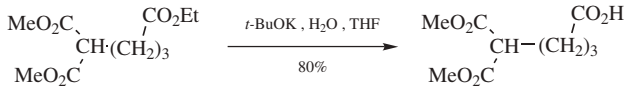
[1517]Butler, A.R.; Gold, V. *J. Chem. Soc.* ***1961***, 4362; Fersht, A.R.; Jencks, W.P. *J. Am. Chem. Soc.* ***1970***, *92*, 5432, 5442; Deady, L.W.; Finlayson, W.L. *Aust. J. Chem.* ***1983***, *36*, 1951.

16-59 Hydrolysis of Carboxylic Esters

Hydroxy-de-alkoxylation



Ester hydrolysis is usually catalyzed by acids or bases. Since OR is a much poorer leaving group than halide or OCOR, water alone does not hydrolyze most esters. When bases catalyze the reaction, the attacking species is the more powerful nucleophile $^-$OH. This reaction is called *saponification* and gives the salt of the acid. Acids catalyze the reaction by making the carbonyl carbon more positive and therefore more susceptible to attack by the nucleophile. Both reactions are equilibrium reactions, so they are practicable only when there is a way of shifting the equilibrium to the right. Since formation of the salt does just this, ester hydrolysis is almost always done for preparative purposes in basic solution, unless the compound is base sensitive. Even in the case of **92**, however, selective base hydrolysis of the ethyl ester gave an 80%



92 **93**

yield of the acid-dimethyl ester (**93**).[1518] Ester hydrolysis can also be catalyzed[1519] by metal ions, by cyclodextrins,[1520] by enzymes,[1521] and by nucleophiles.[14] Other reagents used to cleave carboxylic esters include Dowex-50,[1522] Me_3SiI,[1523] and $InCl_3$ on moist silica gel using microwave irradiation.[1524] Cleavage of phenolic esters is usually faster than carboxylic esters derived from aliphatic acids. The reagent Sm/I_2 at −78°C has been used,[1525] ammonium acetate in aqueous methanol,[1526]

[1518]Wilk, B.K. *Synth. Commun.* ***1996***, *26*, 3859.

[1519]For a list of catalysts and reagents that have been used to convert carboxylic esters to acids, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1959-1968.

[1520]See Bender, M.L.; Komiyama, M. *Cyclodextrin Chemistry*, Springer, NY, ***1978***, pp. 34–41. The mechanism is shown in Saenger, W. *Angew. Chem. Int. Ed.* ***1980***, *19*, 344.

[1521]For reviews of ester hydrolysis catalyzed by pig liver esterase, see Zhu, L.; Tedford, M.C. *Tetrahedron* ***1990***, *46*, 6587; Ohno, M.; Otsuka, M. *Org. React.* ***1989***, *37*, 1. For reviews of enzymes as catalysts in synthetic organic chemistry, see Wong, C. *Chemtracts: Org. Chem.* ***1990***, *3*, 91; *Science* ***1989***, *244*, 1145; Whitesides, G.M.; Wong, C. *Angew. Chem. Int. Ed.* ***1985***, *24*, 617. Addition of crown ethers can enhance the rate of hydrolysis, see Itoh, T.; Hiyama, Y.; Betchaku, A.; Tsukube, H. *Tetrahedron Lett.* ***1993***, *34*, 2617.

[1522]Basu, M.K.; Sarkar, D.C.; Ranu, B.C. *Synth. Commun.* ***1989***, *19*, 627.

[1523]See Olah, G.A.; Narang, S.C. *Tetrahedron* ***1982***, *38*, 2225; Olah, G.A.; Husain, A.; Singh, B.P.; Mehrotra, A.K. *J. Org. Chem.* ***1983***, *48*, 3667.

[1524]Ranu, B.C.; Dutta, P.; Sarkar, A. *Synth. Commun.* ***2000***, *30, 4167.*

[1525]Yanada, R.; Negoro, N.; Bessho, K.; Yanada, K. *Synlett* ***1995***, 1261.

[1526]Ramesh, C.; Mahender, G.; Ravindranath, N.; Das, B. *Tetrahedron* ***2003***, *59*, 1049.

Amberlyst 15 in methanol,[1527] and phenolic esters have been selectively hydrolyzed in the presence of alkyl esters on alumina with microwave irradiation.[1528] Thiophenol with K_2CO_3 in NMP quantitatively converted methyl benzoate to benzoic acid.[1529] Allylic esters were cleaved with 2% Me_3SiOTf in dichloromethane,[1530] with $CeCl_3 \cdot 7H_2O$—NaI,[1531] and with $NaHSO_4$•silica gel.[1532] Lactones also undergo the reaction[1533] (though if the lactone is five- or six-membered, the hydroxy acid often spontaneously reforms the lactone) and thiol esters (RCOSR′) give thiols R′SH. Typical reagents for this latter transformation include NaSMe in methanol,[1534] borohydride exchange resin-$Pd(OAc)_2$ for reductive cleavage of thiol esters to thiols,[1535] and $TiCl_4$/Zn for the conversion of phenylthioacetates to thiophenols.[1536] Sterically hindered esters are hydrolyzed with difficulty (p. 479), but reaction of 2 equivalents of *t*-BuOK with 1 equivalent of water is effective.[1537] Hindered esters can also be cleaved by sequential treatment with zinc bromide and then water,[1538] with silica gel in refluxing toluene,[1539] and on alumina when irradiated with microwaves.[1540] For esters insoluble in water the rate of two-phase ester saponification can be greatly increased by the application of ultrasound,[1541] and phase-transfer techniques have been applied.[1542] Enzymatic hydrolysis of diesters with esterase has been shown to give the hydroxy ester,[1543] and selective hydrolysis of dimethyl succinate to monomethyl succinic acid was accomplished with aq. NaOH in THF.[1544] Hydrolysis of vinyl esters leads to ketones, and the reaction of C-substituted vinyl acetates with an esterase derived from *Marchantia polymorpha* gave substituted ketones with high enantioselectivity.[1545] Scandium triflate was shown to hydrolyze α-acetoxy ketones to α-hydroxy ketones.[1546]

[1527]Das, B.; Banerjee, J.; Ramu, R.; Pal, R.; Ravindranath, N.; Ramesh, C. *Tetrahedron Lett.* ***2003***, *44*, 5465.
[1528]Varma, R.S.; Varma, M.; Chatterjee, A.K. *J. Chem. Soc. Perkin Trans. 1* ***1993***, 999; Blay, G.; Cardona, L.; Garcia, B.; Pedro, J.R. *Synthesis* ***1989***, 438.
[1529]Sharma, L.; Nayak, M.K.; Chakraborti, A.K. *Tetrahedron* ***1999***, *55*, 9595.
[1530]Nishizawa, M.; Yamamoto, H.; Seo, K.; Imagawa, H.; Sugihara, T. *Org. Lett.* ***2002***, *4*, 1947.
[1531]Yadav, J.S.; Reddy, B.V.S.; Rao, C.V.; Chand, P.K.; Prasad, A.R. *Synlett* ***2002***, 137.
[1532]Ramesh, C.; Mahender, G.; Ravindranath, N.; Das, B. *Tetrahedron Lett.* ***2003***, *44*, 1465.
[1533]For a review of the mechanisms of lactone hydrolysis, see Kaiser, E.T.; Kézdy, F.J. *Prog. Bioorg. Chem.* ***1976***, *4*, 239, pp. 254–265.
[1534]Wallace, O.B.; Springer, D.M. *Tetrahedron Lett.* ***1998***, *39*, 2693.
[1535]Choi, J.; Yoon, N.M. *Synth. Commun.* ***1995***, *25*, 2655.
[1536]Jin, C.K.; Jeong, H.J.; Kim, M.K.; Kim, J.Y.; Yoon, Y.-J.; Lee, S.-G. *Synlett* ***2001***, 1956.
[1537]Gassman, P.G.; Schenk, W.N. *J. Org. Chem.* ***1977***, *42*, 918.
[1538]Wu, Y.-g.; Limburg, D.C.; Wilkinson, D.E.; Vaal, M.J.; Hamilton, G.S. *Tetrahedron Lett.* ***2000***, *41*, 2847.
[1539]Jackson, R.W. *Tetrahedron Lett.* ***2001***, *42*, 5163.
[1540]Ley, S.V.; Mynett, D.M. *Synlett* ***1993***, 793.
[1541]Moon, S.; Duchin, L.; Cooney, J.V. *Tetrahedron Lett.* ***1979***, 3917.
[1542]Loupy, A.; Pedoussaut, M.; Sansoulet, J. *J. Org. Chem.* ***1986***, *51*, 740.
[1543]Houille, O.; Schmittberger, T.; Uguen, D. *Tetrahedron Lett.* ***1996***, *37*, 625; Nair, R.V.; Shukla, M.R.; Patil, P.N.; Salunkhe, M.M. *Synth. Commun.* ***1999***, *29*, 1671.
[1544]Niwayama, S. *J. Org. Chem.* ***2000***, *65*, 5834.
[1545]Hirata, T.; Shimoda, K.; Kawano, T. *Tetrahedron Asymmetry* ***2000***, *11*, 1063.
[1546]Kajiro, H.; Mitamura, S.; Mori, A.; Hiyama, T. *Bull. Chem. Soc. Jpn.* ***1999***, *72*, 1553.

Ingold[1547] has classified the acid- and base-catalyzed hydrolyses of esters (and the formation of esters, since these are reversible reactions and thus have the same mechanisms) into eight possible mechanisms (Table 16.3), depending on the

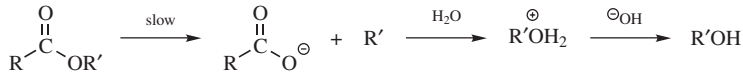
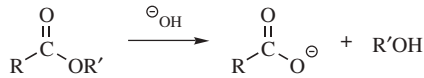
TABLE 16.3. Classification of the Eight Mechanisms for Ester Hydrolysis and Formation[1547]

	Name	
Ingold	IUPAC[1548]	Type
$A_{AC}1$	$A_h + D_N + A_N + D_h$	S_N1
$A_{AC}2$	$A_h + A_N + A_hD_h + D_h$	Tetrahedral
$A_{AL}1$	$A_h + D_N + A_N + D_h$	S_N1
$A_{AL}2$	$A_h + A_ND_N + D_h$	S_N2
$B_{AC}1$	$D_N + A_N + A_{xh}D_h$	S_N1
$B_{AC}2$	$A_N + D_N + A_{xh}D_h$	Tetrahedral

[1547]Ingold, C.K. *Structure and Mechanism in Organic Chemistry*, 2nd ed., Cornell University Press, Ithaca, NY, ***1969***, pp. 1129–1131.

[1548]As given here, the IUPAC designations for $B_{AC}1$ and $B_{AL}1$ are the same, but Rule A.2 adds further symbols so that they can be distinguished: Su-AL for $B_{AL}1$ and Su-AC for $B_{AC}1$. See the IUPAC rules: Guthrie, R.D. *Pure Appl. Chem.* ***1989***, *61*, 23, see p. 49.

TABLE 16.3. (*Continued*)

	Name	
Ingold	IUPAC	Type
$B_{AL}1$	$D_N + A_N + A_{xh}D_h$	S_N1
		
$B_{AL}2$	A_ND_N	S_N2
		

following criteria: (*1*) acid- or base-catalyzed, (*2*) unimolecular or bimolecular, and (*3*) acyl cleavage or alkyl cleavage.[1549] All eight of these are S_N1, S_N2, or tetrahedral mechanisms. The acid-catalyzed mechanisms are shown with reversible arrows. They are not only reversible, but symmetrical; that is, the mechanisms for ester formation are exactly the same as for hydrolysis, except that H replaces R. Internal proton transfers, such as shown for **B** and **C**, may not actually be direct but may take place through the solvent. There is much physical evidence to show that esters are initially protonated on the carbonyl and not on the alkyl oxygen (Chapter 8, Ref. 17). We have nevertheless shown the $A_{AC}1$ mechanism as proceeding through the ether-protonated intermediate **A**, since it is difficult to envision OR′ as a leaving group here. It is of course possible for a reaction to proceed through an intermediate even if only a tiny concentration is present. The designations $A_{AC}1$, and so on., are those of Ingold. The $A_{AC}2$ and $A_{AC}1$ mechanisms are also called A2 and A1, respectively. Note that the $A_{AC}1$ mechanism is actually the same as the S_N1cA mechanism for this type of substrate and that $A_{AL}2$ is analogous to S_N2cA. Some authors use A1 and A2 to refer to all types of nucleophilic substitution in which the leaving group first acquires a proton. The base-catalyzed reactions are not shown with reversible arrows, since they are reversible only in theory and not in practice. Hydrolyses taking place under neutral conditions are classified as B mechanisms.

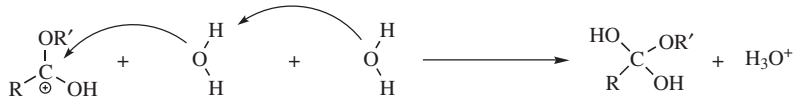
Of the eight mechanisms, seven have actually been observed in hydrolysis of carboxylic esters. The one that has not been observed is the $B_{AC}1$ mechanism.[1550] The most common mechanisms are the $B_{AC}2$ for basic catalysis and the $A_{AC}2$[1551]

[1549]For reviews of the mechanisms of ester hydrolysis and formation, see Kirby, A.J., in Bamford, C.H.; Tipper, C.F.H., *Comprehensive Chemical Kinetics*, Vol. 10, ***1972***, pp. 57–207; Euranto, E.K., in Patai, S. *The Chemistry of Carboxylic Acids and Esters*, Wiley, NY, ***1969***, pp. 505–588.

[1550]This is an S_N1 mechanism with OR′ as leaving group, which does not happen.

[1551]For a discussion of this mechanism with specific attention to the proton transfers involved, see Zimmermann, H.; Rudolph, J. *Angew. Chem. Int. Ed.* ***1965***, *4*, 40.

for acid catalysis, that is, the two tetrahedral mechanisms. Both involve acyl-oxygen cleavage. The evidence is (*1*) hydrolysis with $H_2{}^{18}O$ results in the ^{18}O appearing in the acid and not in the alcohol;[1552] (*2*) esters with chiral R′ groups give alcohols with *retention* of configuration;[1553] (*3*) allylic R′ gives no allylic rearrangement;[1554] (*4*) neopentyl R′ gives no rearrangement;[1555] all these facts indicate that the O—R′ bond is not broken. It has been concluded that two molecules of water are required in the $A_{AC}2$ mechanism.



If this is so, the protonated derivatives **B** and **C** would not appear at all. This conclusion stems from a value of *w* (see p. 371) of ~5, indicating that water acts as a proton donor here, as well as a nucleophile.[1556] Termolecular processes are rare, but in this case the two water molecules are already connected by a hydrogen bond. (A similar mechanism, called $B_{AC}3$, also involving two molecules of water, has been found for esters that hydrolyze without a catalyst.[1557] Such esters are mostly those containing halogen atoms in the R group.)

The other mechanism involving acyl cleavage is the $A_{AC}1$ mechanism. This is rare, being found only where R is very bulky, so that bimolecular attack is sterically hindered, and only in ionizing solvents. The mechanism has been demonstrated for esters of 2,4,6-trimethylbenzoic acid (mesitoic acid). This acid depresses the freezing point of sulfuric acid four times as much as would be predicted from its molecular weight, which is evidence for the equilibrium

$$\mathrm{ArCOOH} + 2\,\mathrm{H_2SO_4} \rightleftharpoons \mathrm{ArCO^{\oplus}} + \mathrm{H_3O^+} + 2\,\mathrm{HSO_4^-}$$

In a comparable solution of benzoic acid the freezing point is depressed only twice the predicted amount, indicating only a normal acid-base reaction. Further, a sulfuric acid solution of methyl mesitoate when poured into water gave mesitoic acid, while a similar solution of methyl benzoate similarly treated did not.[1558] The $A_{AC}1$ mechanism is also found when acetates of phenols or of primary alcohols are

[1552]For one of several examples, see Polanyi, M.; Szabo, A.L. *Trans. Faraday Soc.* ***1934***, *30*, 508.
[1553]Holmberg, B. *Ber.* ***1912***, *45*, 2997.
[1554]Ingold, C.K.; Ingold, E.H. *J. Chem. Soc.* ***1932***, 758.
[1555]Norton, H.M.; Quayle, O.R. *J. Am. Chem. Soc.* ***1940***, *62*, 1170.
[1556]Martin, R.B. *J. Am. Chem. Soc.* ***1962***, *84*, 4130. See also, Lane, C.A.; Cheung, M.F.; Dorsey, G.F. *J. Am. Chem. Soc.* ***1968***, *90*, 6492; Yates, K. *Acc. Chem. Res.* ***1971***, *6*, 136; Huskey, W.P.; Warren, C.T.; Hogg, J.L. *J. Org. Chem.* ***1981***, *46*, 59.
[1557]Euranto, E.K.; Kanerva, L.T.; Cleve, N.J. *J. Chem. Soc. Perkin Trans. 2* ***1984***, 2085; Neuvonen, H. *J. Chem. Soc. Perkin Trans. 2* ***1986***, 1141; Euranto, E.K.; Kanerva, L.T. *Acta Chem. Scand. Ser. B* ***1988***, *42* 717.
[1558]Treffers, H.P.; Hammett, L.P. *J. Am. Chem. Soc.* ***1937***, *59*, 1708. For other evidence for this mechanism, see Bender, M.L.; Chen, M.C. *J. Am. Chem. Soc.* ***1963***, *85*, 37.

hydrolyzed in concentrated (>90%) H_2SO_4 (the mechanism under the more usual dilute acid conditions is the normal $A_{AC}2$).[1559]

The mechanisms involving alkyl-oxygen cleavage are ordinary S_N1 and S_N2 mechanisms in which OCOR (an acyloxy group) or its conjugate acid is the leaving group. Two of the three mechanisms, the $B_{AL}1$ and $A_{AL}1$ mechanisms, occur most readily when R′ comes off as a stable carbocation, that is, when R′ is tertiary alkyl, allylic, benzylic, and so on. For acid catalysis, most esters with this type of alkyl group (especially tertiary alkyl) cleave by this mechanism, but even for these substrates, the $B_{AL}1$ mechanism occurs only in neutral or weakly basic solution, where the rate of attack by hydroxide is so slowed that the normally slow (by comparison) unimolecular cleavage takes over. These two mechanisms have been established by kinetic studies, ^{18}O labeling, and isomerization of R′.[1560] Secondary and benzylic acetates hydrolyze by the $A_{AC}2$ mechanism in dilute H_2SO_4, but in concentrated acid the mechanism changes to $A_{AL}1$.[1559] Despite its designation, the $B_{AL}1$ mechanism is actually uncatalyzed (as is the unknown $B_{AC}1$ mechanism).

The two remaining mechanisms, $B_{AL}2$ and $A_{AL}2$, are very rare, the $B_{AL}2$ because it requires hydroxide ion to attack an alkyl carbon when an acyl carbon is also available,[1561] and the $A_{AL}2$ because it requires water to be a nucleophile in an S_N2 process. Both have been observed, however. The $B_{AL}2$ has been seen in the hydrolysis of β-lactones under neutral conditions[1562] (because cleavage of the C—O bond in the transition state opens the four-membered ring and relieves strain), the alkaline hydrolysis of methyl 2,4,6-tri-*tert*-butyl benzoate,[1563] and in the unusual reaction[1564]

$$\mathrm{ArCOOMe} + \mathrm{RO^-} \longrightarrow \mathrm{ArCOO^-} + \mathrm{ROMe}$$

When it does occur, the $B_{AL}2$ mechanism is easy to detect, since it is the only one of the base-catalyzed mechanisms that requires inversion at R′. However, in the last example given, the mechanism is evident from the nature of the product, since the ether could have been formed in no other way. The $A_{AL}2$ mechanism has been reported in the acid cleavage of γ-lactones.[1565]

To sum up the acid-catalysis mechanisms, $A_{AC}2$ and $A_{AL}1$ are the common mechanisms, the latter for R′ that give stable carbocations, the former for practically

[1559]Yates, K. *Acc. Chem. Res.* ***1971***, *6*, 136; Al-Shalchi, W.; Selwood, T.; Tillett J.G. *J. Chem. Res. (S)* ***1985***, 10.

[1560]For discussions, see Kirby, A.J., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9, Elsevier, NY, ***1973***, pp. 86–101; Ingold, C.K. *Structure and Mechanism in Organic Chemistry*, 2nd ed., Cornell University Press, Ithaca, NY, ***1969***, pp. 1137–1142, 1157–1163.

[1561]Douglas, J.E.; Campbell, G.; Wigfield, D.C. *Can. J. Chem.* ***1993***, *71*, 1841.

[1562]Cowdrey, W.A.; Hughes, E.D.; Ingold, C.K.; Masterman, S.; Scott, A.D. *J. Chem. Soc.* ***1937***, 1264; Long, F.A.; Purchase, M. *J. Am. Chem. Soc.* ***1950***, *73*, 3267.

[1563]Barclay, L.R.C.; Hall, N.D.; Cooke, G.A. *Can. J. Chem.* ***1962***, *40*, 1981.

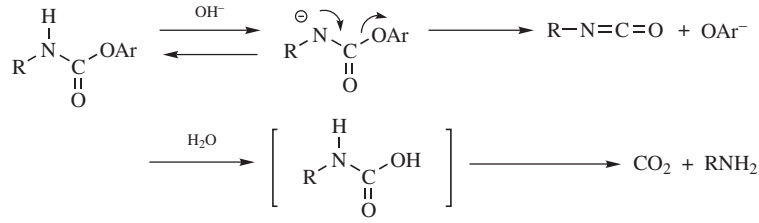
[1564]Sneen, R.A.; Rosenberg, A.M. *J. Org. Chem.* ***1961***, *26*, 2099. See also, Müller, P.; Siegfried, B. *Helv. Chim. Acta* ***1974***, *57*, 987.

[1565]Moore, J.A.; Schwab, J.W. *Tetrahedron Lett.* ***1991***, *32*, 2331.

all the rest. The $A_{AC}1$ mechanism is rare, being found mostly with strong acids and sterically hindered R. The $A_{AL}2$ mechanism is even rarer. For basic catalysis, $B_{AC}2$ is almost universal; $B_{AL}1$ occurs only with R′ that give stable carbocations and then only in weakly basic or neutral solutions; $B_{AL}2$ is very rare; and $B_{AC}1$ has never been observed.

The above results pertain to reactions in solution. In the gas-phase[1566] reactions can take a different course, as illustrated by the reaction of carboxylic esters with MeO^-, which in the gas phase was shown to take place only by the $B_{AL}2$ mechanism,[1567] even with aryl esters,[1568] where this means that an S_N2 mechanism takes place at an aryl substrate. However, when the gas-phase reaction of aryl esters was carried out with MeO^- ions, each of which was solvated with a single molecule of MeOH or H_2O, the $B_{AC}2$ mechanism was observed.[1567]

In the special case of alkaline hydrolysis of *N*-substituted aryl carbamates, there is another mechanism[1569] involving elimination–addition:[1570]



This mechanism does not apply to unsubstituted or *N,N*-disubstituted aryl carbamates, which hydrolyze by the normal mechanisms. Carboxylic esters substituted in the a position by an electron-withdrawing group (e.g., CN or COOEt) can also hydrolyze by a similar mechanism involving a ketene intermediate.[1571]

[1566]Takashima, K.; José, S.M.; do Amaral, A.T.; Riveros, J.M. *J. Chem. Soc., Chem. Commun.* ***1983***, 1255.
[1567]Comisarow, M. *Can. J. Chem.* ***1977***, *55*, 171.
[1568]Fukuda, E.K.; McIver Jr., R.T. *J. Am. Chem. Soc.* ***1979***, *101*, 2498.
[1569]For a review of elimination–addition mechanisms at a carbonyl carbon, see Williams, A.; Douglas, K.T. *Chem. Rev.* ***1975***, *75*, 627649.
[1570]Bender, M.L.; Homer, R.B. *J. Org. Chem.* ***1965***, *30*, 3975; Williams, A. *J. Chem. Soc. Perkin Trans. 2* ***1972***, 808; ***1973***, 1244; Hegarty, A.F.; Frost, L.N. *J. Chem. Soc. Perkin Trans. 2* ***1973***, 1719; Menger, F.M.; Glass, L.E. *J. Org. Chem.* ***1974***, *39*, 2469; Sartoré, G.; Bergon, M.; Calmon, J.P. *J. Chem. Soc. Perkin Trans. 2* ***1977***, 650; Moravcová, J.; Večeřa, M. *Collect. Czech. Chem. Commun.* ***1977***, *42*, 3048; Broxton, T.J.; Chung, R.P. *J. Org. Chem.* ***1986***, *51*, 3112.
[1571]Casanova, J.; Werner, N.D.; Kiefer, H.R. *J. Am. Chem. Soc.* ***1967***, *89*, 2411; Holmquist, B.; Bruice, T.C. *J. Am. Chem. Soc.* ***1969***, *91*, 2993, 3003; Campbell, D.S.; Lawrie, C.W. *Chem. Commun.* ***1971***, 355; Kirby, A.J.; Lloyd, G.J. *J. Chem. Soc. Perkin Trans. 2* ***1976***, 1762; Broxton, T.J.; Duddy, N.W. *J. Org. Chem.* ***1981***, *46*, 1186; Inoue, T.C.; Bruice, T.C. *J. Am. Chem. Soc.* ***1982***, *104*, 1644; *J. Org. Chem.* ***1983***, *48*, 3559; ***1986***, *51*, 959; Alborz, M.; Douglas, K.T. *J. Chem. Soc. Perkin Trans. 2* ***1982***, 331; Thea, S.; Cevasco, G.; Guanti, G.; Kashefi-Naini, N.; Williams, A. *J. Org. Chem.* ***1985***, *50*, 1867; Isaacs, N.S.; Najem, T.S. *Can. J. Chem.* ***1986***, *64*, 1140; *J. Chem. Soc. Perkin Trans. 2* ***1988***, 557.

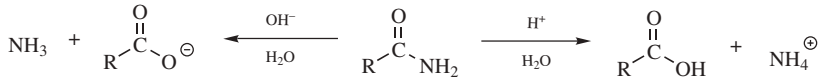
These elimination–addition mechanisms usually are referred to as E1cB mechanisms, because that is the name given to the elimination portion of the mechanism (p. 1488).

The acid-catalyzed hydrolysis of enol esters RCOOCR′=CR can take place either by the normal $A_{AC}2$ mechanism or by a mechanism involving initial protonation on the double-bond carbon, similar to the mechanism for the hydrolysis of enol ethers given in **10-6**,[1572] depending on reaction conditions.[1573] In either case, the products are the carboxylic acid RCOOH and the aldehyde or ketone R—CHCOR′.

OS **I**, 351, 360, 366, 379, 391, 418, 523; **II**, 1, 5, 53, 93, 194, 214, 258, 299, 416, 422, 474, 531, 549; **III**, 3, 33, 101, 209, 213, 234, 267, 272, 281, 300, 495, 510, 526, 531, 615, 637, 652, 705, 737, 774, 785, 809 (but see OS **V**, 1050), 833, 835; **IV**, 15, 55, 169, 317, 417, 444, 532, 549, 555, 582, 590, 608, 616, 628, 630, 633, 635, 804; **V**, 8, 445, 509, 687, 762, 887, 985, 1031; **VI**, 75, 121, 560, 690, 824, 913, 1024; **VII**, 4, 190, 210, 297, 319, 323, 356, 411; **VIII**, 43, 141, 219, 247, 258, 263, 298, 486, 516, 527. Ester hydrolyses with concomitant decarboxylation are listed at reaction **12-40**.

16-60 Hydrolysis of Amides

Hydroxy-de-amination



Unsubstituted amides ($RCONH_2$) can be hydrolyzed with either acidic or basic catalysis, the products being, respectively, the free acid and the ammonium ion or the salt of the acid and ammonia. *N*-Substituted (RCONHR′) and *N,N*-disubstituted ($RCONR''_2$) amides can be hydrolyzed analogously, with the primary or secondary amine, respectively (or their salts), being obtained instead of ammonia. Lactams, imides, cyclic imides, hydrazides, and so on., also undergo the reaction. Water alone is not sufficient to hydrolyze most amides,[1574] since NH_2 is even a poorer leaving group than OR.[1575] Prolonged heating is often required, even with acidic or basic catalysts.[1576] Treatment of primary

[1572]Alkynyl esters also hydrolyze by this mechanism; see Allen, A.D.; Kitamura, T.; Roberts, K.A.; Stang, P.J.; Tidwell, T.T. *J. Am. Chem. Soc.* ***1988***, *110*, 622.

[1573]See, for example, Noyce, D.S.; Pollack, R.M. *J. Am. Chem. Soc.* ***1969***, *91*, 119, 7158; Monthéard, J.; Camps, M.; Chatzopoulos, M.; Benzaïd, A. *Bull. Soc. Chim. Fr.* ***1984***, II-109. For a discussion, see Euranto, E.K. *Pure Appl. Chem.* ***1977***, *49*, 1009.

[1574]See Zahn, D. *Eur. J. Org. Chem.* ***2004***, 4020.

[1575]The very low rate of amide hydrolysis by water alone has been measured: Kahne, D.; Still, W.C. *J. Am. Chem. Soc.* ***1988***, *110*, 7529.

[1576]For a list of catalysts and reagents that have been used to hydrolyze amides, with references, see Larock, R.C. *Comprehensive Organic Transformatinos*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1976–1977. Also see, Bagno, A.; Lovato, G.; Scorrano, G. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 1091.

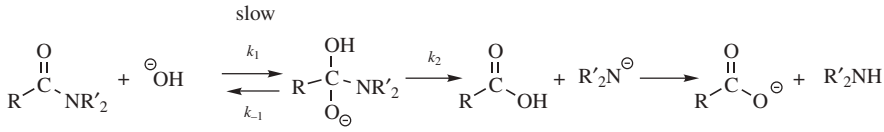
amides with phthalic anhydride at 250°C and 4 atm gives the carboxylic acid and phthalimide.[1577] The conversion of acylhydrazine derivatives to the corresponding carboxylic acid with PhI(OH)(OTs) and water is a variation of amide hydrolysis.[1578] Hydrolysis of carbamates ($RNHCO_2R$) to the corresponding amine can be categorized in this section. Although the product is an amine and the carboxyl unit fragments, this reaction is simply a variation of amide hydrolysis. Strong acids, such as trifluoroacetic acid (in dichloromethane), are usually employed.[1579] Treatment of *N*-Boc derivatives ($RNHCO_2t$-Bu) with $AlCl_3$[1580] or with aqueous sodium *tert*-butoxide[1581] gave the amine. The by-products of this reaction are typically carbon dioxide and isobutylene.

In difficult cases, nitrous acid, NOCl, N_2O_4,[1582] or a similar compound can be used (unsubstituted amides only[1583]).These reactions involve a diazonium ion (see **13-19**) and are much faster than ordinary hydrolysis; for benzamide the nitrous acid reaction took place 2.5×10^7 times faster than ordinary hydrolysis.[1584] Another procedure for difficult cases involves treatment with aqueous sodium peroxide.[1585] In still another method, the amide is treated with water and *t*-BuOK at room temperature.[1586] The strong base removes the proton from **107**, thus preventing the reaction marked k_{-1}. A kinetic study has been done on the alkaline hydrolyses of *N*-trifluoroacetyl aniline derivatives.[1587] Amide hydrolysis can also be catalyzed by nucleophiles (see p. 1259).

The same framework of eight possible mechanisms that was discussed for ester hydrolysis can also be applied to amide hydrolysis.[1588] Both the acid- and base-catalyzed hydrolyses are essentially irreversible, since salts are formed in both

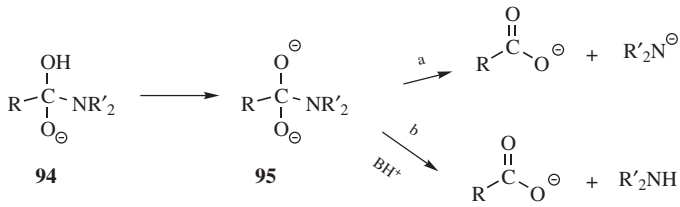
[1577]Chemat, F. *Tetrahedron Lett.* ***2000***, *41*, 3855.
[1578]Wuts, P.G.M.; Goble, M.P. *Org. Lett.* ***2000***, *2*, 2139.
[1579]Schwyzer, R.; Costopanagiotis, A.; Sieber, P. *Helv. Chim. Acta* ***1963***, *46*, 870.
[1580]Bose, D.S.; Lakshminarayana, V. *Synthesis* ***1999***, 66.
[1581]Tom, N.J.; Simon, W.M.; Frost, H.N.; Ewing, M. *Tetrahedron Lett.* ***2004***, *45*, 905.
[1582]Kim, Y.H.; Kim, K.; Park, Y.J. *Tetrahedron Lett.* ***1990***, *31*, 3893.
[1583]*N*-Substituted amides can be converted to *N*-nitrosoamides, which are more easily hydrolyzable than the orginal amide. For example, see Rull, M.; Serratosa, F.; Vilarrasa, J. *Tetrahedron Lett.* ***1977***, 4549. For another method of hydrolyzing *N*-substituted amides, see Flynn, D.L.; Zelle, R.E.; Grieco, P.A. *J. Org. Chem.* ***1983***, *48*, 2424.
[1584]Ladenheim, H.; Bender, M.L. *J. Am. Chem. Soc.* ***1960***, *82*, 1895.
[1585]Vaughan, H.L.; Robbins, M.D. *J. Org. Chem.* ***1975***, *40*, 1187.
[1586]Gassman, P.G.; Hodgson, P.K.G.; Balchunis, R.J. *J. Am. Chem. Soc.* ***1976***, *98*, 1275.
[1587]Hibbert, F.; Malana, M.A. *J. Chem. Soc. Perkin Trans. 2* ***1992***, 755.
[1588]For reviews, see O'Connor, C. *Q. Rev. Chem. Soc.* ***1970***, *24*, 553; Talbot, R.J.E., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9, Elsevier, NY, ***1973***, pp. 257–280; Challis, B.C.; Challis, J.C., in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 731–857.

cases. For basic catalysis,[1589] the mechanism is $B_{AC}2$.



94

There is much evidence for this mechanism, similar to that discussed for ester hydrolysis. A molecular-orbital study on the mechanism of amide hydrolysis is available.[1590] In certain cases, kinetic studies have shown that the reaction is second order in OH^-, indicating that **94** can lose a proton to give **95**.[1591] Depending on the nature

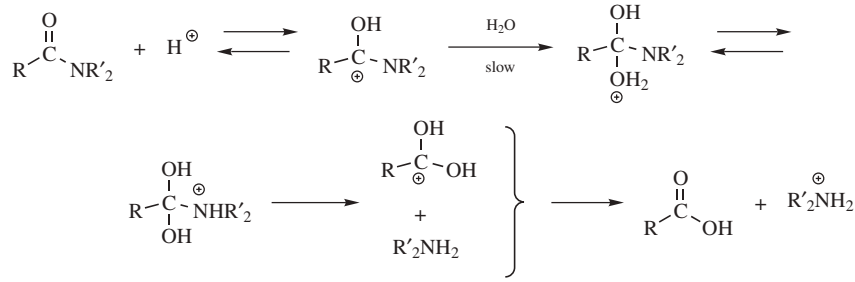


94 **95**

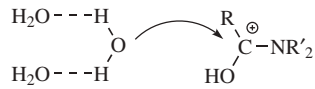
of R′, **95** can cleave directly to give the two negative ions (path *a*) or become *N*-protonated prior to or during the act of cleavage (path *b*), in which case the products are obtained directly and a final proton transfer is not necessary.[1592] Studies of the effect, on the rate of hydrolysis and on the ratio k_{-1}/k_2, of substituents on the aromatic rings in a series of amides $CH_3CONHAr$ led to the conclusion that path *a* is taken when Ar contains electron-withdrawing substituents and path *b* when electron-donating groups are present.[1593] The presence of electron-withdrawing groups helps stabilize the negative charge on the nitrogen, so that NR'^{-}_2 can be a leaving group (path *a*). Otherwise, the C—N bond does not cleave until the nitrogen is protonated (either prior to or in the act of cleavage), so that the leaving group, *even in the base-catalyzed reaction*, is not NR'^{-}_2 but the conjugate NHR'_2(path *b*). Though we have shown formation of **94** as the rate-determining step in the $B_{AC}2$ mechanism, this is true only at high base concentrations. At lower concentrations of base, the cleavage of **107** or **95** becomes rate determining.[1594]

[1589]For a comprehensive list of references, see DeWolfe, R.H.; Newcomb, R.C. *J. Org. Chem.* ***1971***, *36*, 3870.
[1590]Hori, K.; Kamimura, A.; Ando, K.; Mizumura, M.; Ihara, Y. *Tetrahedron* ***1997***, *53*, 4317.
[1591]Biechler, S.S.; Taft, R.W. *J. Am. Chem. Soc.* ***1957***, *79*, 4927. For evidence that a similar intermediate can arise in base-catalyzed ester hydrolysis see Khan, M.N.; Olagbemiro, T.O. *J. Org. Chem.* ***1982***, *47*, 3695.
[1592]Eriksson, S.O. *Acta Chem. Scand.* ***1968***, *22*, 892; *Acta Pharm. Suec.*, ***1969***, *6*, 139.
[1593]Schowen, R.L.; Hopper, C.R.; Bazikian, C.M. *J. Am. Chem. Soc.* ***1972***, *94*, 3095. Gani, V.; Viout, P. *Tetrahedron Lett.* ***1972***, 5241; Menger, F.M.; Donohue, J.A. *J. Am. Chem. Soc.* ***1973***, *95*, 432; Pollack, R.M.; Dumsha, T.C. *J. Am. Chem. Soc.* ***1973***, *95*, 4463; Kijima, A.; Sekiguchi, S. *J. Chem. Soc. Perkin Trans. 2* ***1987***, 1203.
[1594]Schowen, R.L.; Jayaraman, H.; Kershner, L. *J. Am. Chem. Soc.* ***1966***, *88*, 3373. See also, Gani, V.; Viout, P. *Tetrahedron* ***1976***, *32*, 1669, 2883; Bowden, K.; Bromley, K. *J. Chem. Soc. Perkin Trans. 2* ***1990***, 2103.

For acid catalysis, matters are less clear. The reaction is generally second order, and it is known that amides are primarily protonated on the oxygen (Chapter 8, Ref. 24). Because of these facts it has been generally agreed that most acid-catalyzed amide hydrolysis takes place by the $A_{AC}2$ mechanism.



Further evidence for this mechanism is that a small but detectable amount of ^{18}O exchange (see p. 1256) has been found in the acid-catalyzed hydrolysis of benzamide.[1595] (^{18}O exchange has also been detected for the base-catalyzed process,[1596] in accord with the $B_{AC}2$ mechanism). Kinetic data have shown that three molecules of water are involved in the rate-determining step,[1597] suggesting that, as in the $A_{AC}2$ mechanism for ester hydrolysis (**16-59**), additional water molecules take part in a process, such as



The four mechanisms involving alkyl—N cleavage (the AL mechanisms) do not apply to this reaction. They are not possible for unsubstituted amides, since the only N—C bond is the acyl bond. They are possible for *N*-substituted and *N,N*-disubstituted amides, but in these cases they give entirely different products and are not amide hydrolyses at all.

[1595]McClelland, R.A. *J. Am. Chem. Soc.* ***1975***, *97*, 5281; Bennet, A.J.; Ślebocka-Tilk, H.; Brown, R.S.; Guthrie, J.P.; Jodhan, A. *J. Am. Chem. Soc.* ***1990***, *112*, 8497.

[1596]Bender, M.L.; Thomas, R.J. *J. Am. Chem. Soc.* ***1961***, *83*, 4183, Bunton, C.A.; Nayak, B.; O'Connor, C. *J. Org. Chem.* ***1968***, *33*, 572; lebocka-Tilk, H.; Bennet, A.J.; Hogg, H.J.; Brown, R.S. *J. Am. Chem. Soc.* ***1991***, *113*, 1288; McClelland, R.A. *J. Am. Chem. Soc.* ***1975***, *97*, 5281; Bennet, A.J.; Ślebocka-Tilk, H.; Brown, R.S.; Guthrie, J.P.; Jodhan, A. *J. Am. Chem. Soc.* ***1990***, *112*, 8497.

[1597]Moodie, R.B.; Wale, P.D.; Whaite, K. *J. Chem. Soc.* ***1963***, 4273; Yates, K.; Stevens, J.B. *Can. J. Chem.* ***1965***, *43*, 529; Yates, K.; Riordan, J.C. *Can. J. Chem.* ***1965***, *43*, 2328.

This reaction, while rare, has been observed for various *N-tert*-butylamides in 98% sulfuric acid, where the mechanism was the $A_{AL}1$ mechanism,[1598] and for certain amides containing an azo group, where a $B_{AL}1$ mechanism was postulated.[1599] Of the two first-order acyl cleavage mechanisms, only the $A_{AC}1$ has been observed, in concentrated sulfuric acid solutions.[1600] Of course, the diazotization of unsubstituted amides might be expected to follow this mechanism, and there is evidence that this is true.[1584]

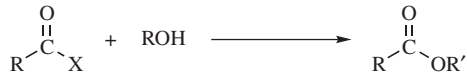
OS **I**, 14, 111, 194, 201, 286; **II**, 19, 25, 28, 49, 76, 208, 330, 374, 384, 457, 462, 491, 503, 519, 612; **III**, 66, 88, 154, 256, 410, 456, 586, 591, 661, 735, 768, 813; **IV**, 39, 42, 55, 58, 420, 441, 496, 664; **V**, 27, 96, 341, 471, 612, 627; **VI**, 56, 252, 507, 951, 967; **VII**, 4, 287; **VIII**, 26, 204, 241, 339, 451.

The oxidation of aldehydes to carboxylic acids can proceed by a nucleophilic mechanism, but more often it does not. The reaction is considered in Chapter 19 (**19-23**). Basic cleavage of β-keto esters and the haloform reaction could be considered at this point, but they are also electrophilic substitutions and are treated in Chapter 12 (**12-43** and **12-44**).

B. Attack by OR at an Acyl Carbon

16-61 Alcoholysis of Acyl Halides

Alkoxy-de-halogenation



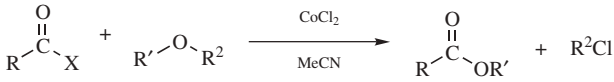
The reaction between acyl halides and alcohols or phenols is the best general method for the preparation of carboxylic esters. It is believed to proceed by a S_N2 mechanism.[1601] As with **16-57**, the mechanism can be S_N1 or tetrahedral.[1510] Pyridine catalyzes the reaction by the nucleophilic catalysis route (see **16-58**). Lewis acids such as lithium perchlorate can be used.[1602] The reaction is of wide scope, and many functional groups do not interfere. A base is frequently added to combine with the HX formed. When aqueous alkali is used, this is called the *Schotten–Baumann procedure*, but pyridine is also frequently used. Both R and R′ may be primary, secondary, or tertiary alkyl or aryl. Enol esters can also be prepared by this method, though *C*-acylation competes in these cases. In difficult cases, especially with hindered acids or tertiary R′, the alkoxide can be used instead of the alcohol.[1603] Activated alumina has also been used as a catalyst, for

[1598]Lacey, R.N. *J. Chem. Soc.* ***1960***, 1633; Druet, L.M.; Yates, K. *Can. J. Chem.* ***1984***, *62*, 2401.
[1599]Stodola, F.H. *J. Org. Chem.* ***1972***, *37*, 178.
[1600]Duffy, J.A.; Leisten, J.A. *J. Chem. Soc.* ***1960***, 545, 853; Barnett, J.W.; O'Connor, C.J. *J. Chem. Soc., Chem. Commun.* ***1972***, 525; *J. Chem. Soc. Perkin Trans. 2* ***1972***, 2378.
[1601]Bentley, T.W.; Llewellyn, G.; McAlister, J.A. *J. Org. Chem.* ***1996***, *61*, 7927; Kevill, D.N.; Knauss, D.C. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 307; Fleming, I.; Winter, S.B.D. *Tetrahedron Lett.* ***1993***, *34*, 7287.
[1602]Bandgar, B.P.; Kamble, V.T.; Sadavarte, V.S.; Uppalla, L.S. *Synlett* ***2002***, 735.
[1603]For an example, see Kaiser, E.M.; Woodruff, R.A. *J. Org. Chem.* ***1970***, *35*, 1198.

tertiary R′.[1604] Thallium salts of phenols give very high yields of phenolic esters,[1605] and BiOCl is very effective for the preparation of phenolic acetates.[1606] Phase-transfer catalysis has been used for hindered phenols.[1607] Zinc has been used to couple alcohols and acyl chlorides,[1608] and catalytic $Cu(acac)_2$ and benzoyl chloride was used to prepare the mono-benzoate of ethylene glycol.[1609] Selective acylation is possible in some cases.[1610]

Acyl halides react with thiols, in the presence of zinc, to give the corresponding thio-ester.[1611] The reaction of acid chlorides or anhydrides (see **16-62**) with diphenyldiselenide, in the presence of $Sm/CoCl_2$[1612] or $Sm/CrCl_3$[1613] gave the corresponding seleno ester (PhSeCOMe).

Acyl halides can also be converted to carboxylic acids by using ethers instead of alcohols, in MeCN in the presence of certain catalysts such as cobalt(II) chloride.[1614] A variation of this reaction has been reported that uses acetic anhydride.[1615]



This is a method for the cleavage of ethers (see also, **10-49**).

OS **I**, 12; **III**, 142, 144, 167, 187, 623, 714; **IV**, 84, 263, 478, 479, 608, 616, 788; **V**, 1, 166, 168, 171; **VI**, 199, 259, 312, 824; **VII**, 190; **VIII**, 257, 516.

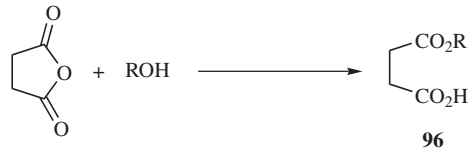
16-62 Alcoholysis of Anhydrides

Alkoxy-de-acyloxy-substitution

The scope of this reaction is similar to that of **16-61**. Anhydrides are somewhat less reactive than acyl halides, and they are often used to prepare carboxylic esters. Benzyl acetates have been prepared via microwave irradiation of benzylic alcohols

[1604]Nagasawa, K.; Yoshitake, S.; Amiya, T.; Ito, K. *Synth. Commun.* ***1990***, *20*, 2033.
[1605]Taylor, E.C.; McLay, G.W.; McKillop, A. *J. Am. Chem. Soc.* ***1968***, *90*, 2422.
[1606]Ghosh, R.; Maiti, S.; Chakraborty, A. *Tetrahedron Lett.* ***2004***, *45*, 6775.
[1607]Illi, V.O. *Tetrahedron Lett.* ***1979***, 2431. For another method, see Nekhoroshev, M.V.; Ivakhnenko, E.P.; Okhlobystin, O.Yu. *J. Org. Chem. USSR* ***1977***, *13*, 608.
[1608]Yadav, J.S.; Reddy, G.S.; Svinivas, D.; Himabindu, K. *Synth. Commun.* ***1998***, *28*, 2337.
[1609]Sirkecioglu, O.; Karliga, B.; Talinli, N. *Tetrahedron Lett.* ***2003***, *44*, 8483.
[1610]Srivastava, V.; Tandon, A.; Ray, S. *Synth. Commun.* ***1992***, *22*, 2703.
[1611]Meshram, H.M.; Reddy, G.S.; Bindu, K.H.; Yadav, J.S. *Synlett* ***1998***, 877.
[1612]Chen, R.; Zhang, Y. *Synth. Commun.* ***2000***, *30* , 1331.
[1613]Liu, Y.; Zhang, Y. *Synth. Commun.* ***1999***, *29* , 4043.
[1614]See Ahmad, S.; Iqbal, J. *Chem. Lett.* ***1987***, 953, and references cited therein.
[1615]Lakouraj, M.; Movassaghi, B.; Fasihi, J. *J. Chem. Res. (S)* ***2001***, 378.

and acetic anhydride.[1616] Acids,[1617] Lewis acids,[1618] and bases, such as pyridine are often used as catalysts.[1619] Acetic anhydride and $NiCl_2$ with microwave irradiation converts benzylic alcohols to the corresponding acetate.[1620] The monoacetate of 1,2-diols have been prepared using $CeCl_3$ as a catalyst.[1621] Pyridine is a nucleophilic-type catalyst (see **16-58**). 4-(*N,N*-Dimethylamino)pyridine is a better catalyst and can be used in cases where pyridine fails.[1622] *N*-Bromosuccinimide has been shown to catalyzed esterification of alcohols with acetic anhydride.[1623] Formic anhydride is not a stable compound but esters of formic acid can be prepared by treating alcohols[1624] or phenols[1625] with acetic-formic anhydride. Cyclic anhydrides give mono-esterified dicarboxylic acids, such as **96**.[1626] The asymmetric alcoholysis of cyclic anhydrides has been reviewed.[1627]



96

Alcohols can also be acylated by mixed organic–inorganic anhydrides, such as acetic-phosphoric anhydride, $MeCOOPO(OH)_2$[1628] (see **16-68**). Thioesters of the type ArS(C=O)Me have been prepared from diphenyl disulfide and PBu_3, followed by treatment with acetic anhydride.[1629]

[1616]Bandgar, B.P.; Kasture, S.P.; Kamble, V.T. *Synth. Commun.* ***2001***, *31*, 2255.

[1617]Nafion-H has been used: Kumareswaran, R.; Pachamuthu, K.; Vankar, Y.D. *Synlett* ***2000***, 1652.

[1618]Some of the catalysts used are **Cu(OTf)$_2$**: Saravanan, P.; Singh, V.K. *Tetrahedron Lett.* ***1999***, *40*, 2611. **In(OTf)$_3$**: Barrero, A.F.; Alvarez-Manzaneda, E.J.; Chahboun, R.; Meneses, R. *Synlett* ***1999***, 1663. $InCl_3$: Chakraborti, A.K.; Gulhane, R. *Tetrahedron Lett.* ***2003***, *44*, 6749. **TiCl$_4$**: Chandrasekhar, S.; Ramachandar, T.; Reddy, M.V.; Takhi, M. *J. Org. Chem.* ***2000***, *65*, 4729. **LiClO$_4$:** Nakae, Y.; Kusaki, I.; Sato, T. *Synlett* ***2001***, 1584; **Ce(OTf)$_3$**: Dalpozzo, R.; DeNino, A.; Maiuolo, L.; Procopio, A.; Nardi, M.; Bartoli, G.; Romeo, R. *Tetrahedron Lett.* ***2003***, *44*, 5621. **Yb(OTf)$_3$**: Dumeunier, R.; Markó, I.E. *Tetrahedron Lett.* ***2004***, *45*, 825. **RuCl$_3$**: De, S.K. *Tetrahedron Lett.* ***2004***, *45*, 2919. **Mg(ClO$_4$)$_2$**: Bartoli, G.; Bosco, M.; Dalpozzo, R.; Marcantoni, E.; Massaccesi, M.; Sambri, L. *Eur. J. Org. Chem.* ***2003***, 4611.

[1619]For a list of catalysts, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1955–1957.

[1620]Constantinou-Kokotou, V.; Peristeraki, A. *Synth. Commun.* ***2004***, *34*, 4227.

[1621]Clarke, P.A.; Kayaleh, N.E.; Smith, M.A.; Baker, J.R.; Bird, S.J.; Chan, C. *J. Org. Chem.* ***2002***, *67*, 5226; Clarke, P.A. *Tetrahedron Lett.* ***2002***, *43*, 4761.

[1622]For reviews, see Scriven, E.F.V. *Chem. Soc. Rev.* ***1983***, *12*, 129; Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem. Int. Ed.* ***1978***, *17*, 569.

[1623]Karimi, B.; Seradj, H. *Synlett* ***2001***, 519.

[1624]For example, see Stevens, W.; van Es, A. *Recl. Trav. Chim. Pays-Bas* ***1964***, *83*, 1287; van Es, A.; Stevens, W. *Recl. Trav. Chim. Pays-Bas* ***1965***, *84*, 704.

[1625]For example, see Stevens, W.; van Es, A. *Recl. Trav. Chim. Pays-Bas* ***1964***, *83*, 1294; Sōfuku, S.; Muramatsu, I.; Hagitani, A. *Bull. Chem. Soc. Jpn.* ***1967***, *40*, 2942.

[1626]For conversion of an anhydride to a mono-ester with high enantioselectivity, see Chen, Y.; Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* ***2000***, *122*, 9542.

[1627]Chen, Y.; McDaid, P.; Deng, L. *Chem. Rev.* ***2003***, *103*, 2965.

[1628]Fatiadi, A.J. *Carbohydr. Res.* ***1968***, *6*, 237.

[1629]Ayers, J.T.; Anderson, S.R. *Synth. Commun* ***1999***, *29*, 351. This transformation has also been accomplished with $Zn/AlCl_3$: see Movassagh, B. Lakouraj, M.M.; Fadaei, Z. *J. Chem. Res. (S)* ***2001***, 22.

OS **I**, 285, 418; **II**, 69, 124; **III**, 11, 127, 141, 169, 237, 281, 428, 432, 690, 833; **IV**, 15, 242, 304; **V**, 8, 459, 591, 887; **VI**, 121, 245, 560, 692; 486; **VIII**, 141, 258.

16-63 Esterification of Carboxylic Acids

Alkoxy-de-hydroxylation

$$RCOOH + R'OH \underset{}{\overset{H+}{\rightleftharpoons}} RCOOR' + H_2O$$

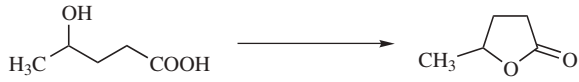
The esterification of carboxylic acids with alcohols[1630] is the reverse of **16-60** and can be accomplished only if a means is available to drive the equilibrium to the right.[1631] There are many ways of doing this, among which are (*1*) addition of an excess of one of the reactants, usually the alcohol; (*2*) removal of the ester or the water by distillation; (*3*) removal of water by azeotropic distillation; and (*4*) removal of water by use of a dehydrating agent, silica gel,[1632] or a molecular sieve. When R′ is methyl, the most common way of driving the equilibrium is by adding excess MeOH; when R′ is ethyl, it is preferable to remove water by azeotropic distillation.[1633] The most common catalysts are H_2SO_4 and TsOH, although some reactive acids (e.g., formic,[1634] trifluoroacetic[1635]) do not require a catalyst. Ammonium salts have been used to initiate esterification,[1636] and boric acid has been used to esterify α-hydroxy acids.[1637] The R′ group may be primary or secondary alkyl groups other than methyl or ethyl, but tertiary alcohols usually give carbocations and elimination. Phenols can sometimes be used to prepare phenolic esters, but yields are generally very low. Selective esterification of an aliphatic carboxylic acid in the presence of an aromatic acid was accomplished with $NaHSO_4{\bullet}SiO_2$ and methanol.[1638]

Diphenylammonium triflate was useful for direct esterification of carboxylic acids with longer chain aliphatic alcohols.[1639] Photoirradiation of carboxylic acid with CBr_4[1640] or CCl_4[1641] in methanol was shown to give the methyl ester, with high selectivity for nonconjugated acids in the case of CBr_4. *O*-Alkylisoureas react

[1630]For a review of some methods, see Haslam, E. *Tetrahedron* ***1980***, *36*, 2409.
[1631]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1932–1941.
[1632]Nascimento, M.de G.; Zanotto, S.P.; Scremin, M.; Rezende, M.C. *Synth. Commun.* ***1996***, *26*, 2715.
[1633]Newman, M.S. *An Advanced Organic Laboratory Course*; Macmillan, NY, ***1972***, pp. 8–10.
[1634]Formates can be prepared if diisopropyl ether is used to remove water by azeotropic distillation: Werner, W. *J. Chem. Res. (S)* ***1980***, 196. For an alternative synthesis of formate esters using trifluoroethyl formate, see Hill, D.R.; Hsiao, C.-N.; Kurukulasuriya, R.; Wittenberger, S.J. *Org. Lett.* ***2002***, *4*, 111.
[1635]Johnston, B.H.; Knipe, A.C.; Watts, W.E. *Tetrahedron Lett.* ***1979***, 4225.
[1636]Wakasugi, K.; Nakamura, A.; Tanabe, Y. *Tetrahedron Lett.* ***2001***, *42*, 7427; Gacem, B.; Jenner, G. *Tetrahedron Lett.* ***2003***, *44*, 1391.
[1637]Houston, T.A.; Wilkinson, B.L.; Blanchfield, J.T. *Org. Lett.* ***2004***, *6*, 679.
[1638]Das, B.; Venkataiah, B.; Madhsudhan, P. *Synlett* ***2000***, 59.
[1639]Wakasugi, K.; Misaki, T.; Yamada, K.; Tanabe, Y. *Tetrahedron Lett.* ***2000***, *41*, 5249.
[1640]Lee, A.S.-Y.; Yang, H.-C.; Su, F.-Y. *Tetrahedron Lett.* ***2001*** *42*, 301.
[1641]Hwu, J.R.; Hsu, C.-Y.; Jain, M.L. *Tetrahedron Lett.* ***2004*** *45*, 5151.

with conjugated carboxylic acids to give the corresponding ester with microwave irradiation,[1642] and a polymer-bound *O*-alkylurea has been used as well.[1643]

Mixing the carboxylic acid and alcohol with *p*-toluenesulfonic acid (neat), gave the ester in 3 min with microwave irradiation.[1644] Esterification has also been accomplished using ionic liquids as the reaction medium,[1645] and a solid-state esterification was reported on P_2O_5/SiO_2.[1646] Diols are converted to the monoacetate by heating with acetic acid on a zeolite.[1647]



97

Both γ- and δ-hydroxy acids such as **97** are easily converted to a lactone by treatment with acids, or often simply on standing, but larger and smaller lactone rings cannot be made in this manner, because polyester formation occurs more readily.[1648] Often the conversion of a group, such as keto or halogen, γ or δ to a carboxyl group, to a hydroxyl group gives the lactone directly, since the hydroxy acid cyclizes too rapidly for isolation. β-Substituted β-hydroxy acids can be converted to β-lactones by treatment with benzenesulfonyl chloride in pyridine at 0–5°C.[1649] ε-Lactones (seven-membered rings) have been made by cyclization of ε-hydroxy acids at high dilution.[1650] Macrocyclic lactones[1651] can be prepared indirectly in very good yields by conversion of the hydroxy acids to 2-pyridinethiol esters and adding these to refluxing xylene.[1652] Palladium-catalyzed aromatic carboxylation

[1642]Crosignani, S.; White, P.D.; Linclau, B. *Org. Lett.* ***2002***, *4*, 2961.

[1643]Crosignani, S.; White, P.D.; Steinauer, R.; Linclau, B. *Org. Lett.* ***2003***, *5*, 853; Crosignani, S.; White, P.D.; Linclau, B. *J. Org. Chem.* ***2004***, *69*, 5897.

[1644]Loupy, A.; Petit, A.; Ramdan, M.; Yvanaeff, C.; Majdoub, M.; Labiad, B.; Villemin, D. *Can. J. Chem.* ***1993***, *71*, 90. See also, Zhang, Z.; Zhou, L.; Zhang, M.; Wu, H.; Chen, Z. *Synth. Commun.* ***2001***, *31*, 2435; Fan, X.; Yuan, K.; Hao, C. Li, N.; Tan, G.; Yu, X. *Org. Prep. Proceed. Int.* ***2000***, *32*, 287.

[1645]Isobe, T.; Ishikawa, T. *J. Org. Chem.* ***1999***, *64*, 6984.

[1646]Eshghi, H.; Rafei, M.; Karimi, M.H. *Synth. Commun.* ***2001***, *31*, 771.

[1647]Srinivas, K.V.N.S.; Mahender, I.; Das, B. *Synlett* ***2003***, 2419.

[1648]For a review of the synthesis of lactones and lactams, see Wolfe, J.F.; Ogliaruso, M.A., in Patai, S. *The Chemistry of Acid Derivatives*, pt. 2, Wiley, NY, ***1979***, pp. 1062–1330. For a list of methods for converting hydroxy acids to lactones, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1989***, pp. 1861–1867.

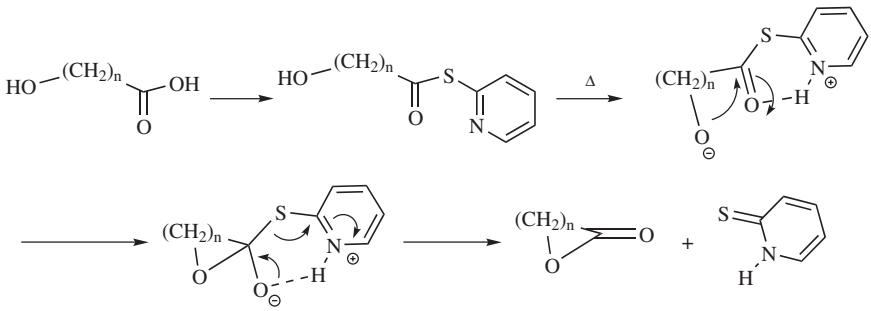
[1649]Adam, W.; Baeza, J.; Liu, J. *J. Am. Chem. Soc.* ***1972***, *94*, 2000. For other methods of converting β-hydroxy acids to β-lactones, see Merger, F. *Chem. Ber.* ***1968***, *101*, 2413; Blume, R.C. *Tetrahedron Lett.* ***1969***, 1047.

[1650]Lardelli, G.; Lamberti,V.; Weller, W.T.; de Jonge, A.P. *Recl. Trav. Chim. Pays-Bas* ***1967***, *86*, 481.

[1651]For reviews on the synthesis of macrocyclic lactones, see Nicolaou, K.C. *Tetrahedron* ***1977***, *33*, 683; Back, T.G. *Tetrahedron* ***1977***, *33*, 3041; Masamune, S.; Bates, G.S.; Corcoran, J.W. *Angew. Chem. Int. Ed.* ***1977***, *16*, 585.

[1652]Corey, E.J.; Brunelle, D.J.; *Tetrahedron Lett.* ***1976***, 3409; Wollenberg, R.H.; Nimitz, J.S.; Gokcek, D.Y. *Tetrahedron Lett.* ***1980***, *21*, 2791; Thalmann, A.; Oertle, K.; Gerlach, H. *Org. Synth.* ***VII***, 470. See also, Schmidt, U.; Heermann, D. *Angew. Chem. Int. Ed.* ***1979***, *18*, 308. For a ruthenium-catalyzed macrocyclization see Trost, B.M.; Chisholm, J.D. *Org. Lett.* ***2002***, *4*, 3743.

reactions generated carboxylic acids *in situ*, and when an alcohol unit is present elsewhere in the molecule cyclization gives the corresponding lactone.[1653]



A closely related method, which often gives higher yields of a macrocyclic lactone, involves treatment of the hydroxy acids with 1-methyl- or 1-phenyl-2-halopyridinium salts, especially 1-methyl-2-chloropyridinium iodide (*Mukaiyama's reagent*).[1654] Another method uses organotin oxides[1655] and both $TiCl_4/AgClO_4$[1656] and $TiCl_2(OSO_2CF_3)_2$[1657] have been used.

Esterification is catalyzed by acids (not bases) in ways that were discussed on p. 1402.[1549] The mechanisms are usually $A_{AC}2$, but $A_{AC}1$ and $A_{AL}1$ have also been observed.[1658] Certain acids, such as 2,6-di-ortho-substituted benzoic acids, cannot be esterified by the $A_{AC}2$ mechanism because of steric hindrance (p. 481). In such cases, esterification can be accomplished by dissolving the acid in 100% H_2SO_4 (forming the ion RCO^+) and pouring the solution into the alcohol ($A_{AC}1$ mechanism). The reluctance of hindered acids to undergo the normal $A_{AC}2$ mechanism can sometimes be put to advantage when, in a molecule containing two COOH groups,

[1653]Kayaki, Y.; Noguchi, Y.; Iwasa, S.; Ikariya, T.; Noyori, R. *Chem. Commun.* ***1999***, 1235.

[1654]For a review of reactions with this and related methods, see Mukaiyama, T. *Angew. Chem. Int. Ed.* ***1979***, *18*, 707. For a polymer-supported Mukaiyama reagent, see Convers, E.; Tye, H.; Whittaker, M. *Tetrahedron Lett.* ***2004***, *45*, 3401.

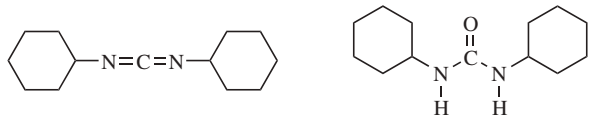
[1655]Steliou, K.; Szczygielska-Nowosielska, A.; Favre, A.; Poupart, M.A.; Hanessian, S. *J. Am. Chem. Soc.* ***1980***, *102*, 7578; Steliou, K.; Poupart, M.A. *J. Am. Chem. Soc.* ***1983***, *105*, 7130. For some other methods, see Masamune, S.; Kamata, S.; Schilling, W. *J. Am. Chem. Soc.* ***1975***, *97*, 3515; Scott, L.T.; Naples, J.O. *Synthesis* ***1976***, 738; Kurihara, T.; Nakajima, Y.; Mitsunobu, O. *Tetrahedron Lett.* ***1976***, 2455; Corey, E.J.; Brunelle, D.J.; Nicolaou, K.C. *J. Am. Chem. Soc.* ***1977***, *99*, 7359; Vorbrüggen, H.; Krolikiewicz, K. *Angew. Chem. Int. Ed.* ***1977***, *16*, 876; Nimitz, J.S.; Wollenberg, R.H. *Tetrahedron Lett.* ***1978***, 3523; Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* ***1979***, *52*, 1989; Venkataraman, K.; Wagle, D.R. *Tetrahedron Lett.* ***1980***, *21*, 1893; Schmidt, U.; Dietsche, M. *Angew. Chem. Int. Ed.* ***1981***, *20*, 771; Taniguchi, N.; Kinoshita, H.; Inomata, K.; Kotake, H. *Chem. Lett.* ***1984***, 1347; Cossy, J.; Pete, J. *Bull. Soc. Chim. Fr.* ***1988***, 989.

[1656]Shiina, I.; Miyoshi, S.; Miyashita, M.; Mukaiyama, T. *Chem. Lett.* ***1994***, 515; Mukaiyama, T.; Izumi, J.; Miyashita, M.; Shiina, I. *Chem. Lett.* ***1993***, 907.

[1657]Hojo, M.; Nagayoshi, M.; Fujii, A.; Yanagi, T.; Ishibashi, N.; Miura, K.; Hosomi, A. *Chem. Lett.* ***1994***, 719.

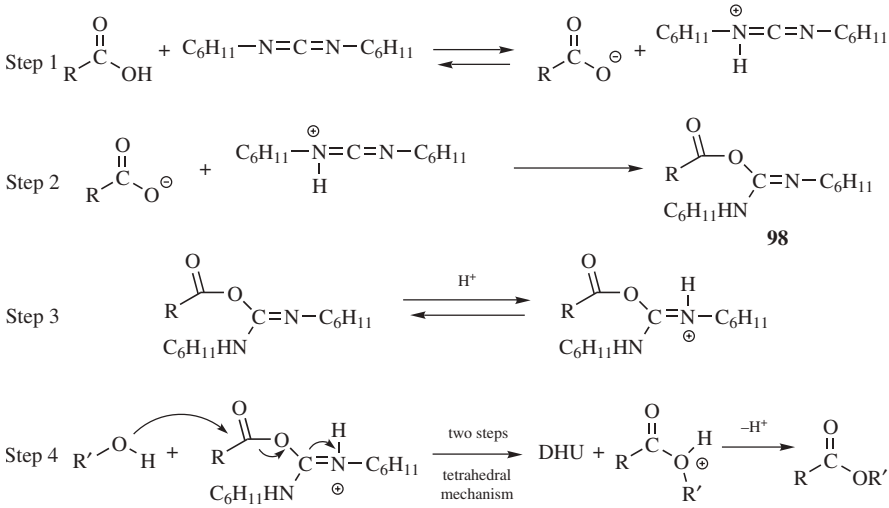
[1658]For a review of aspects of the mechanism, see Salomaa, P.; Kankaanperä, A.; Pihlaja, K., in Patai, S. *The Chemistry of the Hydroxyl Group, pt. 1*, Wiley, NY, ***1971***, pp. 466–481.

only the less hindered one is esterified. The $A_{AC}1$ pathway cannot be applied to unhindered carboxylic acids.



DCC DHU

Another way to esterify a carboxylic acid is to treat it with an alcohol in the presence of a dehydrating agent.[1631] One of these is dicyclohexylcarbodiimide (DCC), which is converted in the process to dicyclohexylurea (DHU). The mechanism[1659] has much in common with the nucleophilic catalysis mechanism; the acid is converted to a compound with a better leaving group. However, the conversion is not by a tetrahedral mechanism (as it is in nucleophilic catalysis), since the C—O bond remains intact during this step:

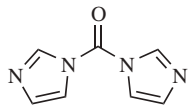


98

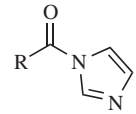
Evidence for this mechanism was the preparation of *O*-acylureas similar to **98** and the finding that when catalyzed by acids they react with alcohols to give esters.[1660] Hindered tertiary alcohols can be coupled via DCC to give the hindered ester.[1661] A polymer-bound carbodiimide has been used to prepare macrocyclic lactones.[1662] In at least one case, the reaction of $HOOCCH_2CN$ with DCC and *tert*-butanol gave the *tert*-butyl ester via a ketene intermediate.[1663]

[1659]Smith, M.; Moffatt, J.G.; Khorana, H.G. *J. Am. Chem. Soc.* ***1958***, *80*, 6204; Balcom, B.J.; Petersen, N.O. *J. Org. Chem.* ***1989***, *54*, 1922.
[1660]Doleschall, G.; Lempert, K. *Tetrahedron Lett.* ***1963***, 1195.
[1661]Shimizu, T.; Hiramoto, K.; Nakata, T. *Synthesis* ***2001***, 1027.
[1662]Keck, G.E.; Sanchez, C.; Wager, C.A. *Tetrahedron Lett.* ***2000***, *41*, 8673.
[1663]Nahmany, M.; Melman, A. *Org. Lett.* ***2001***, *3*, 3733.

There are limitations to the use of DCC; yields are variable and *N*-acylureas are side products. Many other dehydrating agents[1664] have been used, including DCC and an aminopyridine,[1665] Amberlyst-15,[1666] chlorosilanes,[1667] $MeSO_2Cl$-Et_3N,[1668] and *N*,*N*′-carbonyldiimidazole(**99**).[1669] In the latter case, imidazolides (**100**) are intermediates that readily react with alcohols.



99



100

It is known that the Lewis acid BF_3 promotes the esterification by converting the acid to $RCO^+—BF_3\ ^-OH$, so the reaction proceeds by an $A_{AC}1$ type of mechanism. The use of BF_3-etherate is simple and gives high yields.[1670] Other Lewis acids can be used.[1671] Esterification has been done using a LaY zeolite.[1672]

Carboxylic esters can also be prepared by treating carboxylic acids with *tert*-butyl ethers and acid catalysts.[1673]

$$\text{RCOOH} + t\text{-Bu-OR}' \longrightarrow \text{RCOOR}' + \text{H}_2\text{C=CMe}_2 + \text{H}_2\text{O}$$

Carboxylic acids can be converted to *tert*-butyl esters by treatment with *tert*-butyl 2,2,2-trichloroacetimidate (see **10-10**) and BF_3•OEt_2.[1173] Carboxylic esters can be formed from the carboxylate anion and a suitable alkylating agent (**10-26**).

Thioesters of the type RSC(=S)R′ (a dithiocarboxylic ester) and RSC(C=O)R′ (a thiocarboxylic ester) can be generated by reaction of carboxylic acids with thiols.

[1664]For a list of many of these with references, see Arrieta, A.; García, T.; Lago, J.M.; Palomo, C. *Synth. Commun.* ***1983***, *13*, 471.

[1665]Hassner, A.; Alexanian, V. *Tetrahedron Lett.* ***1978***, 4475; Neises, B.; Steglich, W. *Angew. Chem. Int. Ed.* ***1978***, *17*, 522; Boden, E.P.; Keck, G.E. *J. Org. Chem.* ***1985***, *50*, 2394.

[1666]Petrini, M.; Ballini, R.; Marcantoni, E.; Rosini, G. *Synth. Commun.* ***1988***, *18*, 847.

[1667]Nakao, R.; Oka, K.; Fukumoto, T. *Bull. Chem. Soc. Jpn.* ***1981***, *54*, 1267; Brook, M.A.; Chan, T.H. *Synthesis* ***1983***, 201.

[1668]Chandrasekaran, S.; Turner, J.V. *Synth. Commun.* ***1982***, *12*, 727.

[1669]For a review, see Staab, H.A.; Rohr, W. *Newer Methods Prep. Org. Chem.* ***1968***, *5*, 61. See also, Morton, R.C.; Mangroo, D.; Gerber, G.E. *Can. J. Chem.* ***1988***, *66*, 1701.

[1670]For examples, see Marshall, J.L.; Erickson, K.C.; Folsom, T.K. *Tetrahedron Lett.* ***1970***, 4011; Kadaba, P.K. *Synthesis* ***1972***, 628; *Synth. Commun.* ***1974***, *4*, 167.

[1671]Lewis acids used for esterification include **$FeCl_3$**: Sharma, G.V.M.; Mahalingam, A.K.; Nagarajan, M.; Ilangovan, P.; Radhakrishna, P. *Synlett* ***1999***, 1200. **$Hf(Cl_4(thf)_2$:** Ishihara, K.; Nakayama, M.; Ohara, S.;Yamamoto, H. *Synlett* ***2001***, 1117 and Ishihara, K.; Nakayama, M.; Ohara, S.; Yamamoto, H. *Tetrahedron* ***2002***, *58*, 8179; **$Bi(OTf)_3$•*x* H_2O**: Carrigan,. D.; Freiberg, D.A.; Smith, R.C.; Zerth, H.M.; Mohan, R.S. *Synthesis* ***2001***, 2091; **$BiCl_3$**: Mohammadpoor-Baltork, I.; Khosropour, A.R.; Aliyan, H. *J. Chem. Res* ***2001***, 280; **$Fe_2(SO_4)_3$•*x* H_2O**: Zhang, G.-S. *Synth. Commun.* ***1999***, *29*, 607. **Ceric ammonium nitrate**: Pan, W.-B.; Chang, F.-R.; Wei, L.-M.; Wu, M.J.; Wu, Y.-C. *Tetrahedron Lett.* ***2003***, *44*, 331.

[1672]Narender, N.; Srinivasu, P.; Kulkarni, S.J.; Raghavan, K.V. *Synth. Commun.* ***2000***, *30* , 1887.

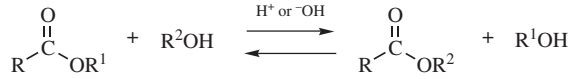
[1673]Derevitskaya, V.A.; Klimov, E.M.; Kochetkov, N.K. *Tetrahedron Lett.* ***1970***, 4269. See also, Mohacsi, E. *Synth. Commun.* ***1982***, *12*, 453.

In one example, phosphorous pentasulfide was used in conjunction with a thiol to make dithiocarboxylic esters[1674] or thiocarboxylic esters.[1675] Thiocarboxylic esters were prepared from thiols and triflic acid.[1676]

OS **I**, 42, 138, 237, 241, 246, 254, 261, 451; **II**, 260, 264, 276, 292, 365, 414, 526; **III**, 46, 203, 237, 381, 413, 526, 531, 610; **IV**, 169, 178, 302, 329, 390, 398, 427, 506, 532, 635, 677; **V**, 80, 762, 946; **VI**, 471, 797; **VII**, 93, 99, 210, 319, 356, 386, 470; **VIII**, 141, 251, 597; **IX**, 24, 58; **75**, 116; **75**, 129. Also see, OS **III**, 536, 742.

16-64 Transesterification

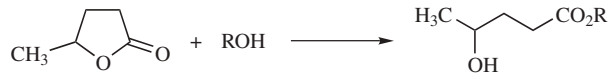
Alkoxy-de-alkoxylation



Transesterification[1677] is catalyzed[1678] by acids[1679] or bases,[1680] or performed under neutral conditions.[1681] It is an equilibrium reaction and must be shifted in the desired direction. In many cases low-boiling esters can be converted to higher boiling ones by the distillation of the lower boiling alcohol as fast as it is formed. Reagents used to catalyze[1682] transesterification include Montmorillonite K10[1683] and various Lewis acids.[1684] A polymer-bound siloxane has been used to induce transesterification.[1685] This reaction has been used as a method for the acylation of a primary OH in the presence of a secondary OH.[1686] Regioselectivity has

[1674]Sudalai, A.; Kanagasabapathy, S.; Benicewicz, B.C. *Org. Lett.* ***2000***, *2*, 3213.
[1675]Curphey, T.J. *Tetrahedron Lett.* ***2002***, *43*, 371.
[1676]Iimura, S.; Manabe, K.; Kobayashi, S. *Chem. Commun.* ***2002***, 94.
[1677]Otera, J. *Chem. Rev.* ***1993***, *93*, 1449.
[1678]For a list of catalysts, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1969–1973.
[1679]Catalysts other than mineral acids can be used, for example, Amberlyst-15 resin. See Chavan, S.P.; Subbarao, Y.T.; Dantale, S.W.; Sivappa, R. *Synth. Commun.* ***2001***, *31*, 289.
[1680]Stanton, M.G.; Gagné, M.R. *J. Org. Chem.* ***1997***, *62*, 8240; Vasin, V.A.; Razin, V.V. *Synlett* ***2001***, 658.
[1681]For some methods of transesterification under neutral conditions, see Otera, J.; Yano, T.; Kawabata, A.; Nozaki, H. *Tetrahedron Lett.* ***1986***, *27*, 2383; Imwinkelried, R.; Schiess, M.; Seebach, D. *Org. Synth.*, *65*, 230; Bandgar, B.P.; Uppalla, L.S.; Sadavarte, V.S. *Synlett* ***2001***, 1715.
[1682]For a review see Grasa, G.A.; Singh, R.; Nolan, S.P. *Synthesis* ***2004***, 971.
[1683]Ponde, D.E.; Deshpande, V.H.; Bulbule, V.J.; Sudalai, A.; Gajare, A.S. *J. Org. Chem.* ***1998***, *63*, 1058.
[1684]Lewis acids used for this reaction include **Ti(OEt)$_4$**: Krasik, P. *Tetrahedron Lett.* ***1998***, *39*, 4223. **TlCl$_4$**: Mahrwald, R.; Quint, S. *Tetrahedron* ***2000***, *56*, 7463. **Cu(NO$_3$)$_2$:** Iranpoor, N.; Firouzabadi, H.; Zolfigol, M.A. *Synth. Commun.* ***1998***, *28*, 1923. **Sn(OTf)$_2$**: Mukaiyama, T.; Shiina, I.; Miyashita, M. *Chem. Lett.* ***1992***, 625. **Yb(OTf)$_3$:** Sharma, G.V.M.; Ilangovan, A. *Synlett* ***1999***, 1963. **LiClO$_4$:** Bandgar, B.P.; Sadavarte, V.S.; Uppalla, L.S. *Synlett* ***2001***, 1338. **FeSO$_4$**: Bandgar, B.P.; Sadavarte, V.S.; Uppalla, L.S. *Synth. Commun.* ***2001***, *31*, 2063. **Ceric ammonium nitrate**: Štefane, B.; Kočevar, M.; Polanc, S. *Synth. Commun.* ***2002***, *32*, 1703.
[1685]Hagiwara, H.; Koseki, A.; Isobe, K.; Shimizu, K.-i.; Hoshi, T.; Suzuki, T. *Synlett* ***2004***, 2188.
[1686]Yamada, S. *Tetrahedron Lett.* ***1992***, *33*, 2171. See also, Costa, A.; Riego, J.M. *Can. J. Chem.* ***1987***, *65*, 2327.

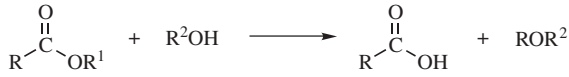
also been accomplished by using enzymes (lipases) as catalysts.[1687] Lactones, such as **101**, are easily opened by treatment with alcohols[1688] to give open-chain hydroxy esters.



101

Transesterification has been carried out with phase-transfer catalysts, without an added solvent.[1689] Nonionic superbases (see p. 365) of the type $P(RNCH_2CH_2)_3N$ catalyze the transesterification of carboxylic acid esters at 25°C.[1690] Silyl esters ($R'CO_2SiR_3$) have been converted to alkyl esters ($R'CO_2R$) via reaction with alkyl halides and tetrabutylammonium fluoride.[1691] Thioesters are converted to phenolic esters by treatment with triphosgene–pyridine and then phenol.[1692]

Transesterification occurs by mechanisms[1693] that are identical with those of ester hydrolysis, except that ROH replaces HOH (by the acyl-oxygen fission mechanisms). When alkyl fission takes place, the products are the *acid* and the *ether*:



Therefore, transesterification reactions frequently fail when R′ is tertiary, since this type of substrate most often reacts by alkyl–oxygen cleavage. In such cases, the reaction is of the Williamson type with OCOR as the leaving group (see **10-10**).

102

With enol esters such as **102**, reaction with an alcohol gives an ester and the enol of a ketone, which readily tautomerizes to the ketone as shown. Hence, enol esters are good acylating agents for alcohols.[1694] This transformation has been

[1687]Wong, C.H.; Whitesides, G. M. in Baldwin, J.E. *Enzymes in Synthetic Organic Chemistry*, *Tetrahedron Organic Chemistry Series* Vol. 12, Pergamon Press, NY, ***1994***; Faber, K. *Biotransformations in Organic Chemistry. A Textbook*, 2nd ed; Springer-Verlag, NY, ***1995***; Córdova, A.; Janda, K.D. *J. Org. Chem.* ***2001***, *66*, 1906; Ciuffreda, P.; Casati, S.; Santaniello, E. *Tetrahedron Lett.* ***2003***, *44*, 3663.

[1688]Anand, R.C.; Sevlapalam, N. *Synth. Commun.* ***1994***, *24*, 2743.

[1689]Barry, J.; Bram, G.; Petit, A. *Tetrahedron Lett.* ***1988***, *29*, 4567. See also, Nishiguchi, T.; Taya, H. *J. Chem. Soc. Perkin Trans. 1* ***1990***, 172.

[1690]Ilankumaran, P.; Verkade, J.G. *J. Org. Chem.* ***1999***, *64*, 3086.

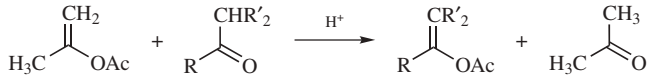
[1691]Ooi, T.; Sugimoto, H.; Maruoka, K. *Heterocycles* ***2001***, *54*, 593.

[1692]Joshi, U.M.; Patkar, L.N.; Rajappa, S. *Synth. Commun.* ***2004***, *34*, 33.

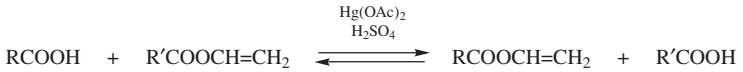
[1693]For a review, see Koskikallio, E.A., in Patai, S. *The Chemistry of Carboxylic Acids and Esters*, Wiley, NY, ***1969***, pp. 103–136.

[1694]Rothman, E.S.; Hecht, S.S.; Pfeffer, P.E.; Silbert, L.S. *J. Org. Chem.* ***1972***, *37*, 3551; Ilankumaran, P.; Verkade, J.G. *J. Org. Chem.* ***1999***, *64*, 9063.

accomplished in ionic liquid media,[1695] and there is a $PdCl_2/CuCl_2$ mediated version.[1696] Isopropenyl acetate can also be used to convert other ketones to the corresponding enol acetates in an exchange reaction:[1697]



Enol esters can also be prepared in the opposite type of exchange reaction, catalyzed by mercuric acetate[1698] or Pd(II) chloride,[1699] for example,

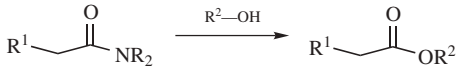


A closely related reaction is equilibration of a dicarboxylic acid and its diester to produce monoesters: The reaction of a carboxylic acid with ethyl acetate, in the presence of $NaHSO_4{\bullet}SiO_2$, was shown to give the corresponding ethyl ester.[1700] Iodine catalyzes the transesterification of β-keto esters.[1701]

OS **II**, 5, 122, 360; **III**, 123, 146, 165, 231, 281, 581, 605; **IV**, 10, 549, 630, 977; **V**, 155, 545, 863; **VI**, 278; **VII**, 4, 164, 411; **VIII**, 155, 201, 235, 263, 350, 444, 528. See also, OS **VII**, 87; **VIII**, 71.

16-65 Alcoholysis of Amides

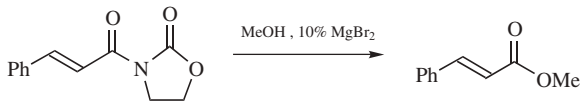
Alkoxy-de-amidation



Alcoholysis of amides is possible,[1702] although it is usually difficult. It has been most common with the imidazolide type of amides (e.g., **100**). For other amides, an activating agent is usually necessary before the alcohol will replace the NR_2 unit. Dimethylformamide, however, reacted with primary alcohols in the presence of 2,4,6-trichloro-1,3,5-pyrazine (cyanuric acid) to give the corresponding formate ester.[1703] Treatment of an amide with triflic anhydride ($CF_3SO_2OSO_2CF_3$) in the

[1695]Grasa, G.A.; Kissling, R.M.; Nolan, S.P. *Org. Lett.* ***2002***, *4*, 3583.
[1696]Bosco, J.W.J.; Saikia, A.K. *Chem. Commun.* ***2004***, 1116.
[1697]For examples, see Deghenghi, R.; Engel, C.R. *J. Am. Chem. Soc.* ***1960***, *82*, 3201; House, H.O.; Trost, B.M. *J. Org. Chem.* ***1965***, *30*, 2502.
[1698]For example, see Hopff, H.; Osman, M.A. *Tetrahedron* ***1968***, *24*, 2205, 3887; Mondal, M.A.S.; van der Meer, R.; German, A.L.; Heikens, D. *Tetrahedron* ***1974***, *30*, 4205.
[1699]Henry, P.M. *J. Am. Chem. Soc.* ***1971***, *93*, 3853; *Acc. Chem. Res.* ***1973***, *6*, 16.
[1700]Das, B.; Venkataiah, B. *Synthesis* ***2000***, 1671.
[1701]Chavan, S.P.; Kale, R.R.; Shivasankar, K.; Chandake, S.I.; Benjamin, S.B. *Synthesis* ***2003***, 2695.
[1702]For example, see Czarnik, A.W. *Tetrahedron Lett.* ***1984***, *25*, 4875. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 197–1978.
[1703]DeLuca, L.; Giacomelli, G.; Porcheddu, A. *J. Org. Chem.* ***2002***, *67*, 5152.

presence of pyridine and then with an excess of alcohol leads to the ester,[1704] as does treatment with $Me_2NCH(OMe)_2$ followed by the alcohol.[1705] Trimethyloxonium tetrafluoroborate converted primary amides to methyl esters.[1706] The reaction of acetanilide derivatives with sodium nitrite in the presence of acetic anhydride–acetic acid leads to phenolic acetates.[1707] Acyl hydrazides ($RCONHNH_2$) were converted to esters by reaction with alcohols and various reagents,[1708] and methoxyamides (RCONHOMe) were converted to esters with $TiCl_4$/ROH.[1709] The reaction of an oxazolidinone amide **103** with methanol and 10% $MgBr_2$ gave the corresponding methyl ester.[1710]



103

C. Attack by OCOR at an Acyl Carbon

16-66 Acylation of Carboxylic Acids With Acyl Halides

Acyloxy-de-halogenation

$$RCOCl + R'COO^- \longrightarrow RCOOCOR'$$

Unsymmetrical, as well as symmetrical, anhydrides are often prepared by the treatment of an acyl halide with a carboxylic acid salt. Cobalt(II) chloride ($CoCl_2$) has been used as a catalyst.[1711] If a metallic salt is used, Na^+, K^+, or Ag^+ are the most common cations, but more often pyridine or another tertiary amine is added to the free acid and the resulting salt is subsequently treated with the acyl halide. Mixed formic anhydrides are prepared from sodium formate and an aryl halide, by use of a solid-phase copolymer of pyridine-1-oxide.[1712] Symmetrical anhydrides can be prepared by reaction of the acyl halide with aq. NaOH or

[1704]Charette, A.B.; Chua, P. *Synlett* ***1998***, 163.
[1705]Anelli, P.L.; Brocchetta, M.; Palano, D.; Visigalli, M. *Tetrahedron Lett.* ***1997***, *38*, 2367.
[1706]Kiessling, A.J.; McClure, C.K. *Synth. Commun.* ***1997***, *27*, 923.
[1707]Glatzhofer, D.T.; Roy, R.R.; Cossey, K.N. *Org. Lett.* ***2002***, *4*, 2349.
[1708]Prakash, O.; Sharma, V.; Sadana, A. *J. Chem. Res. (S)* ***1996***, 100; Štefane, B.; Koevar, M.; Polanc, S. *Tetrahedron Lett.* ***1999***, *40*, 4429; Yamaguchi, J.-i.; Aoyagi, T.; Fujikura, R.; Suyama, T. *Chem. Lett.* ***2001***, 466.
[1709]Fisher, L.E.; Caroon, J.M.; Stabler, S.R.; Lundberg, S.; Zaidi, S.; Sorensen, C.M.; Sparacino, M.L.; Muchowski, J.M. *Can. J. Chem.* ***1994***, *72*, 142.
[1710]Orita, A.; Nagano, Y.; Hirano, J.; Otera, J. *Synlett* ***2001***, 637.
[1711]Srivastava, R.R.; Kabalka, G.W. *Tetrahedron Lett.* ***1992***, *33*, 593.
[1712]Fife, W.K.; Zhang, Z. *J. Org. Chem.* ***1986***, *51*, 3744. See also, Fife, W.K.; Zhang, Z., *Tetrahedron Lett.* ***1986***, *27*, 4933, 4937. For a review of acetic formic anhydride see Strazzolini, P.; Giumanini, A.G.; Cauci, S. *Tetrahedron* ***1990***, *46* 1081.

$NaHCO_3$ under phase-transfer conditions,[1713] or with sodium bicarbonate with ultrasound.[1714]

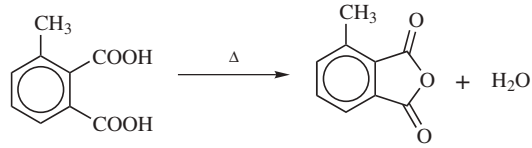
OS **III**, 28, 422, 488; **IV**, 285; **VI**, 8, 910; **VIII**, 132. See also, OS **VI**, 418.

16-67 Acylation of Carboxylic Acids With Carboxylic Acids

Acyloxy-de-hydroxylation

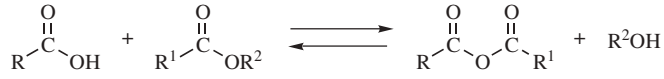
$$2\ RCOOH \xrightleftharpoons{P_2O_5} (RCO)_2O + H_2O$$

Anhydrides can be formed from two molecules of an ordinary carboxylic acid only if a dehydrating agent is present so that the equilibrium can be driven to the right. Common dehydrating agents[1715] are acetic anhydride, trifluoroacetic anhydride, dicyclohexylcarbodiimide,[1716] and P_2O_5. Triphenylphosphine/CCl_3CN with triethylamine has also been used with benzoic acid derivatives.[1717] The method is very poor for the formation of mixed anhydrides, which in any case generally undergo disproportionation to the two simple anhydrides when they are heated. However, simple heating of dicarboxylic acids does give cyclic anhydrides, provided that the ring formed contains five, six, or seven members, for example,



Malonic acid and its derivatives, which would give four-membered cyclic anhydrides, do not give this reaction when heated but undergo decarboxylation (**12-40**) instead.

Carboxylic acids exchange with amides and esters; these methods are sometimes used to prepare anhydrides if the equilibrium can be shifted, for example,



[1713]Plusquellec, D.; Roulleau, F.; Lefeuvre, M.; Brown, E. *Tetrahedron* ***1988***, *44*, 2471; Wang, J.; Hu, Y.; Cui, W. *J. Chem. Res. (S)* ***1990***, 84.

[1714]Hu, Y.; Wang, J.-X.; Li, S. *Synth. Commun.* ***1997***, *27*, 243.

[1715]For lists of other dehydrating agents with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1930–1932; Ogliaruso, M.A.; Wolfe, J.F., in Patai, S. *The Chemistry of Acid Derivatives*, pt.1, Wiley, NY, ***1979***, pp. 437–438.

[1716]For example, see Schüssler, H.; Zahn, H. *Chem. Ber.* ***1962***, *95*, 1076; Rammler, D.H.; Khorana, H.G. *J. Am. Chem. Soc.* ***1963***, *85*, 1997. See also, Hata, T.; Tajima, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* ***1968***, *41*, 2746.

[1717]Kim, J.; Jang, D.O. *Synth. Commun.* ***2001***, *31*, 395.

Enolic esters are especially good for this purpose, because the equilibrium is shifted by formation of the ketone.

The combination of KF with 2-acetoxypropene under microwave conditions was effective.[1718] Carboxylic acids also exchange with anhydrides; indeed, this is how acetic anhydride acts as a dehydrating agent in this reaction.

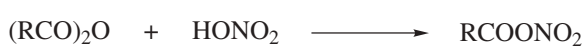
Anhydrides can be formed from certain carboxylic acid salts; for example, by treatment of trimethylammonium carboxylates with phosgene:[1719]

or of thallium(I) carboxylates with thionyl chloride,[1605] or of sodium carboxylates with CCl_4 and a catalyst such as CuCl or $FeCl_2$.[1720]

OS **I**, 91, 410; **II**, 194, 368, 560; **III**, 164, 449; **IV**, 242, 630, 790; **V**, 8, 822; **IX**, 151. Also see, OS **VI**, 757; **VII**, 506.

16-68 Preparation of Mixed Organic–Inorganic Anhydrides

Nitrooxy-de-acyloxy-substitution

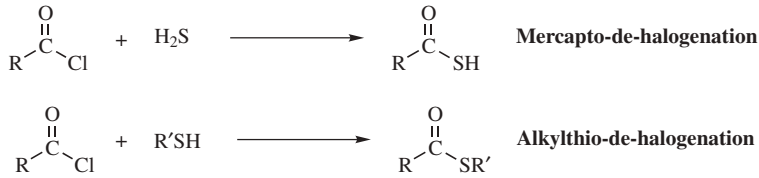


Mixed organic–inorganic anhydrides are seldom isolated, though they are often intermediates when acylation is carried out with acid derivatives catalyzed by inorganic acids. Sulfuric, perchloric, phosphoric, and other acids form similar anhydrides, most of which are unstable or not easily obtained because the equilibrium lies in the wrong direction. These intermediates are formed from amides, carboxylic acids, and esters, as well as anhydrides. Organic anhydrides of phosphoric acid are more stable than most others and, for example, $RCOOPO(OH)_2$ can be prepared in the form of its salts.[1721] Mixed anhydrides of carboxylic and sulfonic acids ($RCOOSO_2R'$) are obtained in high yields by treatment of sulfonic acids with acyl halides or (less preferred) anhydrides.[1722]

OS **I**, 495; **VI**, 207; **VII**, 81.

[1718]Villemin, D.; Labiad, B.; Loupy, A. *Synth. Commun.* ***1993***, *23*, 419.
[1719]Rinderknecht, H.; Ma, V. *Helv. Chim. Acta* ***1964***, *47*, 152. See also, Nangia, A.; Chandrasekaran, S. *J. Chem. Res. (S)* ***1984***, 100.
[1720]Weiss, J.; Havelka, F.; Nefedov, B.K. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1978***, *27*, 193.
[1721]Avison, A.W.D. *J. Chem. Soc.* ***1955***, 732.
[1722]Karger, M.H.; Mazur, Y. *J. Org. Chem.* ***1971***, *36*, 528.

16-69 Attack by SH or SR at an Acyl Carbon[1723]



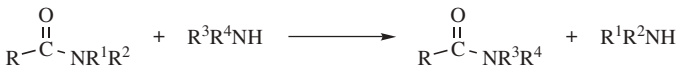
Thiol acids and thiol esters[1724] can be prepared in this manner, which is analogous to **16-57** and **16-64**. Anhydrides[1725] and aryl esters (RCOOAr)[1726] are also used as substrates, but the reagents in these cases are usually HS^- and RS^-. Thiol esters can also be prepared by treatment of carboxylic acids with P_4S_{10}—Ph_3SbO,[1727] or with a thiol RSH and either polyphosphate ester or phenyl dichlorophosphate $PhOPOCl_2$.[1728] Esters RCOOR′ can be converted to thiol esters $RCOSR^2$ by treatment with trimethylsilyl sulfides Me_3SiSR^2 and $AlCl_3$.[1729]

Alcohols, when treated with a thiol acid and zinc iodide, give thiol esters (R′COSR)[1730]

OS **III**, 116, 599; **IV**, 924, 928; **VII**, 81; **VIII**, 71.

16-70 Transamidation

Alkylamino-de-amidation



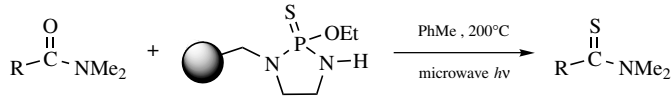
It is sometimes necessary to replace one amide group with another, particularly when the group attached to nitrogen functions as a protecting group[1731] *N*-Benzyl amides can be converted to the corresponding *N*-allyl amide with allylamine and titanium catalysts.[1732] Reaction of *N*-Boc 2-phenylethylamine (Boc = *tert*-butoxy carbonyl) with $Ti(OiPr)_4$ and benzyl alcohol, for example, gives the *N*-Cbz derivative (Cbz = carbobenzoylcarbonyl).[1733] *N*-Carbamoyl amines were converted to

[1723]For a review, see Satchell, D.P.N. *Q. Rev. Chem. Soc.* ***1963***, *17*, 160, pp. 182–184.
[1724]For a review of these compounds, see Scheithauer, S.; Mayer, R. *Top. Sulfur Chem.* ***1979***, *4*, 1.
[1725]Ahmad, S.; Iqbal, J. *Tetrahedron Lett.* ***1986***, *27*, 3791.
[1726]Hirabayashi, Y.; Mizuta, M.; Mazume, T. *Bull. Chem. Soc. Jpn.* ***1965***, *38*, 320.
[1727]Nomura, R.; Miyazaki, S.; Nakano, T.; Matsuda, H. *Chem. Ber.* ***1990***, *123*, 2081.
[1728]Imamoto, T.; Kodera, M.; Yokoyama, M. *Synthesis* ***1982***, 134; Liu, H.; Sabesan, S.I. *Can. J. Chem.* ***1980***, *58*, 2645. For other methods of converting carboxylic acids to thiol esters, see the references given in these papers. See also, Dellaria, Jr., F.F.; Nordeen, C.; Swett, L.R. *Synth. Commun.* ***1986***, *16*, 1043.
[1729]Mukaiyama, T.; Takeda, T.; Atsumi, K. *Chem. Lett.* ***1974***, 187. See also, Hatch, R.P.; Weinreb, S.M. *J. Org. Chem.* ***1977***, *42*, 3960; Cohen, T.; Gapinski, R.E. *Tetrahedron Lett.* ***1978***, 4319.
[1730]Gauthier, J.Y.; Bourdon, F.; Young, R.N. *Tetrahedron Lett.* ***1986***, *27*, 15.
[1731]See, for example, Swain, C.G.; Ketley, A.D.; Bader, R.F.W. *J. Am. Chem. Soc.* ***1959***, *81*, 2353; Knipe, A.C. *J. Chem. Soc. Perkin Trans. 2* ***1973***, 589.
[1732]Eldred, S.E.; Stone, D.A.; Gellman, S.H.; Stahl, S.S. *J. Am. Chem. Soc.* ***2003***, *125*, 3422.
[1733]Shapiro, G.; Marzi, M. *J. Org. Chem.* ***1997***, *62*, 7096.

N-acetyl amines with acetic anhydride, Bu_3SnH, and $Pd(PPh_3)_4$.[1734] Triethylaluminum converts methyl carbamates ($ArNHCO_2Me$) to the corresponding propanamide.[1735]

A related process reacts acetamide with amines and aluminum chloride to give the *N*-acetyl amine.[1736] Another related process converted imides to *O*-benzyloxy amides by the samarium-catalyzed reaction with *O*-benzylhydroxylamine.[1737]

Thioamides can be prepared from amide by reaction with an appropriate sulfur reagent. The reaction of *N,N*-dimethylacetamide under microwave irradiation, with the polymer-bound reagent **104** gave **105**.[1738] Reaction of the thioamide with $Bi(NO_3)_3$•5 H_2O converts regenerates the amide.[1739] Oxone® and a thioamide, on the solid-phase, regenerates the amide.[1740] Selenoamides ($RC(=Se)NR'_2$ have also been prepared from amides.[1741]



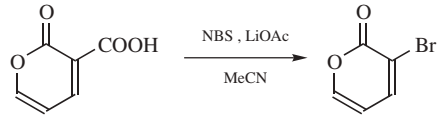
104 **105**

D. Attack by Halogen

16-71 The Conversion of Carboxylic Acids to Halides

Halo-de-oxido,oxo-tersubstitution

In certain cases, carboxyl groups can be replaced by halide. Acrylic acid derivatives ArCH=CHCOOH, for example, react with 3 equivalents of Oxone in the presence of NaBr to give a vinyl bromide ArCH=CHBr.[1742] In other cases, conjugated acids, such as, **106**, have been converted to the bromide by reaction with *N*-bromosuccinimide (NBS, p. 962) and LiOAc.[1743]



106

[1734]Roos, E.C.; Bernabé, P.; Hiemstra, H.; Speckamp, W.N.; Kaptein, B.; Boesten, W.H.J. *J. Org. Chem.* ***1995***, *60*, 1733.
[1735]El Kaim, L.; Grimaud, L.; Lee, A.; Perroux, Y.; Tiria, C. *Org. Lett.* ***2004***, *6*, 381.
[1736]Bon, E.; Bigg, D.C.H.; Bertrand, G. *J. Org. Chem.* ***1994***, *59*, 4035.
[1737]Sibi, M.P.; Hasegawa, H.; Ghorpade, S.R. *Org. Lett.* ***2002***, *4*, 3343.
[1738]Ley, S.V.; Leach, A.G.; Storer, R.I. *J. Chem. Soc. Perkin Trans. 1* ***2001***, 358.
[1739]Mohammadpoor-Baltork, I.; Khodaei, M.M.; Nikoofar, K. *Tetrahedron Lett.* ***2003***, *44*, 591.
[1740]Mohammadpoor-Baltork, I.; Sadeghi, M.M.; Esmayilpour, K. *Synth. Commun.* ***2003***, *33*, 953.
[1741]Saravanan, V.; Mukherjee, C.; Das, S.; Chandrasekaran, S. *Tetrahedron Lett.* ***2004***, *45*, 681.
[1742]You, H.-W.; Lee, K.-J. *Synlett* ***2001***, 105.
[1743]Cho, C.-G.; Park, J.-S.; Jung, I.-H.; Lee, H. *Tetrahedron Lett.* ***2001***, *42*, 1065.

E. Attack by Nitrogen at an Acyl Carbon[1744]

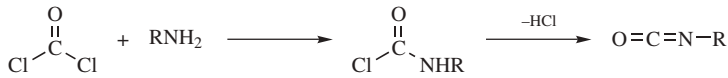
16-72 Acylation of Amines by Acyl Halides

Amino-de-halogenation

$$RCOX + NH_3 \longrightarrow RCONH_2 + HX$$

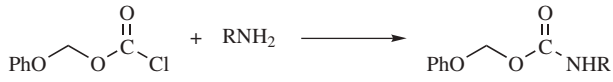
The treatment of acyl halides with ammonia or amines is a very general reaction for the preparation of amides.[1745] The reaction is highly exothermic and must be carefully controlled, usually by cooling or dilution. Ammonia gives unsubstituted amides, primary amines give *N*-substituted amides,[1746] and secondary amines give *N,N*-disubstituted amides. Arylamines can be similarly acylated. Hydroxamic acids have been prepared by this route.[1747] In some cases, aqueous alkali is added to combine with the liberated HCl. This is called the *Schotten–Baumann procedure*, as in **16-61**. Activated zinc can be used to increase the rate of amide formation when hindered amines and/or acid chlorides are used.[1748] An indium-mediated amidation reaction[1749] and a BiOCl-mediated reaction[1750] have been reported. A variation of this basic reaction uses DMF with acyl halides to give *N,N*-dimethylamides.[1751] A solvent-free reaction was reported using DABCO and methanol.[1752]

Hydrazine and hydroxylamine also react with acyl halides to give, respectively, hydrazides ($RCONHNH_2$)[1753] and hydroxamic acids (RCONHOH).[1754] When phosgene is the acyl halide, both aliphatic and aromatic primary amines give chloroformamides (ClCONHR) that lose HCl to give isocyanates (RNCO).[1755] This is one of the most common methods for



[1744]For a review, see Challis, M.S.; Butler, A.R., in Patai, S. *The Chemistry of the Amino Group*, Wiley, NY, ***1968***, pp. 279–290.
[1745]For a review, see Beckwith, A.L.J., in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 73–185. See Jedrzejczak, M.; Motie, R.E.; Satchell, D.P.N. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 599 for a discussion of the kinetics of this reaction.
[1746]See Bhattacharyya, S.; Gooding, O.W.; Labadie, J. *Tetrahedron Lett.* ***2003***, *44*, 6099.
[1747]Reddy, A.S.; Kumar, M.S.; Reddy, G.R. *Tetrahedron Lett.* ***2000***, *41*, 6285.
[1748]Meshram, H.M.; Reddy, G.S.; Reddy, M.M.; Yadav, J.S. *Tetrahedron Lett.* ***1998***, *39*, 4103.
[1749]Cho, D.H.; Jang, D.O. *Tetrahedron Lett.* ***2004***, *45*, 2285.
[1750]Ghosh, R.; Maiti, S.; Chakraborty, A. *Tetrahedron Lett.* ***2004***, *45*, 6775.
[1751]Lee, W.S.; Park, K.H.; Yoon, Y-J. *Synth. Commun.* ***2000***, *30*, 4241.
[1752]Hajipour, A.R.; Mazloumi, Gh. *Synth. Commun.* ***2002***, *32*, 23.
[1753]For a review of hydrazides, see Paulsen, H.; Stoye, D., in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 515–600.
[1754]For an improved method, see Ando, W.; Tsumaki, H. *Synth. Commun.* ***1983***, *13*, 1053.
[1755]For reviews of the preparation and reactions of isocyanates and isothiocyanates, see, respectively, the articles by Richter, R.; Ulrich, H. pp. 619–818, and Drobnica, L.; Kristián, P.; Augustín, J. pp. 1003–1221, in Patai S. *The Chemistry of Cyanates and Their Thio Derivatives*, pt. 2, Wiley, NY, ***1977***.

the preparation of isocyanates.[1756] Thiophosgene,[1757] similarly treated, gives isothiocyanates. A safer substitute for phosgene in this reaction is trichloromethyl chloroformate CCl_3OCOCl.[1758] When chloroformates ROCOCl are treated with primary amines, carbamates ROCONHR′ are obtained.[1759] An example of this reaction is the use of benzyl chloroformate to protect the amino group of amino acids and peptides.



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The $PhCH_2OCO$ group in **107** is called the carbobenzoxy group,[1760] and is often abbreviated Cbz or Z. Another important group similarly used is the *tert*-butoxycarbonyl group Me_3COCO, abbreviated as Boc. In this case, the chloride ($Me_3COCOCl$) is unstable, so the anhydride, $(Me_3COCO)_2O$, is used instead, in an example of **16-73**. Amino groups in general are often protected by conversion to amides.[1761] The treatment of acyl halides with lithium nitride gives *N,N*-diacyl amides (triacylamines), **108**.[1762] The reactions proceed by the tetrahedral mechanism.[1763]

$$3\ RCOCl + Li_3N \longrightarrow (RCO)_3N$$

108

A novel variation of this reaction uses nitrogen gas as the nitrogen source in the amide. The reaction of benzoyl chloride with $TiCl_4$/Li/Me_3SiCl/CsF and N_2, gave a 77% yield of benzamide.[1764]

An interesting variation of this transformation reacts carbamoyl chlorides with organocuprates to give the corresponding amide.[1765]

[1756]For examples, see Ozaki, S. *Chem. Rev.* ***1972***, *72*, 457, see pp. 457–460. For a review of the industrial preparation of isocyanates by this reaction, see Twitchett, H.J. *Chem. Soc. Rev.* ***1974***, *3*, 209.

[1757]For a review of thiophosgene, see Sharma, S. *Sulfur Rep.* ***1986***, *5*, 1.

[1758]Kurita, K.; Iwakura, Y. *Org. Synth.* ***VI***, 715.

[1759]For example see Ariza, X.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* ***1999***, *40*, 7515. See also, Mormeneo, D.; Llebaria, A.; Delgado, A. *Tetrahedron Lett.* ***2004***, *45*, 6831. For a variation involving azide and a palladium catalyst, see Okumoto, H.; Nishihara, S.; Yamamoto, S.; Hino, H.; Nozawa, A.; Suzuki, A. *Synlett* ***2000***, 991.

[1760]For an alternative reagent to prepare *N*- Cbz derivatives, see Yasuhara, T.; Nagaoka, Y.; Tomioka, K. *J. Chem. Soc. Perkin Trans. 1* ***1999***, 2233.

[1761]Greene, T.W. *Protective Groups in Organic Synthesis*, Wiley, NY, ***1980***, pp. 222–248, 324–326; Wuts, P.G.M.; Greene, T.W. *Protective Groups in Organic Synthesis*, 2nd ed., Wiley, NY, ***1991***, pp. 327–330; Wuts, P.G.M.; Greene, T.W. *Protective Groups in Organic Synthesis*, 3rd ed., Wiley, NY, ***1999***, pp. 518–525; 737–739.

[1762]Baldwin, F.P.; Blanchard, E.J.; Koening, P.E. *J. Org. Chem.* ***1965***, *30*, 671.

[1763]Kivinen, A., in Patai, S. *The Chemistry of Acyl Halides*, Wiley, NY, ***1972***; Bender, M.L.; Jones, J.M. *J. Org. Chem.* ***1962***, *27*, 3771. See also, Song, B.D.; Jencks, W.P. *J. Am. Chem. Soc.* ***1989***, *111*, 8479.

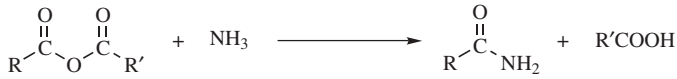
[1764]Kawaguchi, M.; Hamaoka, S.; Mori, M. *Tetrahedron Lett.* ***1993***, *34*, 6907.

[1765]Lemoucheux, L.; Seitz, T.; Rouden, J.; Lasne, M.-C. *Org. Lett.* ***2004***, *6*, 3703.

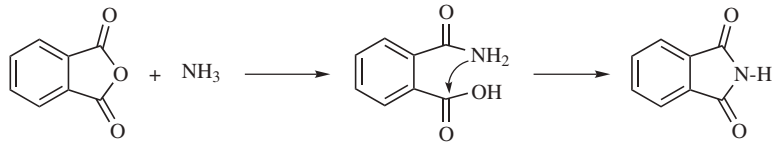
OS **I**, 99, 165; **II**, 76, 208, 278, 328, 453; **III**, 167, 375, 415, 488, 490, 613; **IV**, 339, 411, 521, 620, 780; **V**, 201, 336; **VI**, 382, 715; **VII**, 56, 287, 307; **VIII**,16, 339; **IX**, 559; **81**, 254. See also, OS **VII**, 302.

16-73 Acylation of Amines by Anhydrides

Amino-de-acyloxy-substitution



This reaction, similar in scope and mechanism[1766] to **16-72**, can be carried out with ammonia or primary or secondary amines.[1767] Note that there is a report where a tertiary amine (an *N*-alkylpyrrolidine) reacted with acetic anhydride at 120°C, in the presence of a BF_3•etherate catalyst, to give *N*-acetylpyrrolidine (an acylative dealkylation).[1768] Amino acids can be *N*-acylated using acetic anhydride and ultrasound.[1769] However, ammonia and primary amines can also give imides, in which two acyl groups are attached to the nitrogen. The conversion of cyclic anhydrides to cyclic imides is generally facile,[1770] although elevated temperatures are occasionally required to generate the imide.[1771] Microwave irradiation of formamide and a cyclic anhydride generates the cyclic imide.[1772] Cyclic imides have also been formed in ionic liquids.[1773] Cyclic imides were also formed by microwave irradiation of a polymer-bound phthalate after initial reaction with an amine.[1774]



The second step for imide formation, which is much slower than the first, is the attack of the amide nitrogen on the carboxylic carbon. Unsubstituted and *N*-substituted amides have been used instead of ammonia. Since the other product

[1766]For a discussion of the mechanism, see Kluger, R.; Hunt, J.C. *J. Am. Chem. Soc.* ***1989***, *111*, 3325.

[1767]For a review, see Beckwith, A.L.J., in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 86–96. See also, Naik, S.; Bhattacharjya, G.; Talukdar, B.; Patel, B.K. *Eur. J. Org. Chem.* ***2004***, 1254.

[1768]Dave, P. R.; Kumar, K. A.; Duddu, R.; Axenrod, T.; Dai, R.; Das, K. K.; Guan, X.-P.; Sun, J.; Trivedi, N. J.; Gilardi, R. D. *J. Org. Chem.* ***2000***, *65*, 1207.

[1769]Anuradha, M.V.; Ravindranath, B. *Tetrahedron* ***1997***, *53*, 1123.

[1770]For reviews of imides, see Wheeler, O.H.; Rosado, O., in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 335–381; Hargreaves, M.K.; Pritchard, J.G.; Dave, H.R. *Chem. Rev.* ***1970***, *70*, 439 (cyclic imides).

[1771]Tsubouchi, H.; Tsuji, K.; Ishikawa, H. *Synlett* ***1994***, 63.

[1772]Peng, Y.; Song, G.; Qian, X. *Synth. Commun.* ***2001***, *31*, 1927; Kacprzak, K. *Synth. Commun.* ***2003***, *33*, 1499.

[1773]In bmim PF_6, 1-butyl-3-methylimidazolium hexafluorophosphate: Le, Z.-G.; Chen, Z.-C.; Hu, Y.; Zheng, Q.-G. *Synthesis* ***2004***, 995.

[1774]Martin, B.; Sekljic, H.; Chassaing, C. *Org. Lett.* ***2003***, *5*, 1851.

of this reaction is RCOOH, this is a way of "hydrolyzing" such amides in the absence of water.[1775]

Even though formic anhydride is not a stable compound (see p. 723), amines can be formylated with the mixed anhydride of acetic and formic acids (HCOOCOMe)[1776] or with a mixture of formic acid and acetic anhydride. Acetamides are not formed with these reagents. Secondary amines can be acylated in the presence of a primary amine by conversion to their salts and addition of 18-crown-6.[1777] The crown ether complexes the primary ammonium salt, preventing its acylation, while the secondary ammonium salts, which do not fit easily into the cavity, are free to be acylated. Dimethyl carbonate can be used to prepare methyl carbamates in a related procedure.[1778] *N*-Acetylsulfonamides were prepared from acetic anhydride and a primary sulfonamide, catalyzed by Montmorillonite K10–FeO[1779] or sulfuric acid.[1780]

The reaction of anhydrides with aryl azides, in the presence of Me_3SiCl and NaI, gives *N*-aryl imides.[1781]

OS **I**, 457; **II**, 11; **III**, 151, 456, 661, 813; **IV**, 5, 42, 106, 657; **V**, 27, 373, 650, 944, 973; **VI**, 1; **VII**, 4, 70; **VIII**, 132; **76**, 123.

16-74 Acylation of Amines by Carboxylic Acids

Amino-de-hydroxylation

$$RCOOH + NH_3 \longrightarrow RCOO^-NH_4^+ \xrightarrow{\text{pyrolysis}} RCONH_2$$

When carboxylic acids are treated with ammonia or amines, salts are obtained. The salts of ammonia or primary or secondary amines can be pyrolyzed to give amides,[1782] but the method is less convenient than **16-72**, **16-73**, and **16-75** and is seldom of preparative value.[1783] Heating in the presence of a base such as hexamethyldisilazide makes the amide-forming process more efficient.[1784] Boronic acids catalyze the direct conversion of carboxylic acid and amine to amides.[1785]

[1775]Eaton, J.T.; Rounds, W.D.; Urbanowicz, J.H.; Gribble, G.W. *Tetrahedron Lett.* ***1988***, *29*, 6553.
[1776]For the formylation of amines with the mixed anhydride of formic and trimethylacetic acid, see Vlietstra, E.J.; Zwikker, J.W.; Nolte, R.J.M.; Drenth, W. *Recl. Trav. Chim. Pays-Bas* ***1982***, *101*, 460.
[1777]Barrett, A.G.M.; Lana, J.C.A. *J. Chem. Soc., Chem. Commun.* ***1978***, 471.
[1778]Vauthey, I.; Valot, F.; Gozzi, C.; Fache, F.; Lemaire, M. *Tetrahedron Lett.* ***2000***, *41*, 6347.
[1779]Singh, D.U.; Singh, P.R.; Samant, S.D. *Tetahedron Lett.* ***2004***, *45*, 4805.
[1780]Martin, M.T.; Roschangar, F.; Eaddy, J.F. *Tetrahedron Lett.* ***2003***, *44*, 5461.
[1781]Kamal, A.; Laxman, E.; Laxman, N.; Rao, N.V. *Tetrahedron Lett.* ***1998***, *39*, 8733.
[1782]For example, see Mitchell, J.A.; Reid, E.E. *J. Am. Chem. Soc.* ***1931***, *53*, 1879. Also see, Jursic, B.S.; Zdravkovski, Z. *Synth. Commun.* ***1993***, *23*, 2761.
[1783]For a review of amide formation from carboxylic acids, see Beckwith, A.L.J., in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 105–109.
[1784]Chou, W.-C.; Chou, M.-C.; Lu, Y.-Y.; Chen, S.-F. *Tetrahedron Lett.* ***1999***, *40*, 3419. For alternative approaches using specialized reagents, see Jang, D.O.; Park, D.J.; Kim, J. *Tetrahedron Lett.* ***1999***, *40*, 5323; Bailén, M.A.; Chinchilla, R.; Dodsworth, D.J.; Nájera, C. *Tetrahedron Lett.* ***2000***, *41*, 9809 and ***2001***, *42*, 5013; White, J.M.; Tunoori, A.R.; Turunen, B.J.; Georg, G.I *J. Org. Chem.* ***2004***, *69*, 2573.
[1785]Ishihara, K.; Kondo, S.; Yamamoto, H. *Synlett* ***2001***, 1371.

Polymer-bound reagents have also been used.[1786] The synthetically important Weinreb amides [RCON(Me)OMe, see **16-82**] can be prepared from the carboxylic acid and MeO(Me)NH•HCl in the presence of tributylphosphine and 2-pyridine-*N*-oxide disulfide.[1787] Di(2-pyridyl)carbonate has been used in a related reaction that generates amides directly.[1788] The reaction of a carboxylic acid and imidazole under microwave irradiation gives the amide.[1789] Microwave irradiation of a secondary amine, formic acid, 2-chloro-4,6-dimethoxy[1,3,5]triazine, and a catalytic amount of DMAP (4-dimethylaminopyridine) leads to the formamide.[1790] Ammonium bicarbonate and formamide converts acids to amides with microwave irradiation.[1791] Lactams are readily produced from γ- or δ-amino acids,[1792] for example,

This lactamization process can be promoted by enzymes, such as pancreatic porcine lipase.[1793] Reduction of ω-azido carboxylic acids leads to macrocyclic lactams.[1794]

Although treatment of carboxylic acids with amines does not directly give amides, the reaction can be made to proceed in good yield at room temperature or slightly above by the use of coupling agents,[1795] the most important of which is dicyclohexylcarbodiimide. This reagent is very convenient and is used[1796] a great deal in peptide synthesis.[1797] A polymer-supported carbodiimide has been used.[1798] The mechanism is probably the same as in **16-63** up to the formation

[1786]Buchstaller, H.P.; Ebert, H.M.; Anlauf, U. *Synth. Commun.* ***2001***, *31*, 1001; Crosignani, S.; Gonzalez, J.; Swinnen, D. *Org. Lett.* ***2004***, *6*, 4579; Chichilla, R.; Dodsworth, D.J.; Nájera, C.; Soriano, J.M. *Tetrahedron Lett.* ***2003***, *44*, 463.

[1787]Banwell, M.; Smith, J. *Synth. Commun.* ***2001***, *31*, 2011. For another procedure, see Kim, M.; Lee, H.; Han, K.-J.; Kay,K.-Y. *Synth. Commun.* ***2003***, *33*, 4013.

[1788]Shiina, I.; Suenaga, Y.; Nakano, M.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* ***2000***, *73*, 2811.

[1789]Khalafi-Nezhad, A.; Mokhtari, B.; Rad, M.N.S. *Tetrahedron Lett.* ***2003***, *44*, 7325; Perreux, L.; Loupy, A.; Volatron, F. *Tetrahedron* ***2002***, *58*, 2155.

[1790]De Lucca, L.; Giacomelli, G.; Porcheddu, A.; Salaris, M. *Synlett* ***2004***, 2570.

[1791]Peng, Y.; Song, G. *Org. Prep. Proceed. Int.* ***2002***, *34*, 95.

[1792]See, for example, Bladé-Font, A. *Tetrahedron Lett.* ***1980***, *21*, 2443. See Wei, Z.-Y.; Knaus, E.E. *Tetrahedron Lett.* ***1993***, *34*, 4439 for a variation of this reaction.

[1793]Gutman, A.L.; Meyer, E.; Yue, X.; Abell, C. *Tetrahedron Lett.* ***1992***, *33*, 3943.

[1794]Bosch, I.; Romea, P.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* ***1993***, *34*, 4671. See Bai, D.; Shi, Y. *Tetrahedron Lett.* ***1992***, *33*, 943 for the preparation of lactam units in para-cyclophanes.

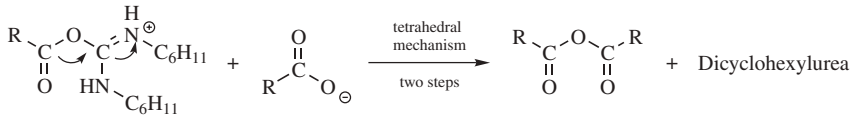
[1795]For a review of peptide synthesis with dicyclohexylcarbodiimide and other coupling agents, see Klausner, Y.S.; Bodansky, M. *Synthesis* ***1972***, 453.

[1796]It was first used this way by Sheehan, J.C.; Hess, G.P. *J. Am. Chem. Soc.* ***1955***, *77*, 1067.

[1797]For a treatise on peptide synthesis, see Gross, E.; Meienhofer, J. *The Peptides*, 3 vols., Academic Press, NY, ***1979–1981***. For a monograph, see Bodanszky, M.; Bodanszky, A. *The Practice of Peptide Synthesis*, Springer, NY, ***1984***.

[1798]Feuerstein, M.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* ***2001***, *42*, 6667.

of **109**. This intermediate is then attacked by another molecule of $RCOO^-$ to give the anhydride $(RCO)_2O$, which is the actual species that reacts with the amine:



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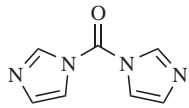
The anhydride has been isolated from the reaction mixture and then used to acylate an amine.[1799] Other promoting agents[1800] are $ArB(OH)_2$ reagents,[1801] $Sn[N(TMS)_2]_2$,[1802] *N*,*N*′-carbonyldiimidazole (**110**, p. 1418),[1803] which behaves as in reaction **16-63**, $POCl_3$,[1804] $TiCl_4$,[1805] molecular sieves,[1806] Lawesson's reagent (p. 1278),[1807] and $(MeO)_2POCl$.[1808] Certain dicarboxylic acids form amides simply on treatment with primary aromatic amines. In these cases, the cyclic anhydride is an intermediate and is the species actually attacked by the amine.[1809] Carboxylic acids can also be converted to amides by heating with amides of carboxylic acids (exchange),[1810] sulfonic acids, or phosphoric acids, for example,[1811]



110

[1799]Schüssler, H.; Zahn, H. *Chem. Ber.* ***1962***, *95*, 1076; Rebek, J.; Feitler, D. *J. Am. Chem. Soc.* ***1974***, *96*, 1606. There is evidence that some of the **98** is converted to products by another mechanism. See Rebek, J.; Feitler, D. *J. Am. Chem. Soc.* ***1973***, *95*, 4052.

[1800]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1941–1949.

[1801]Ishihara, K.; Ohara, S.; Yamamoto, H. *J. Org. Chem.* ***1996***, *61*, 4196.

[1802]Burnell-Curty, C.; Roskamp, E.J. *Tetrahedron Lett.* ***1993***, *34*, 5193.

[1803]See Vaidyanathan, R.; Kalthod, V.G.; Ngo, D.; Manley, J.M.; Lapekas, S.P. *J. Org. Chem.* ***2004***, *69*, 2565. A modified but related reagent has also been used. See Grzyb, J.A.; Batey, R.A. *Tetrahedron Lett.* ***2003***, *44*, 7485.

[1804]Klosa, J. *J. Prakt. Chem.* ***1963***, *[4] 19*, 45.

[1805]Wilson, J.D.; Weingarten, H. *Can. J. Chem.* ***1970***, *48*, 983.

[1806]Cossy, J.; Pale-Grosdemange, C. *Tetrahedron Lett.* ***1989***, *30*, 2771.

[1807]Thorsen, M.; Andersen, T.P.; Pedersen, U.; Yde, B.; Lawesson, S. *Tetrahedron* ***1985***, *41*, 5633.

[1808]Jászay, Z.M.; Petneházy, I.; Töke, L. *Synth. Commun.* ***1998***, *28*, 2761.

[1809]Higuchi, T.; Miki, T.; Shah, A.C.; Herd, A.K. *J. Am. Chem. Soc.* ***1963***, *85*, 3655.

[1810]For example, see Schindbauer, H. *Monatsh. Chem.* ***1968***, *99*, 1799.

[1811]Zhmurova, I.N.; Voitsekhovskaya, I.Yu.; Kirsanov, A.V. *J. Gen. Chem. USSR* ***1959***, *29*, 2052. See also, Kopecky, J.; Smejkal, J. *Chem. Ind. (London)* ***1966***, 1529; Liu, H.; Chan, W.H.; Lee, S.P. *Synth. Commun.* ***1979***, *9*, 31.

or by treatment with trisalkylaminoboranes, $B(NHR')_3$, with trisdialkylaminoboranes, $B(NR'_2)_3$,[1812]

$$RCOOH + B(NR_2')_3 \longrightarrow RCONR_2'$$

or with bis(diorganoamino)magnesium reagents $(R_2N)_2Mg$.[1813] The reaction of thiocarboxylic acids and azides, in the presence of triphenylphosphine, gives the corresponding amide.[1814]

An important technique, discovered by R.B. Merrifield in 1963[1815] and since used for the synthesis of many peptides,[1816] is called *solid phase synthesis* or *polymer-supported synthesis*.[1817] The reactions used are the same as in ordinary synthesis, but one of the reactants is anchored onto a solid polymer. For example, if it is desired to couple two amino acids (to form a dipeptide), the polymer selected might be polystyrene with CH_2Cl side chains. One of the amino acids, protected by a *tert*-butoxycarbonyl group (Boc), would then be coupled to the side chains. It is not necessary that all the side chains be converted, but a random selection will be. The Boc group is then removed by hydrolysis with trifluoroacetic acid in CH_2Cl_2 and the second amino acid is coupled to the first, using DCC or some other coupling agent. The second Boc group is removed, resulting in a dipeptide that is still anchored to the polymer. If this dipeptide is the desired product, it can be cleaved from the polymer by various methods,[1818] one of which is treatment with HF. If a longer peptide is wanted, additional amino acids can be added by repeating the requisite steps.

[1812]Pelter, A.; Levitt, T.E.; Nelson, P. *Tetrahedron* ***1970***, *26*, 1539; Pelter, A.; Levitt, T.E. *Tetrahedron* ***1970***, *26*, 1545, 1899.

[1813]Sanchez, R.; Vest, G.; Despres, L. *Synth. Commun.* ***1989***, *19*, 2909.

[1814]Park, S.-D.; Oh, J.-H.; Lim, D. *Tetrahedron Lett.* ***2002***, *43*, 6309.

[1815]Merrifield, R.B. *J. Am. Chem. Soc.* ***1963***, *85*, 2149.

[1816]For a monograph on solid-state peptide synthesis, see Birr, C. *Aspects of the Merrifield Peptide Synthesis*, Springer, NY, ***1978***. For reviews, see Bayer, E. *Angew. Chem. Int. Ed.* ***1991***, *30*, 113; Kaiser, E.T. *Acc. Chem. Res.* ***1989***, *22*, 47; Jacquier, R. *Bull. Soc. Chim. Fr.* ***1989***, 220; Barany, G.; Kneib-Cordonier, N.; Mullen, D.G. *Int. J. Pept. Protein Res.* ***1987***, *30*, 705; Andreev, S.M.; Samoilova, N.A.; Davidovich, Yu.A.; Rogozhin, S.V. *Russ. Chem. Rev.* ***1987***, *56*, 366; Gross, E.; Meienhofer, J. *The Peptides*, Vol. 2, Academic Press, NY, ***1980***, the articles by Barany, G.; Merrifield, R.B. pp. 1–184, Fridkin, M. pp. 333–363; Erickson, B.W.; Merrifield, R.B. in Neurath, H.; Hill, R.L.; Boeder, C.-L. *The Proteins*, 3rd ed., Vol. 2, Academic Press, NY, ***1976***, pp. 255–527. For R. B. Merrifield's Nobel Prize lecture, see Merrifield, R.B. *Angew. Chem. Int. Ed.* ***1985***, *24*, 799; *Chem. Scr.* ***1985***, *25*, 121.

[1817]For monographs on solid-phase synthesis in general, see Laszlo, P. *Preparative Organic Chemistry Using Supported Reagents*, Academic Press, NY, ***1987***; Mathur, N.K.; Narang, C.K.; Williams, R.E. *Polymers as Aids in Organic Chemistry*, Academic Press, NY ***1980***; Hodge, P.; Sherrington, D.C. *Polymer-Supported Reactions in Organic Synthesis*, Wiley, NY, ***1980***. For reviews, see Pillai, V.N.R.; Mutter, M. *Top. Curr. Chem.* ***1982***, *106*, 119; Akelah, A.; Sherrington, D.C. *Chem. Rev.* ***1981***, *81*, 557; Akelah, A. *Synthesis* ***1981***, 413; Rebek, J. *Tetrahedron* ***1979***, *35*, 723; McKillop, A.; Young, D.W. *Synthesis* ***1979***, 401, 481; Crowley, J.I.; Rapoport, H. *Acc. Chem. Res.* ***1976***, *9*, 135; Patchornik, A.; Kraus, M.A. *Pure Appl. Chem.* ***1975***, *43*, 503.

[1818]For some of these methods, see Whitney, D.B.; Tam, J.P.; Merrifield, R.B. *Tetrahedron* ***1984***, *40*, 4237.

The basic advantage of the polymer-support techniques is that the polymer (including all chains attached to it) is easily separated from all other reagents, because it is insoluble in the solvents used. Excess reagents, other reaction products (e.g., dicyclohexylurea), side products, and the solvents themselves are quickly washed away. Purification of the polymeric species is rapid and complete. The process can even be automated,[1819] to the extent that six or more amino acids can be added to a peptide chain in one day. Commercial automated peptide synthesizers are now available.[1820]

Although the solid-phase technique was first developed for the synthesis of peptide chains and has seen considerable use for this purpose, it has also been used to synthesize chains of polysaccharides and polynucleotides; in the latter case, solid-phase synthesis has almost completely replaced synthesis in solution.[1821] The technique has been applied less often to reactions in which only two molecules are brought together (nonrepetitive syntheses), but many examples have been reported.[1822] Combinatorial chemistry had its beginning with the Merrifield synthesis, particularly when applied to peptide synthesis, and continues as an important part of modern organic chemistry.[1823]

OS **I**, 3, 82, 111, 172, 327; **II**, 65, 562; **III**, 95, 328, 475, 590, 646, 656, 768; **IV**, 6, 62, 513; **V**, 670, 1070; **VIII**, 241; **81**, 262. Also see OS **III**, 360; **VI**, 263; **VIII**, 68.

16-75 Acylation of Amines by Carboxylic Esters

Amino-de-alkoxylation

$$\mathrm{RCOOR' + NH_3 \longrightarrow RCONH_2 + R'OH}$$

The conversion of carboxylic esters to amides is a useful reaction, and unsubstituted, *N*-substituted, and *N,N*-disubstituted amides can be prepared this way from the appropriate amine.[1824] Both R and R′ can be alkyl or aryl, but an especially

[1819]This was first reported by Merrifield, R.B.; Stewart, J.M.; Jernberg, N. *Anal. Chem.* ***1966***, *38*, 1905.
[1820]For a discussion of automated organic synthesis, see Frisbee, A.R.; Nantz, M.H.; Kramer, G.W.; Fuchs, P.L. *J. Am. Chem. Soc.* ***1984***, *106*, 7143. For an improved method, see Schnorrenberg, G.; Gerhardt, H. *Tetrahedron* ***1989***, *45*, 7759.
[1821]For a review, see Bannwarth, W. *Chimia* ***1987***, *41*, 302.
[1822]For reviews, see Fréchet, J.M.J. *Tetrahedron* ***1981***, *37*, 663; Fréchet, J.M.J. in Hodge, P.; Sherrington, D.C. *Polymer-Supported Reactions in Organic Synthesis*, Wiley, NY, ***1980***, pp. 293–342, Leznoff, C.C. *Acc. Chem. Res.* ***1978***, *11*, 327; *Chem. Soc. Rev.* ***1974***, *3*, 64.
[1823]Czarnik, A.W.; DeWitt, S.H. *A Practical Guide to Combinatorial Chemistry*, American Chemical Society, Washington, DC, ***1997***; Chaiken, I.N.; Janda, K.D. *Molecular Diversity and Combinatorial Chemistry: Libraries and Drug Discovery*, American Chemical Society, Washington, DC ***1996***; Balkenhol, F.; von dem Bussche-Hünnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem. Int. Ed.* ***1996***, *35*, 2289; Thompson, L.A.; Ellman, J.A. *Chem. Rev.* ***1996***, 96, 555; Pavia, M.R.; Sawyer, T.K.; Moos, W.H. *Bioorg. Med. Chem. Lett. Symposia–in–print no. 4* ***1993***, *3*, 387; Crowley, J.I.; Rapoport, H. *Acc. Chem. Res.* ***1976***, *9*, 135; Leznoff, C.C. *Acc. Chem. Res.* ***1978***, *11*, 327.
[1824]For a review, see Beckwith, A.L.J., in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 96–105. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1973–1976.

good leaving group is *p*-nitrophenyl. Ethyl trifluoroacetate was found to react selectively with primary amines to form the corresponding trifluoroacetyl amide.[1825] Many simple esters (R = Me, Et, etc.) are not very reactive, and strongly basic catalysis has been used in such cases,[1826] but catalysis by cyanide ion[1827] $MgBr_2$,[1828] InI_3,[1829] and acceleration by high pressure[1830] have been reported. Methyl esters have been converted to the corresponding amide under microwave irradiation,[1831] and also ethyl esters.[1832] Lithium amides have been used to convert esters to amides as well.[1833] β-Keto esters undergo the reaction especially easily.[1834] In another procedure, esters are treated with dimethylaluminum amides (Me_2AlNRR') to give good yields of amides under mild conditions.[1835] The reagents are easily prepared from Me_3Al and NH_3 or a primary or secondary amine or their salts. This is particularly effective when a reactive substituent, such as a primary halide, is present elsewhere in the molecule.[1836] Tin reagents, such as $Sn[N(TMS)_2]_2$, in the presence of an amine can also be use to convert an ester to an amide.[1837] This reagent can also be used to convert β-amino esters to β-lactams.[1838] Aniline was treated with *n*-butyllithium to form the lithium amide, which reacted with an ester to give the amide.[1839] The ester-to-amide conversion has also been accomplished electrochemically, by passing electric current in the cathodic compartment.[1840] An enzyme-mediated amidation is known using amino cyclase I.[1841] The reaction of dimethyl carbonate and an amine is an effective way to prepare methyl carbamates.[1842]

[1825]Xu, D.; Prasad, K.; Repic, O.; Blacklock, T.J. *Tetrahedron Lett.* ***1995***, *36*, 7357.

[1826]For references, see Matsumoto, K.; Hashimoto, S.; Uchida, T.; Okamoto, T.; Otani, S. *Chem. Ber.* ***1989***, *122*, 1357.

[1827]Högberg, T.; Ström, P.; Ebner, M.; Rämsby, S. *J. Org. Chem.* ***1987***, *52*, 2033.

[1828]Guo, Z.; Dowdy, E.D.; Li, W.-S.; Polniaszek, R.; Delaney, E. *Tetrahedron Lett.* ***2001***, *42*, 1843.

[1829]Ranu, B.C.; Dutta, P. *Synth. Commun.* ***2003***, *33*, 297.

[1830]Matsumoto, K.; Hashimoto, S.; Uchida, T.; Okamoto, T.; Otani, S. *Chem. Ber.* ***1989***, *122*, 1357.

[1831]Varma, R.S.; Naicker, K.P. *Tetrahedron Lett.* ***1999***, *40*, 6177.

[1832]Suri, O.P.; Satti, N.K.; Suri, K.A. *Synth. Commun.* ***2000***, *30*, 3709; Zradni, F.-Z.; Hamelin, J.; Derdour, A. *Synth. Commun.* ***2002***, *32*, 3525.

[1833]See Wang, J.; Rosingana, M.; Discordia, R.P.; Soundararajan, N.; Polniaszek, R. *Synlett* ***2001***, 1485.

[1834]Labelle, M.; Gravel, D. *J. Chem. Soc., Chem. Commun.* ***1985***, 105.

[1835]Basha, A.; Lipton, M.; Weinreb, S.M. *Org. Synth.* ***VI***, 492; Levin, J.I.; Turos, E.; Weinreb, S.M. *Synth. Commun.* ***1982***, *12*, 989; Barrett, A.G.M.; Dhanak, D. *Tetrahedron Lett.* ***1987***, *28*, 3327. For the extension of this method to the formation of hydrazides, see Benderly, A.; Stavchansky, S. *Tetrahedron Lett.* ***1988***, *29*, 739.

[1836]Shimizu, T.; Osako, K.; Nakata, T. *Tetrahedron Lett.* ***1997***, *38*, 2685.

[1837]Smith, L.A.; Wang, W.-B.; Burnell-Curty, C.; Roskamp, E.J. *Synlett* ***1993***, 850; Wang, W.-B.; Roskamp, E.J. *J. Org. Chem.* ***1992***, *57*, 6101.

[1838]Wang, W.-B.; Roskamp, E.J. *J. Am. Chem. Soc.* ***1993***, *115*, 9417.

[1839]Ooi, T.; Tayama, E.; Yamada, M.; Maruoka, K. *Synlett.* ***1999***, 729.

[1840]Arai, K.; Shaw, C.; Nozawa, K.; Kawai, K.; Nakajima, S. *Tetrahedron Lett.* ***1987***, *28*, 441.

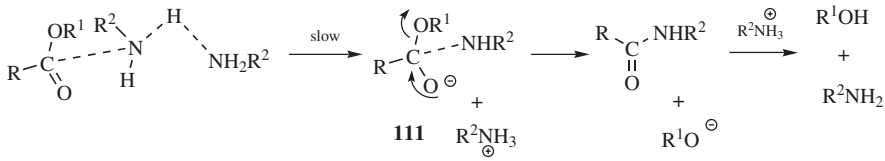
[1841]Youshko, M.I.; van Rantwijk, F.; Sheldon, R.A. *Tetrahedron Asymmetry* ***2001***, *12*, 3267.

[1842]Distaso, M.; Quaranta, E. *Tetrahedron* ***2004***, *60*, 1531; Curini, M.; Epifano, F.; Maltese, F.; Rosati, O. *Tetrahedron Lett.* ***2002***, *43*, 4895.

As in **16-72**, hydrazides and hydroxamic acids can be prepared from carboxylic esters, with hydrazine and hydroxylamine, respectively. Both hydrazine and hydroxylamine react more rapidly than ammonia or primary amines (the alpha effect, p. 495). Imidates $RC(=NH)OR'$ give amidines $RC(=NH)NH_2$. Lactones, when treated with ammonia or primary amines, give lactams. Lactams are also produced from γ- and δ-amino esters in an internal example of this reaction. Isopropenyl formate is a useful compound for the formylation of primary and secondary amines.[1843]

$$R_2NH + HCOOCMe{=}CH_2 \longrightarrow R_2NCHO + CH_2{=}CMeOH \longrightarrow MeCOMe$$

Although more studies have been devoted to the mechanism of the acylation of amines with carboxylic esters than with other reagents, the mechanistic details are not yet entirely clear.[1844] In its broad outlines, the mechanism appears to be essentially $B_{AC}2$.[1845] Under the normal basic conditions, the reaction is general base-catalyzed,[1846] indicating that a proton is being transferred in the rate-determining step and that two molecules of amine are involved.[1847]



Alternatively, another base, such as H_2O or OH^-, can substitute for the second molecule of amine. With some substrates and under some conditions, especially at low pH, the breakdown of **111** can become rate determining.[1848] The reaction also takes place under acidic conditions and is general acid catalyzed, so that

[1843]van Melick, J.E.W.; Wolters, E.T.M. *Synth. Commun.* ***1972***, *2*, 83.

[1844]For a discussion of the mechanism, see Satchell, D.P.N.; Satchell, R.S., in Patai, S. *The Chemistry of Carboxylic Acids and Esters*, Wiley, NY, ***1969***, pp. 410–431. For a computational study see Ilieva, S.; Galabov, B.; Musaev, D.G.; Morokuma, K.; Schaefer III, H.F. *J. Org. Chem.* ***2003***, *68*, 1496.

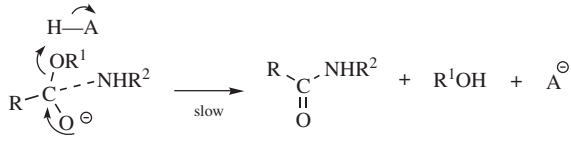
[1845]Bunnett, J.F.; Davis, G.T. *J. Am. Chem. Soc.* ***1960***, *82*, 665; Bruice, T.C.; Donzel, A.; Huffman, R.W.; Butler, A.R. *J. Am. Chem. Soc.* ***1967***, *89*, 2106.

[1846]Bunnett, J.F.; Davis, G.T. *J. Am. Chem. Soc.* ***1960***, *82*, 665, Jencks, W.P.; Carriuolo, J. *J. Am. Chem. Soc.* ***1960***, *82*, 675; Bruice, T.C.; Mayahi, M.F. *J. Am. Chem. Soc.* ***1960***, *82*, 3067.

[1847]Blackburn, G.M.; Jencks, W.P. *J. Am. Chem. Soc.* ***1968***, *90*, 2638; Bruice, T.C.; Felton, S.M. *J. Am. Chem. Soc.* ***1969***, *91*, 2799; Felton, S.M.; Bruice, T.C. *J. Am. Chem. Soc.* ***1969***, *91*, 6721; Nagy, O.B.; Reuliaux,V.; Bertrand, N.; Van Der Mensbrugghe, A.; Leseul, J.; Nagy, J.B. *Bull. Soc. Chim. Belg.* ***1985***, *94*, 1055.

[1848]Hansen, B. *Acta Chem. Scand.* ***1963***, *17*, 1307; Gresser, M.J.; Jencks, W.P. *J. Am. Chem. Soc.* ***1977***, *99*, 6963, 6970. See also, Yang, C.C.; Jencks, W.P. *J. Am. Chem. Soc.* ***1988***, *110*, 2972.

breakdown of **111** is rate determining and proceeds as follows:[1849]



111

HA may be $R^2NH_3^+$ or another acid. Intermediate **111** may or may not be further protonated on the nitrogen. Even under basic conditions, a proton donor may be necessary to assist leaving-group removal. Evidence for this is that the rate is lower with NR_2^- in liquid ammonia than with NHR_2 in water, apparently owing to the lack of acids to protonate the leaving oxygen.[1850]

In the special case of β-lactones, where small-angle strain is an important factor, alkyl–oxygen cleavage is observed ($B_{AL}2$ mechanism, as in the similar case of hydrolysis of β-lactones, **16-59**), and the product is not an amide but a β-amino acid (β-alanine).

β-Alanine

A similar result has been found for certain sterically hindered esters.[1851] This reaction is similar to **10-31**, with OCOR as the leaving group. Other lactones have been opened to ω-hydroxy amides with Dibal:$BnNH_2$.[1852]

OS **I**, 153, 179; **II**, 67, 85; **III**, 10, 96, 108, 404, 440, 516, 536, 751, 765; **IV**, 80, 357, 441, 486, 532, 566, 819; **V**, 168, 301, 645; **VI**, 203, 492, 620, 936; **VII**, 4, 30, 41, 411; **VIII**, 26, 204, 528. Also see, OS **I**, 5; **V**, 582; **VII**, 75.

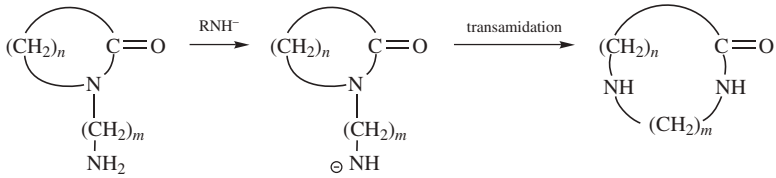
16-76 Acylation of Amines by Amides

Alkylamino-de-amination

This is an exchange reaction and is usually carried out with the salt of the amine.[1853] The leaving group is usually NH_2 rather than NHR or NR_2 and primary

[1849]Blackburn, G.M.; Jencks, W.P. *J. Am. Chem. Soc.* ***1968***, *90*, 2638.
[1850]Bunnett, J.F.; Davis, G.T. *J. Am. Chem. Soc.* ***1960***, *82*, 665.
[1851]Zaugg, H.E.; Helgren, P.F.; Schaefer, A.D. *J. Org. Chem.* ***1963***, *28*, 2617. See also, Weintraub, L.; Terrell, R. *J. Org. Chem.* ***1965***, *30*, 2470; Harada, R.; Kinoshita, Y. *Bull. Chem. Soc. Jpn.* ***1967***, *40*, 2706.
[1852]Huang, P.-Q.; Zheng, X.; Deng, X.-M. *Tetrahedron Lett.* ***2001***, *42*, 9039. See also, Taylor, S.K.; Ide, N.D.; Silver, M.E.; Stephan, M. *Synth. Commun.* ***2001***, *31*, 2391.
[1853]For a list of procedures, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1978–1982.

amines (in the form of their salts) are the most common reagents. Boron trifluoride can be added to complex with the leaving ammonia. Neutral amines also react in some cases to give the new amide.[1854] The reaction is often used to convert urea to substituted ureas: $NH_2CONH_2 + RNH_3^+ \rightarrow NH_2CONHR + NH_4^+$.[1855] An *N*-aryl group of a urea can be converted to a *N,N*-dialkyl group by heating the urea with the amine in an autoclave.[1856] *N*-R-Substituted amides are converted to *N*-R′-substituted amides by treatment with N_2O_4 to give an *N*-nitroso compound, followed by treatment of this with a primary amine $R'NH_2$.[1857] Lactams can be converted to ring-expanded lactams if



a side chain containing an amino group is present on the nitrogen. A strong base is used to convert the NH_2 to NH^-, which then acts as a nucleophile, expanding the ring by means of a transamidation.[1858] The discoverers call it the *Zip reaction*, by analogy with the action of zippers.[1859]

Lactams can be opened to ω-amino amides by reaction with amines at 10 kbar.[1860]

OS **I**, 302 (but see **V**, 589), 450, 453; **II**, 461; **III**, 151, 404; **IV**, 52, 361. See also, OS **VIII**, 573.

16-77 Acylation of Amines by Other Acid Derivatives

Acylamino-de-halogenation or dealkoxlaton

$$RCOCl + H_2NCOR' \longrightarrow RCONHCOR'$$

Acid derivatives that can be converted to amides include thiol acids RCOSH, thiol esters RCOSR,[1861] acyloxyboranes $RCOB(OR')_2$,[1862] silicic esters $(RCOO)_4Si$,

[1854]Murakami, Y.; Kondo, K.; Miki, K.; Akiyama, Y.; Watanabe, T.; Yokoyama, Y. *Tetrahedron Lett.* ***1997***, *38*, 3751.

[1855]For a discussion of the mechanism, see Chimishkyan, A.L.; Snagovskii, Yu.S.; Gulyaev, N.D.; Leonova, T.V.; Kusakin, M.S. *J. Org. Chem. USSR* ***1985***, *21*, 1955.

[1856]Yang, Y.; Lu, S. *Org. Prep. Proceed. Int.* ***1999***, *31*, 559.

[1857]Garcia, J.; Vilarrasa, J. *Tetrahedron Lett.* ***1982***, *23*, 1127.

[1858]Askitoğlu, E.; Guggisberg, A.; Hesse, M. *Helv. Chim. Acta* ***1985***, *68*, 750, and references cited therein. For a carbon analog, see Süsse, M.; Hájiček, J.; Hesse, M. *Helv. Chim. Acta* ***1985***, *68*, 1986.

[1859]For a review of this reaction, and of other ring expansions to form macrocyclic rings, see Stach, H.; Hesse, M. *Tetrahedron* ***1988***, *44*, 1573.

[1860]Kotsuki, H.; Iwasaki, M.; Nishizawa, H. *Tetrahedron Lett.* ***1992***, *33*, 4945.

[1861]For a discussion of the mechanism, see Douglas, K.T. *Acc. Chem. Res.* ***1986***, *19*, 186.

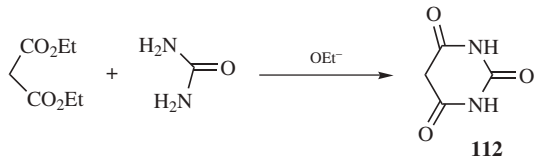
[1862]The best results are obtained when the acyloxyboranes are made from a carboxylic acid and catecholborane (p. 1123): Collum, D.B.; Chen, S.; Ganem, B. *J. Org. Chem.* ***1978***, *43*, 4393.

1,1,1-trihalo ketones $RCOCX_3$,[1863] α-keto nitriles, acyl azides, and non-enolizable ketones (see the Haller–Bauer reaction **12-34**). A polymer-bound acyl derivative was converted to an amide using tributylvinyl tin, trifluoroacetic acid, $AsPh_3$ and a palladium catalyst.[1864] The source of amine in this reaction was the polymer itself, which was an amide resin. *N*-Acylsulfonamides react with primary amines to the amide (AcNHR).[1865] Aniline derivatives are converted to acetamides with *N*-acyl oxymethylpyradazin-3-ones in dichloromethane.[1866] Carbonylation reactions can be used to prepare amides and related compounds. The reaction of a primary amine, an alkyl halide with CO_2, in the presence of Cs_2CO_3/Bu_4NI, gave the corresponding carbamate.[1867]

OS **III**, 394; **IV**, 6, 569; **V**, 160, 166; **VI**, 1004.

Imides can be prepared by the attack of amides or their salts on acyl halides, anhydrides, and carboxylic acids or esters.[1868] The best synthetic method for the preparation of acyclic imides is the reaction between an amide and an anhydride at 100°C catalyzed by H_2SO_4.[1869] When acyl chlorides are treated with amides in a 2:1 molar ratio at low temperatures in the presence of pyridine, the products are *N,N*-diacylamides, $(RCO)_3N$.[1870]

This reaction is often used to prepare urea derivatives, an important example being the preparation of barbituric acid, **112**.[1871]



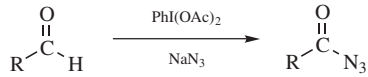
112

When the substrate is oxalyl chloride (ClCOCOCl) and the reagent an unsubstituted amide, an acyl isocyanate (RCONCO) is formed. The ''normal'' product (RCONH-COCOCl) does not form, or if it does, it rapidly loses CO and HCl.[1872]

OS **II**, 60, 79, 422; **III**, 763; **IV**, 245, 247, 496, 566, 638, 662, 744; **V**, 204, 944.

[1863]See, for example, Salim, J.R.; Nome, F.; Rezende, M.C. *Synth. Commun.* ***1989***, *19*, 1181; Druzian, J.; Zucco, C.; Rezende, M.C.; Nome, F. *J. Org. Chem.* ***1989***, *54*, 4767.
[1864]Deshpande, M.S. *Tetrahedron Lett.* ***1994***, *35*, 5613.
[1865]Coniglio, S.; Aramini, A.; Cesta, M.C.; Colagioia, S.; Curti, R.; D'Alessandro, F.; D'anniballe, G.; D'Elia, V.; Nano, G.; Orlando, V.; Allegretti, M. *Tetrahedron Lett.* ***2004***, *45*, 5375.
[1866]Kang, Y.-J.; Chung, H.-A.; Kim, J.-J.; Yoon, Y.-J. *Synthesis* ***2002***, 733.
[1867]Salvatore, R.N.; Shin, S.I.; Nagle, A.S.; Jung, K.W. *J. Org. Chem.* ***2001***, *66*, 1035.
[1868]For a review, see Challis, B.C.; Challis, J.A., in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 759–773.
[1869]Baburao, K.; Costello, A.M.; Petterson, R.C.; Sander, G.E. *J. Chem. Soc. C* ***1968***, 2779; Davidson, D.; Skovronek, H. *J. Am. Chem. Soc.* ***1958***, *80*, 376.
[1870]For example, see LaLonde, R.T.; Davis, C.B. *J. Org. Chem.* ***1970***, *35*, 771.
[1871]For a review of barbituric acid, see Bojarski, J.T.; Mokrosz, J.L.; Barto, H.J.; Paluchowska, M.H. *Adv. Heterocycl. Chem.* ***1985***, *38*, 229.
[1872]Speziale, A.J.; Smith, L.R.; Fedder, J.E. *J. Org. Chem.* ***1965***, *30*, 4306.

16-78 Acylation of Azides



The reaction of an aldehyde with sodium azide and Et_4 $I(OAc)_2$ or polymer-bound $PhI(OAc)_2$ leads to an acyl azide.[1873]

F. Attack by Halogen at an Acyl Carbon

16-79 Formation of Acyl Halides from Carboxylic Acids

Halo-de-hydroxylation

$$\text{RCOOH} + \text{Halogenating agent} \longrightarrow \text{RCOX}$$

Halogenating agent = $SOCl_2$, $SOBr_2$, PCl_3, $POCl_3$, PBr_3, and so on.

The same inorganic acid halides that convert alcohols to alkyl halides (**10-48**) also convert carboxylic acids to acyl halides.[1874] The reaction is the best and the most common method for the preparation of acyl chlorides. Bromides and iodides[1875] are also made in this manner, but much less often. Acyl bromides can be prepared with BBr_3 on alumina.[1876] Thionyl chloride[1877] is a good reagent, since the by-products are gases and the acyl halide is easily isolated, but PX_3 and PX_5 (X = Cl or Br) are also commonly used.[1878] Hydrogen halides do not give the reaction. A particularly mild procedure, similar to one mentioned in **10-48**, involves reaction of the acid with Ph_3P in CCl_4, whereupon acyl chlorides are produced without obtaining any acidic compound as a by-product.[1879] Acyl fluorides can be prepared by treatment of carboxylic acids with cyanuric fluoride.[1880] Acid salts

[1873]Marinescu, L.G.; Pedersen, C.M.; Bols, M. *Tetrahedron* ***2005***, *61*, 123. Aldehydes are converted to acyl azides by reaction with IN_3, see Marinescu, L.; Thinggaard, J.; Thomsen, I. B.; Bols, M. *J. Org. Chem.* ***2003***, *68*, 9453. See Hünig, S.; Schaller, R. *Angew. Chem. Int. Ed.* ***1982***, *21*, 36.

[1874]For a review, see Ansell, M.F., in Patai, S. *The Chemistry of Acyl Halides*, Wiley, NY, ***1972***, pp. 35–68.

[1875]Carboxylic acids and some of their derivatives react with diiodosilane SiH_2I_2 to give good yields of acyl iodides: Keinan, E.; Sahai, M. *J. Org. Chem.* ***1990***, *55*, 3922.

[1876]Bains, S.; Green, J.; Tan, L.C.; Pagni, R.M.; Kabalka, G.W. *Tetrahedron Lett.* ***1992***, *33*, 7475.

[1877]For a review of thionyl chloride ($SOCl_2$), see Pizey, J.S. *Synthetic Reagents*, Vol. 1, Wiley, NY, ***1974***, pp. 321–357. See Mohanazadeh, F.; Momeni, A.R. *Org. Prep. Proceed. Int.* ***1996***, *28*, 492 for the use of $SOCl_2$ on silica gel.

[1878]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1929–1930.

[1879]Lee, J.B. *J. Am. Chem. Soc.* ***1966***, *88*, 3440. For other methods of preparing acyl chlorides, see Venkataraman, K.; Wagle, D.R. *Tetrahedron Lett.* ***1979***, 3037; Devos, A.; Remion, J.; Frisque-Hesbain, A.; Colens, A.; Ghosez, L. *J. Chem. Soc., Chem. Commun.* ***1979***, 1180.

[1880]Olah, G.A.; Nojima, M.; Kerekes, I. *Synthesis* ***1973***, 487. For other methods of preparing acyl fluorides, see Mukaiyama, T.; Tanaka, T. *Chem. Lett.* ***1976***, 303; Ishikawa, N.; Sasaki, S. *Chem. Lett.* ***1976***, 1407.

are also sometimes used as substrates. Acyl halides are also used as reagents in an exchange reaction:

$$\text{RCOOH} + \text{R'COCl} \rightleftharpoons \text{RCOCl} + \text{R'COOH}$$

which probably involves an anhydride intermediate. This is an equilibrium reaction that must be driven to the desired side.

A mild, and often superior reagent is oxalyl chloride (**113**) and oxalyl bromide, since oxalic acid decomposes to CO and CO_2, and the equilibrium is thus driven to the side of the other acyl halide.[1881] These reagents are commonly the reagent of choice, particularly when sensitive functionality is present elsewhere in the molecule.

113

OS **I**, 12, 147, 394; **II**, 74, 156, 169, 569; **III**, 169, 490, 547, 555, 613, 623, 712, 714; **IV**, 34, 88, 154, 263, 339, 348, 554, 608, 616, 620, 715, 739, 900; **V**, 171, 258, 887; **VI**, 95, 190, 549, 715; **VII**, 467; **VIII**, 441, 486, 498.

16-80 Formation of Acyl Halides from Acid Derivatives

Halo-de-acyloxy-substitution

Halo-de-halogenation

$$(\text{RCO})_2\text{O} + \text{HF} \longrightarrow \text{RCOF}$$
$$\text{RCOCl} + \text{HF} \longrightarrow \text{RCOF}$$

These reactions are most important for the preparation of acyl fluorides.[1882] Acyl chlorides and anhydrides can be converted to acyl fluorides by treatment with polyhydrogen fluoride–pyridine solution[1883] or with liquid HF at $-10°C$.[1884] Formyl fluoride, which is a stable compound, was prepared by the latter procedure from the mixed anhydride of formic and acetic acids.[1885] Acyl fluorides can also be obtained by reaction of acyl chlorides with KF in acetic acid[1886] or with diethylaminosulfur trifluoride (DAST).[1887] Carboxylic esters and anhydrides can be

[1881]Adams, R.; Ulich, L.H., *J. Am. Chem. Soc.* ***1920***, *42*, 599; Wood, T.R.; Jackson, F.L.; Baldwin, A.R.; Longenecker, H.E. *J. Am. Chem. Soc.* ***1944***, *66*, 287. For a typical example see Zhang, A.; Nie, J. *J. Agric. Food Chem.* ***2005***, *53*, 2451.

[1882]For lists of reagents converting acid derivatives to acyl halides, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1950–1951, 1955, 1968.

[1883]Olah, G.A.; Welch, J.; Vankar, Y.D.; Nojima, M.; Kerekes, I.; Olah, J.A. *J. Org. Chem.* ***1979***, *44*, 3872. See also, Yin, J.; Zarkowsky, D.S.; Thomas, D.W.; Zhao, M.W.; Huffman, M.A. *Org. Lett.* ***2004***, *6*, 1465.

[1884]Olah, G.A.; Kuhn, S.J. *J. Org. Chem.* ***1961***, *26*, 237.

[1885]Olah, G.A.; Kuhn, S.J. *J. Am. Chem. Soc.* ***1960***, *82*, 2380.

[1886]Emsley, J.; Gold, V.; Hibbert, F.; Szeto, W.T.A. *J. Chem. Soc. Perkin Trans. 2* ***1988***, 923.

[1887]Markovski, L.N.; Pashinnik, V.E. *Synthesis* ***1975***, 801.

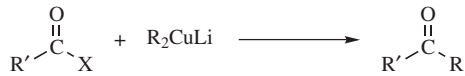
converted to acyl halides other than fluorides by the inorganic acid halides mentioned in **16-79**, as well as with Ph_3PX_2 (X = Cl or Br),[1888] but this is seldom done. Halide exchange can be carried out in a similar manner. When halide exchange is done, it is always acyl bromides and iodides that are made from chlorides, since chlorides are by far the most readily available.[1889]

OS **II**, 528; **III**, 422; **V**, 66, 1103; **IX**, 13. See also, OS **IV**, 307.

G. Attack by Carbon at an Acyl Carbon[1890]

16-81 The Conversion of Acyl Halides to Ketones With Organometallic Compounds[1891]

Alkyl-de-halogenation



Acyl halides react cleanly and under mild conditions with lithium dialkylcopper reagents (see **10-58**)[1892] to give high yields of ketones.[1893] The R′ group may be primary, secondary, or tertiary alkyl or aryl and may contain iodo, keto, ester, nitro, or cyano groups. The R groups that have been used successfully are methyl, primary alkyl, and vinylic. Secondary and tertiary alkyl groups can be introduced by the use of PhS(R)CuLi (p. 602) instead of R_2CuLi,[1894] or by the use of either the mixed homocuprate $(R'SO_2CH_2CuR)^- Li^+$,[1895] or a magnesium dialkylcopper reagent "RMeCuMgX."[1896] Secondary alkyl groups can also be introduced with the copper–zinc reagents RCu(CN)ZnI.[1897] The R group may be alkynyl if a

[1888]Burton, D.J.; Koppes, W.M. *J. Chem. Soc., Chem. Commun.* ***1973***, 425; *J. Org. Chem.* ***1975***, *40*, 3026; Anderson Jr., A.G.; Kono, D.H. *Tetrahedron Lett.* ***1973***, 5121.

[1889]For methods of converting acyl chlorides to bromides or iodides, see Schmidt, A.H.; Russ, M.; Grosse, D. *Synthesis* ***1981***, 216; Hoffmann, H.M.R.; Haase, K. *Synthesis* ***1981***, 715.

[1890]For a discussion of many of the reactions in this section, see House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 691–694, 734–765.

[1891]For a review, see Cais, M.; Mandelbaum, A., in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***, Vol. 1, pp. 303–330.

[1892]See Posner, G.H. *An Introduction to Synthesis Using Organocopper Reagents*,Wiley, NY, ***1980***, pp. 81–85. Ryu, I.; Ikebe, M.; Sonoda, N.; Yamamoto, S.-y.; Yamamura, G.-h.; Komatsu, M. *Tetrahedron Lett.* ***2002***, *43*, 1257.

[1893]Vig, O.P.; Sharma, S.D.; Kapur, J.C. *J. Indian Chem. Soc.* ***1969***, *46*, 167; Jukes, A.E.; Dua, S.S.; Gilman, H. *J. Organomet. Chem.* ***1970***, *21*, 241; Posner, G.H.; Whitten, C.E.; McFarland, P.E. *J. Am. Chem. Soc.* ***1972***, *94*, 5106; Luong-Thi, N.; Rivière, H. *J. Organomet. Chem.* ***1974***, *77*, C52.

[1894]Posner, G.H.; Whitten, C.E.; Sterling, H.J. *J. Am. Chem. Soc.* ***1973***, *95*, 7788; Posner, G.H.; Whitten, C.E. *Tetrahedron Lett.* ***1973***, 1815; Bennett, G.B.; Nadelson, J.; Alden, L.; Jani, A. *Org. Prep. Proced. Int.* ***1976***, *8*, 13.

[1895]Johnson, C.R.; Dhanoa, D.S. *J. Org. Chem.* ***1987***, *52*, 1885.

[1896]Bergbreiter, D.E.; Killough, J.M. *J. Org. Chem.* ***1976***, *41*, 2750.

[1897]Knochel, P.; Yeh, M.C.P.; Berk, S.C.; Talbert, J. *J. Org. Chem.* ***1988***, *53*, 2390.

cuprous acetylide $R^2C{\equiv}CCu$ is the reagent.[1898] Organocopper reagents generated *in situ* from highly reactive copper, and containing such functional groups as cyano, chloro, and ester, react with acyl halides to give ketones.[1899]

Many other organometallic reagents[1900] give good yields of ketones when treated with acyl halides because, as with R_2CuLi, R_2Cd, these compounds do not generally react with the ketone product. A particularly useful class of organometallic reagent are organocadmium reagents R_2Cd, prepared from Grignard reagents (**12-22**). In this case, R may be aryl or primary alkyl. In general, secondary and tertiary alkylcadmium reagents are not stable enough to be useful in this reaction.[1901] An ester group may be present in either $R'COX$ or R_2Cd. Direct treatment of the acid chloride with an alkyl halide and cadmium metal leads to the ketone in some cases.[1902] Organozinc compounds behave similarly to dialkylcadmium reagents, but are used less often.[1903] Organotin reagents R_4Sn react with acyl halides to give high yields of ketones, if a Pd complex is present.[1904] Organolead reagents R_4Pb behave similarly.[1905] Allylic halides and indium metal react with acyl chlorides to give the ketone.[1906] Various other groups, for example, nitrile, ester, and aldehyde can be present in the acyl halide without interference. Other reagents include organomanganese compounds[1907] (R can be primary, secondary, or tertiary alkyl, vinylic, alkynyl, or aryl), organozinc,[1908] and organothallium compounds (R can be primary alkyl or aryl).[1909] The reaction of an α-halo-ketone and an acyl chloride with SmI_2 leads to a β-diketone.[1910] Initial reaction of an acyl chloride with palladium(0), followed by reaction with potassium acetate and then a trialkylborane gave a ketone.[1911] Arylboronic acids and acid chloride give the ketone in

[1898]Castro, C.E.; Havlin, R.; Honwad, V.K.; Malte, A.; Mojé, S. *J. Am. Chem. Soc.* ***1969***, *91*, 6464. For methods of preparing acetylenic ketones, see Verkruijsse, H.D.; Heus-Kloos, Y.A.; Brandsma, L. *J. Organomet. Chem.* ***1988***, *338*, 289.

[1899]Wehmeyer, R.M.; Rieke, R.D. *Tetrahedron Lett.* ***1988***, *29*, 4513; Stack, D.E.; Dawson, B.T.; Rieke, R.D. *J. Am. Chem. Soc.* ***1992***, *114*, 5110.

[1900]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1389–1400.

[1901]Cason, J.; Fessenden, R. *J. Org. Chem.* ***1960***, *25*, 477.

[1902]Baruah, B.; Boruah. A.; Prajapati, D.; Sandhu, J.S. *Tetrahedron Lett.* ***1996***, *37*, 9087.

[1903]For examples, see Grey, R.A. *J. Org. Chem.* ***1984***, *49*, 2288; Tamaru, Y.; Ochiai, H.; Nakamura, T.; Yoshida, Z. *Org. Synth. 67*, 98.

[1904]Labadie, J.W.; Stille, J.K. *J. Am. Chem. Soc.* ***1983***, *105*, 669, 6129; Labadie, J.W.; Tueting, D.; Stille, J.K. *J. Org. Chem.* ***1983***, *48*, 4634. For a Me_3SiSnR_3 reagent, see Geng, F.; Maleczka, Jr., R.E. *Tetrahedron Lett.* ***1999***, *40*, 3113. For an allylic SnR_3 reagent, see Inoue, K.; Shimizu, Y.; Shibata, I.; Baba, A. *Synlett* ***2001***, 1659.

[1905]Yamada, J.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* ***1987***, 1302.

[1906]Yadav, J.S.; Srinivas, D.; Reddy, G.S.; Bindu, K.H. *Tetrahedron Lett.* ***1997***, *38*, 8745. Also see, Bryan, V.J.; Chan, T.-H. *Tetrahedron Lett.* ***1997***, *38*, 6493 for a similar reaction with an acyl imidazole.

[1907]Kim, S.-H.; Rieke, R.D. *J. Org. Chem.* ***1998***, *63*, 6766; Cahiez, G.; Martin, A.; Delacroix, T. *Tetrahedron Lett.* ***1999***, *40*, 6407.

[1908]Hanson, M.V.; Brown, J.D.; Rieke, R.D.; Niu, Q.J. *Tetrahedron Lett.* ***1994***, *35*, 7205; Filon, H.; Gosmini, C.; Périchon, J. *Tetrahedron* ***2003***, *59*, 8199.

[1909]Markó, I.E.; Southern, J.M. *J. Org. Chem.* ***1990***, *55*, 3368.

[1910]Ying, T.; Bao, W.; Zhang, Y.; Xu, W. *Tetrahedron Lett.* ***1996***, *37*, 3885.

[1911]Kabalka, G.W.; Malladi, R.R.; Tejedor, D.; Kelley, S. *Tetrahedron Lett.* ***2000***, *41*, 999.

the presence of a palladium catalyst.[1912] Similar reaction of acid chlorides, $NaBPh_4$, KF, and a palladium catalyst gave the aryl ketone.[1913] Antimony alkynes such as $Ph_2Sb{-}C{\equiv}C{-}Ph$ react with acid chloride in the presence of a palladium catalyst to give the conjugated alkynyl ketone.[1914] Such conjugated ketones can also be prepared from an acyl halide, a terminal alkyne and a CuI catalyst[1915] a palladium catalyst,[1916] or with indium metal.[1917] Terminal alkynes react with chloroformates and a palladium catalyst to give the corresponding propargyl ester.[1918] Similar reaction of an alkyne with an acid chloride and a palladium–copper[1919] or CuI catalyst,[1920] both with microwave irradiation, gave the alkynyl ketones.

When the organometallic compound is a Grignard reagent,[1921] ketones are generally not obtained because the initially formed ketone reacts with a second molecule of RMgX to give the salt of a tertiary alcohol (**16-82**). Ketones *have* been prepared in this manner by the use of low temperatures, inverse addition (i.e., addition of the Grignard reagent to the acyl halide rather than the other way), excess acyl halide, and so on., but the yields are usually low, though high yields have been reported in THF at −78°C.[1922] Pretreatment with a trialkylphosphine and then the Grignard reagent can lead to the ketone.[1923] Using CuBr[1924] or a nickel catalyst[1925] with the Grignard reagent can lead to the ketone. Some ketones are unreactive toward Grignard reagents for steric or other reasons; these can be prepared in this way.[1926] Other methods involve running the reaction in the presence of Me_3SiCl[1927] (which reacts with the initial adduct in the tetrahedral mechanism, p. 1254), and the use of a combined Grignard-lithium diethylamide reagent.[1928] Also, certain metallic halides, notably ferric and cuprous halides, are catalysts

[1912]Urawa, Y.; Ogura, K. *Tetrahedron Lett.* ***2003***, *44*, 271.
[1913]Wang, J.-X.; Wei, B.; Hu, Y.; Liu, Z.; Yang, Y. *Synth. Commun.* ***2001***, *31*, 3885.
[1914]Kakusawa, N.; Yamaguchi, K.; Kurita, J.; Tsuchiya, T. *Tetrahedron Lett.* ***2000***, *41*, 4143.
[1915]Chowdhury, C.; Kundu, N.G. *Tetrahedron* ***1999***, *55*, 7011; Wang, J.-X.; Wei, B.; Hu, Y.; Liua, Z.; Kang, L. *J. Chem. Res. (S)* ***2001***, 146.
[1916]Karpov, A.S.; Müller, T.J.J. *Org. Lett.* ***2003***, *5*, 3451.
[1917]Augé, J.; Lubin-Germain, N.; Seghrouchni, L. *Tetrahedron Lett.* ***2003***, *44*, 819.
[1918]Böttcher, A.; Becker, H.; Brunner, M.; Preiss, T.; Henkelmann, J..; De Bakker, C.; Gleiter, R. *J. Chem. Soc., Perkin Trans.1* ***1999***, 3555.
[1919]Wang, J.-x.; Wei, B.; Huang, D.; Hu, Y.; Bai, L. *Synth. Commun.* ***2001***, *31*, 3337.
[1920]Wang, J.-X.; Wei, B.; Hu, Y.; Liu, Z.; Fu, Y. *Synth. Commun.* ***2001***, *31*, 3527.
[1921]For a review, see Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood, NJ, ***1954***, pp. 712–724.
[1922]Sato, M.; Inoue, M.; Oguro, K.; Sato, M. *Tetrahedron Lett.* ***1979***, 4303; Eberle, M.K.; Kahle, G.G. *Tetrahedron Lett.* ***1980***, *21*, 2303; Föhlisch, B.; Flogaus, R. *Synthesis* ***1984***, 734.
[1923]Maeda, H.; Okamoto, J.; Ohmori, H. *Tetrahedron Lett.* ***1996***, *37*, 5381.
[1924]Babudri, F.; Fiandanese, V.; Marchese, G.; Punzi, A. *Tetrahedron* ***1996***, *52*, 13513; *Tetrahedron Lett.* ***1995***, *36*, 7305.
[1925]Malanga, C.; Aronica, L.A.; Lardicci, L. *Tetrahedron Lett.* ***1995***, *36*, 9185. For the preparation of an amide from a *N,N*-dialkylcarbamyl chloride (R_2NCOCl) and a Grignard reagent, with a nickel catalyst, see Lemoucheux, L.; Rouden, J.; Lasne, M.-C. *Tetrahedron Lett.* ***2000***, *41*, 9997.
[1926]For example, see Lion, C.; Dubois, J.E.; Bonzougou, Y. *J. Chem. Res. (S)* ***1978***, 46; Dubois, J.E.; Lion, C.; Arouisse, A. *Bull. Soc. Chim. Belg.* ***1984***, *93*, 1083.
[1927]Cooke, Jr., M.P. *J. Org. Chem.* ***1986***, *51*, 951.
[1928]Fehr, C.; Galindo, J.; Perret, R. *Helv. Chim. Acta* ***1987***, *70*, 1745.

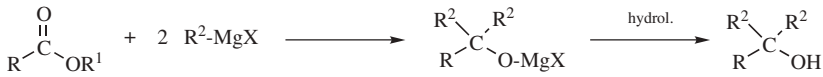
that improve the yields of ketone at the expense of tertiary alcohol.[1929] For these catalysis, both free radical and ionic mechanisms have been proposed.[1930]

Grignard reagents react with ethyl chloroformate to give carboxylic esters $EtOCOCl + RMgX \rightarrow EtOCOR$. Acyl halides can also be converted to ketones by treatment with $Na_2Fe(CO)_4$ followed by R′X (**10-76**).

OS **II**, 198; **III**, 601; **IV**, 708; **VI**, 248, 991; **VII**, 226, 334; **VIII**, 268, 274, 371, 441, 486.

16-82 The Conversion of Anhydrides, Carboxylic Esters, or Amides to Ketones With Organometallic Compounds[1931]

Dialkyl,hydroxy-de-alkoxy,oxo-tersubstitution; Alkyl-de-acyloxy- or de-amido substitution



When carboxylic esters are treated with Grignard reagents, addition to the carbonyl (**16-24**) generates a ketone. Under the reaction conditions, the initially formed ketones usually undergoes acyl substitution of R^2 for OR′ (**16-81**), so that tertiary alcohols are formed in which two R groups are the same. Isolation of the ketone as the major product is possible in some cases, particularly when the reaction is done at low temperature[1932] and when there is steric hindrance to the carbonyl in the first-formed ketone. Esters, RCO_2Me, react with $Zn(BH_4)_2$/EtMgBr to give an alcohol, RCH(OH)Et.[1933] Formates give secondary alcohols and carbonates give tertiary alcohols in which all three R groups are the same: $(EtO)_2C{=}O + RMgX \rightarrow R_3COMgX$. Acyl halides and anhydrides behave similarly, though these substrates are employed less often.[1934] Many side reactions are possible, especially when the acid derivative or the Grignard reagent is branched: enolizations, reductions (not for esters, but for halides), condensations, and cleavages, but the most important is simple substitution (**16-81**), which in some cases can be made to predominate. When 1,4-dimagnesium compounds are used, carboxylic esters are converted to cyclopentanols.[1935] 1,5-Dimagnesium

[1929]For examples, see Cason, J.; Kraus, K.W. *J. Org. Chem.* ***1961***, *26*, 1768, 1772; MacPhee, J.A.; Dubois, J.E. *Tetrahedron Lett.* ***1972***, 467; Cardellicchio, C.; Fiandanese, V.; Marchese, G.; Ronzini, L. *Tetrahedron Lett.* ***1987***, *28*, 2053; Fujisawa, T.; Sato, T. *Org. Synth. 66*, 116; Babudri, F.; D'Ettole, A.; Fiandanese, V.; Marchese, G.; Naso, F. *J. Organomet. Chem.* ***1991***, *405*, 53.

[1930]For example, see Dubois, J.E.; Boussu, M. *Tetrahedron Lett.* ***1970***, 2523; *Tetrahedron* ***1973***, *29*, 3943; MacPhee, J.A.; Boussu, M.; Dubois, J.E. *J. Chem. Soc. Perkin Trans. 2* ***1974***, 1525.

[1931]For a review, see Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood, NJ, ***1954***, pp. 561–562, 846–908.

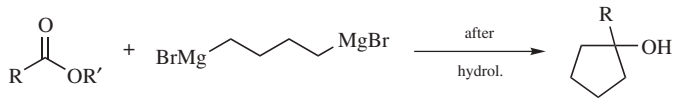
[1932]Deskus, J.; Fan, D.; Smith, M.B. *Synth. Commun.* ***1998***, *28*, 1649.

[1933]Hallouis, S.; Saluzzo, C.; Amouroux, R. *Synth. Commun.* ***2000***, *30*, 313.

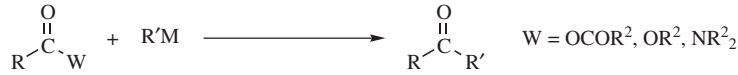
[1934]For a review of these reactions, see Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood Cliffs, NJ, ***1954***, pp. 549–766, 846–869.

[1935]Canonne, P.; Bernatchez, M. *J. Org. Chem.* ***1986***, *51*, 2147; ***1987***, *52*, 4025.

compounds give cyclohexanols, but in lower yields.[1936]



As is the case with acyl halides (**16-81**), anhydrides and carboxylic esters give tertiary alcohols (**16-82**) when treated with Grignard reagents. Low temperatures,[1937] the solvent HMPA,[1938] and inverse addition have been used to increase the yields of ketone.[1939] Amides give better yields of ketone at room temperature, but still not very high.[1940] Anhydrides can react with arylmagnesium halides at low temperature, and in the presence of (−)-sparteine, to give a keto acid with good enantioselectivity.[1941] Organocadmium reagents are less successful with these substrates than with acyl halides (**16-81**). Esters of formic acid, dialkylformamides, and lithium or sodium formate[1942] give good yields of aldehydes, when treated with Grignard reagents.



Alkyllithium compounds have been used to give ketones from carboxylic esters. The reaction must be carried out in a high-boiling solvent, such as toluene, since reaction at lower temperatures gives tertiary alcohols.[1943] Alkyllithium reagents also give good yields of carbonyl compounds with *N*,*N*-disubstituted amides.[1944] Dialkylformamides give aldehydes and other disubstituted amides give ketones and other acid derivatives have been used.[1945]

[1936]Kresge, A.J.; Weeks, D.P. *J. Am. Chem. Soc.* ***1984***, *106*, 7140. See also, Fife, T.H. *J. Am. Chem. Soc.* ***1967***, *89*, 3228; Craze, G.; Kirby, A.J.; Osborne, R. *J. Chem. Soc. Perkin Trans. 2* ***1978***, 357; Amyes, T.L.; Jencks, W.P. *J. Am. Chem. Soc.* ***1989***, *111*, 7888, 7900.

[1937]See, for example, Newman, M.S.; Smith, A.S. *J. Org. Chem.* ***1948***, *13*, 592; Edwards, Jr., W.R.; Kammann Jr., K.P. *J. Org. Chem.* ***1964***, *29*, 913; Araki, M.; Sakat, S.; Takei, H.; Mukaiyama, T. *Chem. Lett.* ***1974***, 687.

[1938]Huet, F.; Pellet, M.; Conia, J.M. *Tetrahedron Lett.* ***1976***, 3579.

[1939]For a list of preparations of ketones by the reaction of organometallic compounds with carboxylic esters, salts, anhydyrides, or amides, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1386–1389, 1400–1419.

[1940]For an improved procedure with amides, see Olah, G.S.; Prakash, G.K.S.; Arvanaghi, M. *Synthesis* ***1984***, 228. See Martín, R.; Romea, P.; Tey, C.; Urpí, F.; Vilarrasa, J. *Synlett* ***1997***, 1414 for reaction with an amide derived from morpholine and Grignard reagents, which gives the ketone in good yield. See Kashima, C.; Kita, I.; Takahashi, K.; Hosomi, A. *J. Heterocyclic Chem.* ***1995***, *32*, 25 for a related reaction.

[1941]Shintani, R.; Fu, G.C. *Angew. Chem. Int. Ed.* ***2002***, *41*, 1057.

[1942]Bogavac, M.; Arsenijević, L.; Pavlov, S.; Arsenijević, V. *Tetrahedron Lett.* ***1984***, *25*, 1843.

[1943]Petrov, A.D.; Kaplan, E.P.; Tsir, Ya. *J. Gen. Chem. USSR* ***1962***, *32*, 691.

[1944]Evans, E.A. *J. Chem. Soc.* ***1956***, 4691. For the synthesis of a silyl ketone from a silyllithium reagent, see Clark, C.T.; Milgram, B.C.; Scheidt, K.A. *Org. Lett.* ***2004***, *6*, 3977. For a review, see Wakefield, B.J. *Organolithium Methods*, Academic Press, NY, ***1988***, pp. 82–88.

[1945]Mueller-Westerhoff, U.T.; Zhou, M. *Synlett* ***1994***, 975.

Ketones can also be obtained by treatment of the lithium salt of a carboxylic acid with an alkyllithium reagent (**16-28**). For an indirect way to convert carboxylic esters to ketones, see **16-82**. A similar reaction with hindered aryl carboxylic acids has been reported.[1946] Treatment of a β-amido acid with two equivalents of *n*-butyllithium, followed by reaction with an acid chloride leads to a β-keto amide.[1947] Carboxylic acids can be treated with 2-chloro-4,6-dimethoxy[1,3,5]-triazine and the RMgX/CuI to give ketones.[1948]

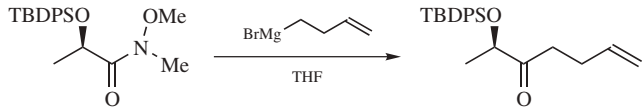
Disubstituted formamides can give addition of 2 equivalents of Grignard reagent. The products of this reaction (called *Bouveault reaction*) are an aldehyde and a tertiary amine.[1949] The use of an amide other than a formamide

can give a ketone instead of an aldehyde, but yields are generally low. The addition of 2 equivalents of phenyllithium to a carbamate gave good yields of the ketone, however.[1950] When butyllithium reacted with an α-carbamoyl secondary amide [$RCH(NHCO_2R')C(=O)NR_2^2$] at −78°C, the amide reacted preferentially to give the α-carbamoyl ketone.[1951] The reaction of *N*-(3-bromopropyl) lactams with *tert*-butyllithium gave cyclization to the bicyclic amino alcohol, and subsequent reduction with $LiAlH_4$ (**19-64**) gave the bicyclic amine.[1952] Ketones can also be prepared by treatment of thioamides with organolithium compounds (alkyl or aryl).[1953] Cerium reagents, such as $MeCeCl_2$, also add two R groups to an amide.[1954] More commonly, an organolithium reagent is treated with $CeCl_3$ to generate the organocerium reagent *in situ*.[1955] It has proven possible to add two different R groups by sequential addition of two Grignard reagents.[1956] Diketones have also been produced by using the bis(imidazole) derivative of oxalic acid.[1957] Alternatively, if R′ contains an α hydrogen, the product may be an enamine, and enamines have been synthesized in goods yields by this method.[1958] When an amide having a *gem*-dibromocyclopropyl unit elsewhere in the molecule was treated

[1946]Zhang, P.; Terefenko, E.A.; Slavin, J. *Tetrahedron Lett.* ***2001***, *42*, 2097.
[1947]Chen, Y.; Sieburth, S.Mc.N. *Synthesis* ***2002***, 2191.
[1948]DeLuca, L.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* ***2001***, *3*, 1519.
[1949]For a review, see Spialtr, L.; Pappalardo, J.A. *The Acyclic Aliphatic Tertiary Amines*, Macmillan, NY, ***1965***, pp. 59–63.
[1950]Prakash, G.K.S.; York, C.; Liao, Q.; Kotian, K.; Olah, G.A. *Heterocycles* ***1995***, *40*, 79.
[1951]Sengupta, S.; Mondal, S.; Das, D. *Tetrahedron Lett.* ***1999***, *40*, 4107.
[1952]Jones, K.; Storey, J.M.D. *J. Chem. Soc., Perkin Trans. 1* ***2000***, 769.
[1953]Tominaga, Y.; Kohra, S.; Hosomi, A. *Tetrahedron Lett.* ***1987***, *28*, 1529.
[1954]Calderwood, D.J.; Davies, R.V.; Rafferty, P.; Twigger, H.L.; Whelan, H.M. *Tetrahedron Lett.* ***1997***, *38*, 1241.
[1955]Ahn, Y.; Cohen, T. *Tetrahedron Lett.* ***1994***, *35*, 203.
[1956]Comins, D.L.; Dernell, W. *Tetrahedron Lett.* ***1981***, *22*, 1085.
[1957]Mitchell, R.H.; Iyer, V.S. *Tetrahedron Lett.* ***1993***, *34*, 3683. Also see, Sibi, M.P.; Sharma, R.; Paulson, K.L. *Tetrahedron Lett.* ***1992***, *33*, 1941.
[1958]Hansson, C.; Wickberg, B. *J. Org. Chem.* ***1973***, *38*, 3074.

with methyllithium, Li—Br exchange was accompanied by intramolecular acyl addition to the amide carbonyl, giving a bicyclic amino alcohol.[1959]

N-Methoxy-*N*-methyl amides, such as, **114**, are referred to as a **Weinreb amide**.[1960] When a Weinreb amide reacts with a Grignard reagent or an organolithium reagent,[1961] the product is the ketone. The reaction of **56** with 3-butenylmagnesium bromide to give ketone **115** is a typical example.[1962] Aryloxy carbamates with a Weinreb amide unit, $ArO_2C—NMe(OMe)$, react with RMgBr and then R′Li to give an unsymmetrical ketone, RC(=O)R′.[1963] Intramolecular displacement of a Weinreb amide by an organolithium reagent generated *in situ* from an iodide precursor leads to cyclic ketones.[1964] Reaction with vinylmagnesium bromide led to a β-*N*-methoxy-*N*-methylamino ketone, presumably by initial formation of the conjugated ketone followed by Michael addition (**15-24**) of the liberated amine.[1965] An interesting extension of this acyl substitution reaction coupled vinylmagnesium bromide with a Weinreb amide to give a conjugated ketone, which reacted with a secondary amine in a second step (see **15-31**) to give a β-amino ketone.[1966]



114 **115**

By the use of the compound *N*-methoxy-*N*,*N*′,*N*′-trimethylurea, it is possible to add two R groups as RLi, the same or different, to a CO group.[1967]

N,*N*-Disubstituted amides can be converted to alkynyl ketones by treatment with alkynylboranes: $RCONR_2^2 + (R'C{\equiv}C)_3B \rightarrow RCOC{\equiv}CR'$.[1968] Lactams react with triallylborane to give cyclic 2,2-diallyl amines after treatment with methanol, and then aqueous hydroxide.[1969] Triallylborane reacts with the carbonyl group of lactams, and after treatment with methanol and then aqueous NaOH gives the

[1959]Baird, M.S.; Huber, F.A.M.; Tverezovsky, V.V.; Bolesov, I.G. *Tetrahedron* ***2001***, *57*, 1593.
[1960]Nahm, S.; Weinreb, S.M. *Tetrahedron Lett.* ***1981***, *22*, 3815.
[1961]See Tallier, C.; Bellosta, V.; Meyer, C.; Cossy, J. *Org. Lett.* ***2004***, *6*, 2145.
[1962]Xie, W.; Zou, B.; Pei, D.; Ma, D. *Org. Lett.* ***2005***, *7*, 2775. For other exmaples see Andrés, J.M.; Pedrosa, R. Pérez-Encabo, A. *Tetrahedron* ***2000***, *56*, 1217.
[1963]Lee, N.R.; Lee, J.I. *Synth. Commun.* ***1999***, *29*, 1249.
[1964]Ruiz, J.; Sotomayor, N.; Lete, E. *Org. Lett.* ***2003***, *5*, 1115.
[1965]Gomtsyan, A. *Org. Lett.* ***2000***, *2*, 11. For a reaction with methyl esters with an excess of vinylmagnesium halide and a copper catalyst to give a 3-butenyl ketone by a similar acyl substitution–Michael addition route, see Hansford, K.A.; Dettwiler, J.E.; Lubell, W.D. *Org. Lett.* ***2003***, *5*, 4887.
[1966]Gomtsyan, A.; Koenig, R.J.; Lee, C.-H. *J. Org. Chem.* ***2001***, *66*, 3613.
[1967]Hlasta, D.J.; Court, J.J. *Tetrahedron Lett.* ***1989***, *30*, 1773. See also, Nahm, S.; Weinreb, S.M. *Tetrahedron Lett.* ***1981***, *22*, 3815.
[1968]Yamaguchi, M.; Waseda, T.; Hirao, I. *Chem. Lett.* ***1983***, 35.
[1969]Bubnov, Y.N.; Pastukhov, F.V.; Yampolsky, I.V.; Ignatenko, A.V. *Eur. J. Org. Chem.* ***2000***, 1503; Li, Z.; Zhang, Y. *Tetrahedron Lett.* ***2001***, *42*, 8507.

gem-diallyl amine: 2-pyrrolidinone → 2,2-diallylpyrrolidine.[1970] *N*,*N*-Disubstituted carbamates ($X = OR^2$) and carbamoyl chlorides ($X = Cl$) react with 2 equivalents of an alkyl- or aryllithium or Grignard reagent to give symmetrical ketones, in which both R groups are derived from the organometallic compound: $R'_2NCOX + 2\,RMgX \rightarrow R_2CO$.[1971] *N*,*N*-Disubstituted amides give ketones in high yields when treated with alkyllanthanum triflates $RLa(OTf)_2$.[1972]

Other organometallic reagents give acyl substitution. Sodium naphthalenide reacts with esters to give naphthyl ketones.[1973] Trimethylaluminum, which exhaustively methylates ketones (**16-24**), also exhaustively methylates carboxylic acids to give *tert*-butyl compounds[1974] (see also, **10-63**). Trimethylaluminum reacts with esters to form ketones, in the presence of *N*,*N*′-dimethylethyelnediamine.[1975] Thioesters (RCOSR′) react with arylboronic acids, in the presence of a palladium catalyst, to give the corresponding ketone,[1976] and esters react similarly with arylboronic acids (a palladium catalyst)[1977] or arylboronates (a ruthenium catalyst).[1978] Trialkylboranes have been similarly used to convert thioesters to ketones.[1979] Thioesters give good yields of ketones when treated with lithium dialkylcopper reagents R''_2CuLi ($R'' =$ primary or secondary alkyl or aryl).[1980] Organozinc reagents also convert thioesters to ketones.[1981] Arylboronic acids also react with dialkyl anhydrides, with a rhodium catalyst[1982] or a palladium catalyst,[1983] to give the ketone. Aryl iodides react with acetic anhydride, with a palladium catalyst, to give the aryl methyl ketone.[1984] Diaryl- or dialkylzinc reagents react with anhydrides and a palladium catalyst[1985] or a nickel catalyst[1986] to give the ketone. Note that in the presence of a SmI_2 catalyst and 2 equivalents of allyl bromide, lactones were converted to the diallyl diol.[1987] *N*-(3-Iodopropyl)succinimide derivatives react with SmI_2 and an iron catalyst to give bicyclic pyrrolizidinone derivatives

[1970]Bubnov, Yu.N.; Klimkina, E.V.; Zhun', I.V.; Pastukhov, F.V.; Yampolsky, I.V. *Pure Appl. Chem.* ***2000***, *72*, 1641.
[1971]Michael, U.; Hörnfeldt, A. *Tetrahedron Lett.* ***1970***, 5219; Scilly, N.F. *Synthesis* ***1973***, 160.
[1972]Collins, S.; Hong, Y. *Tetrahedron Lett.* ***1987***, *28*, 4391.
[1973]Periasamy, M.; Reddy, M.R.; Bharathi, P. *Synth. Commun.* ***1999***, *29*, 677.
[1974]Meisters, A.; Mole, T. *Aust. J. Chem.* ***1974***, *27*, 1665.
[1975]Chung, E.-A.; Cho, C.-W.; Ahn, K.H. *J. Org. Chem.* ***1998***, *63*, 7590.
[1976]Liebeskind, L.S.; Srogl, J. *J. Am. Chem. Soc.* ***2000***, *122*, 11260; Wittenberg, R.; Srogi, J.; Egi, M.; Liebeskind, L.S. *Org. Lett.* ***2003***, *5*, 3033.
[1977]Tatanidani, H.; Kakiuchi, F.; Chatani, N. *Org. Lett.* ***2004***, *6*, 3597.
[1978]Tatanidani, H.; Yokota, K.; Kakiuchi, F.; Chatani, N. *J. Org. Chem.* ***2004***, *69*, 5615.
[1979]Yu, Y.; Liebeskind, L.S. *J. Org. Chem.* ***2004***, *69*, 3554.
[1980]Anderson, R.J.; Henrick, C.A.; Rosenblum, L.D. *J. Am. Chem. Soc.* ***1974***, *96*, 3654. See also, Kim, S.; Lee, J.I. *J. Org. Chem.* ***1983***, *48*, 2608.
[1981]Shimizu, T.; Seki, M. *Tetrahedron Lett.* ***2002***, *43*, 1039.
[1982]Frost, C.G.; Wadsworth, K.J. *Chem. Commun.* ***2001***, 2316.
[1983]Gooßen, L.J.; Ghosh, K. *Eur. J. Org. Chem.* ***2002***, 3254.
[1984]Cacchi, S.; Fabrizi, G.; Gavazza, F.; Goggiamani, A. *Org. Lett.* ***2003***, *5*, 289.
[1985]Wang, D.; Zhang, Z. *Org. Lett.* ***2003***, *5*, 4645; Bercot, E.A.; Rovis, T. *J. Am. Chem. Soc.* ***2004***, *126*, 10248.
[1986]Bercot, E.A.; Rovis, T. *J. Am. Chem. Soc.* ***2002***, *124*, 174; O'Brien, E.M.; Bercot, E.A.; Rovis, T. *J. Am. Chem. Soc.* ***2003***, *125*, 10498.
[1987]Lannou, M.-I.; Hélion, F.; Namy, J.-L. *Tetrahedron Lett.* ***2002***, *43*, 8007.

via intramolecular addition of the organometallic intermediate to one carbonyl.[1988] The reaction of alkylzinc halides and thioesters leads to ketones in the presence of 1.5% Pd/C,[1989] in what has been called *Fukuyama coupling*.[1990]

Carboxylic esters can be converted to their homologs (RCOOEt → RCH_2-COOEt) by treatment with Br_2CHLi followed by BuLi at −90°C. The ynolate RC≡COLi is an intermediate.[1991] If the ynolate is treated with 1,3-cyclohexadiene, followed by $NaBH_4$, the product is the alcohol RCH_2CH_2OH.[1992]

Note that acyl benzotriazoles react with β-keto esters to give diketones via acyl substitution.[1993] Acyl cyanides, RC(=O)CN, react with allylic bromides and indium metal to give the corresponding ketone.[1994] Coupling an acid chloride and a silyl amide, $R_3SiC(=O)NR'_2$, leads to an α-keto amide.[1995] Acyl benzotriazoles have been coupled with SmI_2 to give the 1,2-diketone.[1996] α-Cyanoketone (acyl nitriles) were coupled with YbI_2 in a similar manner.[1997] α-Keto phosphonate esters undergo radical acyl substitution to give cyclic ketones under photochemical conditions.[1998]

Silyl esters are converted to the enolate anion upon treatment with *n*-butyllithium, and subsequent addition of an aldehyde followed by saponification leads to the β-hydroxy acid.[1999]

Vinyl organometallic reagents can be added to acyl derivatives. Reaction of an alkyne with Cp_2ZrEt_2 generates the vinyl zirconium reagent, which react with ethyl chloroformate to give an α,β-unsaturated ester.[2000]

OS **I**, 226; **II**, 179, 602; **III**, 237, 831, 839; **IV**, 601; **VI**, 240, 278; **VIII**, 474, 505.
OS **II**, 282; **72**, 32; **III**, 353; **IV**, 285; **VI**, 611; **VII**, 323, 451; **81**, 14.

16-83 The Coupling of Acyl Halides

De-halogen-coupling

$$2\,RCOCl \xrightarrow{\text{pyrophoric } \mathbf{Pb}} RCOCOR$$

[1988]Ha, D.-C.; Yun, C.-S.; Lee, Y. *J. Org. Chem.* ***2000***, *65*, 621.
[1989]Shimizu, T.; Seki, M. *Tetrahedron Lett.* ***2001***, *42*, 429.
[1990]See Tokuyama, H.; Yokoshima, S.; Yamashita, T.; Fukuyama, T. *Tetrahedron Lett.* ***1998***, *39*, 3189; Mori, Y.; Seki, M. *Tetrahedron Lett.* ***2004***, *45,* 7343. For a different but related cross-coupling, see Zhang, Y.; Rovis, T. *J. Am. Chem. Soc.* ***2004***, *126*, 15964.
[1991]Kowalski, C.J.; Haque, M.S.; Fields, K.W. *J. Am. Chem. Soc.* ***1985***, *107*, 1429; Kowalski, C.J.; Haque, M.S. *J. Org. Chem.* ***1985***, *50*, 5140.
[1992]Kowalski, C.J.; Haque, M.S. *J. Am. Chem. Soc.* ***1986***, *108*, 1325.
[1993]Katritzky, A.R.; Wang, Z.; Wang, M.; Wilkerson, C.R.; Hall, C.D.; Akhmedov, N.G. *J. Org. Chem.* ***2004***, *69*, 6617.
[1994]Yoo, B.W.; Choi, K.H.; Lee, S.J.; Nam, G.S.; Chang, K.Y.; Kim, S.H.; Kim, J.H. *Synth. Commun.* ***2002***, *32*, 839.
[1995]Chen, J.; Cunico, R.F. *J. Org. Chem.* ***2004***, *69*, 5509.
[1996]Wang, X.; Zhang, Y. *Tetrahedron Lett.* ***2002***, *43*, 5431.
[1997]Saikia, P.; Laskar, D.D.; Prajapati, D.; Sandhu, J.S. *Tetahedron Lett.* ***2002***, *43*, 7525.
[1998]Kim, S.; Cho, C.H.; Lim, C.J. *J. Am. Chem. Soc.* ***2003***, *125*, 9574.
[1999]Bellassoued, M.; Grugier, J.; Lensen, N.; Catheline, A. *J. Org. Chem.* ***2002***, *67*, 5611.
[2000]Takahashi, T.; Xi, C.; Ura, Y.; Nakajima, K. *J. Am. Chem. Soc.* ***2000***, *122*, 3228.

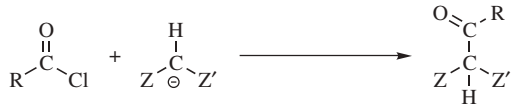
Acyl halides can be coupled with pyrophoric lead to give symmetrical α-diketones in a Wurtz-type reaction.[2001] The reaction has been performed with R = Me and Ph. Samarium iodide SmI_2[2002] gives the same reaction. Benzoyl chloride was coupled to give benzil by subjecting it to ultrasound in the presence of Li wire:

$$2\,PhCOCl + Li \longrightarrow PhCOCOPh.^{2003}$$

Unsymmetrical α-diketones, RCOCOR′, have been prepared by treatment of an acyl halide RCOCl with an acyltin reagent ($R'COSnBu_3$), with a palladium complex catalyst.[2004]

16-84 Acylation at a Carbon Bearing an Active Hydrogen

Bis(ethoxycarbonyl)methyl-de-halogenation, and so on



This reaction is similar to **10-67**, but there are fewer examples.[2005] Either Z or Z′ may be any of the groups listed in **10-67**.[2006] Anhydrides react similarly but are used less often. The product contains three Z groups, since RCO is a Z group. One or two of these can be cleaved (**12-40**, **12-43**). In this way, a compound ZCH_2Z' can be converted to ZCH_2Z[2] or an acyl halide (RCOCl) to a methyl ketone ($RCOCH_3$). *O*-Acylation is sometimes a side reaction.[2007] When thallium(I) salts of ZCH_2Z' are used, it is possible to achieve regioselective acylation at either the C or the O position. For example, treatment of the thallium(I) salt of $MeCOCH_2COMe$ with acetyl chloride at −78°C gave >90% *O*-acylation, while acetyl fluoride at room temperature gave >95% *C*-acylation.[2008] The use of an alkyl chloroformate gives triesters.[2009]

The application of this reaction to simple ketones[2010] (in parallel with **10-68**) requires a strong base, such as $NaNH_2$ or Ph_3CNa, and is often complicated by

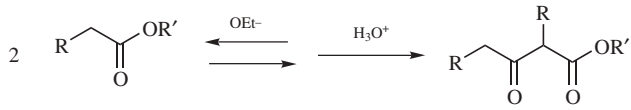
[2001]Mészáros, L. *Tetrahedron Lett.* ***1967***, 4951.
[2002]Souppe, J.; Namy, J.; Kagan, H.B. *Tetrahedron Lett.* ***1984***, *25*, 2869. See also, Collin, J.; Namy, J.; Dallemer, F.; Kagan, H.B. *J. Org. Chem.* ***1991***, *56*, 3118.
[2003]Han, B.H.; Boudjouk, P. *Tetrahedron Lett.* ***1981***, *22*, 2757.
[2004]Verlhac, J.; Chanson, E.; Jousseaume, B.; Quintard, J. *Tetrahedron Lett.* ***1985***, *26*, 6075. For another procedure, see Olah, G.A.; Wu, A. *J. Org. Chem.* ***1991***, *56*, 902.
[2005]For examples of reactions in this section, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1484–1485, 1522–1527.
[2006]For an improved procedure, see Rathke, M.W.; Cowan, P.J. *J. Org. Chem.* ***1985***, *50*, 2622.
[2007]When phase-transfer catalysts are used, *O*-acylation becomes the main reaction: Jones, R.A.; Nokkeo, S.; Singh, S. *Synth. Commun.* ***1977***, *7*, 195.
[2008]Taylor, E.C.; Hawks III, G.H.; McKillop, A. *J. Am. Chem. Soc.* ***1968***, *90*, 2421.
[2009]See, for example, Skarżewski, J. *Tetrahedron* ***1989***, *45*, 4593. For a review of triesters, see Newkome, G.R.; Baker, G.R. *Org. Prep. Proced. Int.* ***1986***, *19*, 117.
[2010]Hegedus, L.S.; Williams, R.E.; McGuire, M.A.; Hayashi, T. *J. Am. Chem. Soc.* ***1980***, *102*, 4973.

O-acylation, which in many cases becomes the principal pathway because acylation at the oxygen is usually much faster. It is possible to increase the proportion of *C*-acylated product by employing an excess (2–3 equivalents) of enolate anion (and adding the substrate to this, rather than vice versa), by the use of a relatively nonpolar solvent and a metal ion (e.g., Mg^{2+}), which is tightly associated with the enolate oxygen atom, by the use of an acyl halide rather than an anhydride,[2011] and by working at low temperatures.[2012] In cases where the use of an excess of enolate anion results in *C*-acylation, it is because *O*-acylation takes place first, and the *O*-acylated product (an enol ester) is then *C*-acylated. Simple ketones can also be acylated by treatment of their silyl enol ethers with an acyl chloride in the presence of $ZnCl_2$ or $SbCl_3$.[2013] Ketones can be acylated by anhydrides to give β-diketones, with BF_3 as catalyst.[2014] Simple esters RCH_2COOEt can be acylated at the a carbon (at −78°C) if a strong base such as lithium *N*-isopropylcyclohexylamide is used to remove the proton.[2015]

OS **II**, 266, 268, 594, 596; **III**, 16, 390, 637; **IV**, 285, 415, 708; **V**, 384, 937; **VI**, 245; **VII**, 213, 359; **VIII**, 71, 326, 467. See also, OS **VI**, 620.

16-85 Acylation of Carboxylic Esters by Carboxylic Esters: The Claisen and Dieckmann Condensations

Alkoxycarbonylalkyl-de-alkoxy-substitution



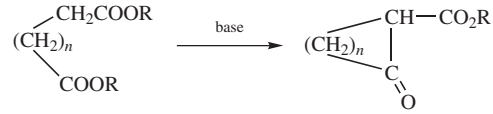
When carboxylic esters containing an α hydrogen are treated with a strong base, such as sodium ethoxide, a condensation occurs to give a β-keto ester via an ester enolate anion.[2016] This reaction is called the *Claisen condensation*. When it is carried out with a mixture of two different esters, each of which possesses an α hydrogen (this reaction is called a mixed Claisen or a crossed Claisen condensation), a mixture of all four products is generally obtained and the reaction is seldom useful synthetically.[2017] However, if only one of the esters has an

[2011]See House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 762–765; House, H.O.; Auerbach, R.A.; Gall, M.; Peet, N.P. *J. Org. Chem.* ***1973***, *38*, 514.
[2012]Seebach, D.; Weller, T.; Protschuk, G.; Beck, A.K.; Hoekstra, M.S. *Helv. Chim. Acta* ***1981***, *64*, 716.
[2013]Tirpak, R.E.; Rathke, M.W. *J. Org. Chem.* ***1982***, *47*, 5099.
[2014]For a review, see Hauser, C.R.; Swamer, F.W.; Adams, J.T. *Org. React.* ***1954***, *8*, 59, 98–106.
[2015]For example, see Rathke, M.W.; Deitch, J. *Tetrahedron Lett.* ***1971***, 2953; Logue, M.W. *J. Org. Chem.* ***1974***, *39*, 3455; Couffignal, R.; Moreau, J. *J. Organomet. Chem.* ***1977***, *127*, C65; Ohta, S.; Shimabayashi, A.; Hayakawa, S.; Sumino, M.; Okamoto, M. *Synthesis* ***1985***, 45; Hayden, W.; Pucher, R.; Griengl, H. *Monatsh. Chem.* ***1987***, *118*, 415.
[2016]For a study of ester and amide enolate stabilization, see Rablen, P.R.; Bentrup, KL.H. *J. Am. Chem. Soc.* ***2003***, *125*, 2142.
[2017]For a method of allowing certain crossed-Claisen reactions to proceed with good yields, see Tanabe, Y. *Bull. Chem. Soc. Jpn.* ***1989***, *62*, 1917.

α hydrogen, the mixed reaction is frequently satisfactory. Among esters lacking a hydrogens (hence acting as the substrate ester) that are commonly used in this way are esters of aromatic acids, and ethyl carbonate and ethyl oxalate. When the ester enolate reacts with ethyl carbonate, the product is a malonic ester, and reaction with ethyl formate introduces a formyl group. Claisen condensation of phenyl esters with $ZrCl_4$ and diisopropylethylamine (Hünigs base) give the corresponding keto ester.[2018]

As with ketone enolate anions (see **16-34**), the use of amide bases under kinetic control conditions (strong base with a weak conjugate acid, aprotic solvents, low temperatures), allows the mixed Claisen condensation to proceed. Self-condensation of the lithium enolate with the parent ester is a problem when LDA is used as a base,[2019] but this is minimized with LICA (lithium isopropylcyclohexyl amide).[2020] Note that solvent-free Claisen condensation reactions have been reported.[2021]

When the two ester groups involved in the condensation are in the same molecule, the product is a cyclic β-keto ester and the reaction is called the *Dieckmann condensation*.[2022]



The Dieckmann condensation is most successful for the formation of five-, six-, and seven-membered rings. Yields for rings of 9–12 members are very low or nonexistent; larger rings can be closed with high-dilution techniques. Reactions in which large rings are to be closed are generally assisted by high dilution, since one end of the molecule has a better chance of finding the other end than of finding another molecule. A solvent-free Dieckmann condensation has been reported on solid potassium *tert*-butoxide.[2023] Dieckmann condensation of unsymmetrical substrates can be made regioselective (unidirectional) by the use of solid-phase supports.[2024]

The mechanism of the Claisen and Dieckmann reactions is the ordinary tetrahedral mechanism,[2025] with one molecule of ester being converted to a nucleophile by

[2018]Tanabe, Y.; Hamasaki, R.; Funakoshi, S. *Chem. Commun.* ***2001***, 1674.

[2019]Rathke, M.W.; Sullivan, D.F. *J. Am. Chem. Soc.* ***1973***, *95*, 3050; Lochmann, L.; Lím, D. *J. Organomet. Chem.* ***1973***, *50*, 9; Sullivan, D.F.; Woodbury, R.P.; Rathke, M.W. *J. Org. Chem.* ***1977***, *42*, 2038.

[2020]Rathke, M.W.; Lindert, A. *J. Am. Chem. Soc.* ***1971***, *93*, 2318.

[2021]Yoshizawa, K.; Toyota, S.; Toda, F. *Tetrahedron Lett.* ***2001***, *42*, 7983.

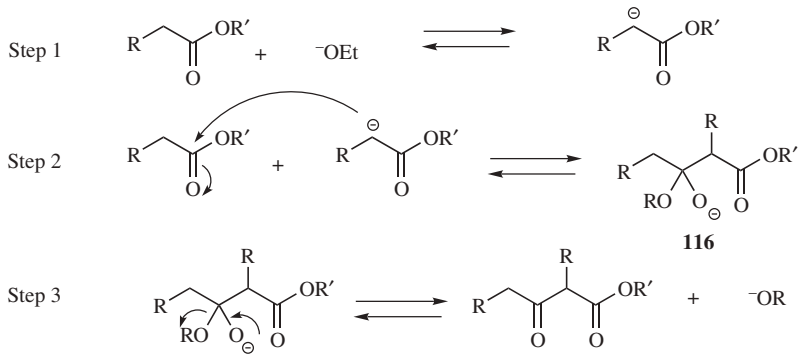
[2022]For a review, see Schaefer, J.P.; Bloomfield, J.J. *Org. React.* ***1967***, *15*, 1.

[2023]Toda, F.; Suzuki, T.; Higa, S. *J. Chem. Soc. Perkin Trans. 1* ***1998***, 3521.

[2024]Crowley, J.I.; Rapoport, H. *J. Org. Chem.* ***1980***, *45*, 3215. For another method, see Yamada, Y.; Ishii, T.; Kimura, M.; Hosaka, K. *Tetrahedron Lett.* ***1981***, *22*, 1353.

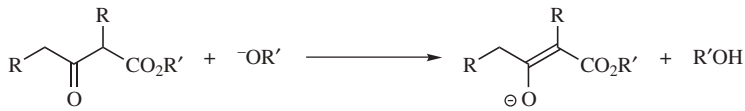
[2025]There is evidence that, at least in some cases, an SET mechanism is involved: Ashby, E.C.; Park, W. *Tetrahedron Lett.* ***1983***, 1667. The transition structures have also been examined by Nishimura, T.; Sunagawa, M.; Okajima, T.; Fukazawa, Y. *Tetrahedron Lett.* ***1997***, *38*, 7063.

the base and the other serving as the substrate.



This reaction illustrates the striking difference in behavior between carboxylic esters on the one hand and aldehydes and ketones on the other. When a carbanion, such as an enolate anion, is added to the carbonyl group of an aldehyde or ketone (**16-38**), the H or R is not lost, since these groups are much poorer leaving groups than OR. Instead the intermediate similar to **116** adds a proton at the oxygen to give a hydroxy compound.

In contrast to **10-67** ordinary esters react quite well, that is, two Z groups are not needed. A lower degree of acidity is satisfactory because it is not necessary to convert the attacking ester entirely to its ion. Step 1 is an equilibrium that lies well to the left. Nevertheless, the small amount of enolate anion formed is sufficient to attack the readily approachable ester substrate. All the steps are equilibria. The reaction proceeds because the product is converted to its conjugate base by the base present (i.e., a β-keto ester is a stronger acid than an alcohol):



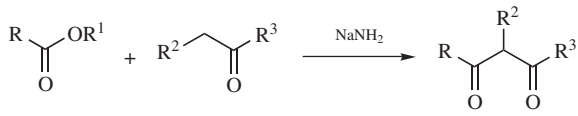
The use of a stronger base, such as $NaNH_2$, NaH, or KH,[2026] often increases the yield. For some esters stronger bases *must* be used, since sodium ethoxide is ineffective. Among these are esters of the type $R_2CHCOOEt$, the products of which ($R_2CHCOCR_2COOEt$) lack an acidic hydrogen, so that they cannot be converted to enolate anions by sodium ethoxide.[2027] The Dieckmann condensation has also been done using $TiCl_3/NBu_3$ with a TMSOTf catalyst.[2028] A Dieckmann-like condensation was reported where an α,ω-dicarboxylic acid was hated to 450°C on graphite, with microwave irradiation, to give the cyclic ketone.[2029]

[2026]Brown, C.A. *Synthesis* ***1975***, 326.
[2027]For a discussion, see Garst, J.F. *J. Chem. Educ.* ***1979***, *56*, 721.
[2028]Yoshida, Y.; Hayashi, R.; Sumihara, H.; Tanabe, Y. *Tetrahedron Lett.* ***1997***, *38*, 8727.
[2029]Marquié, J.; Laporterie, A.; Dubac, J.; Roques, N. *Synlett* ***2001***, 493.

OS **I**, 235; **II**, 116, 194, 272, 288; **III**, 231, 300, 379, 510; **IV**, 141; **V**, 288, 687, 989; **VIII**, 112.

16-86 Acylation of Ketones and Nitriles by Carboxylic Esters

α-Acylalkyl-de-alkoxy-substitution



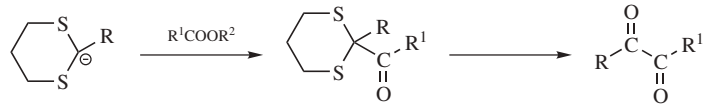
Carboxylic esters can be treated with ketones to give β-diketones. The reaction is so similar that it is sometimes also called the Claisen reaction, though this usage may be confusing. A strong base, such as sodium amide or sodium hydride, is required. Yields can be increased by the catalytic addition of crown ethers.[2030] Esters of formic acid (R = H) give β-keto aldehydes and ethyl carbonate gives β-keto esters. β-Keto esters can also be obtained by treating the lithium enolates of ketones with methyl cyanoformate MeOCOCN[2031] (in this case CN is the leaving group) and by treating ketones with KH and diethyl dicarbonate, $(EtOCO)_2O$.[2032]

In the case of unsymmetrical ketones, the attack usually comes from the less highly substituted side, so that CH_3 is more reactive than RCH_2, and the R_2CH group rarely attacks. This reaction has been used to effect cyclization, especially to prepare five- and six-membered rings. Nitriles are frequently used instead of ketones, the products being β-keto nitriles.

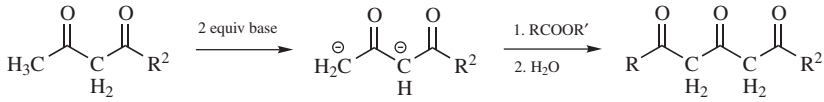
Other nucleophilic carbon reagents, such as acetylide ions, and ions derived from α-methylpyridines have also been used. A particularly useful nucleophile is the methylsulfinyl carbanion, CH_3SOCH_2-,[2033] the conjugate base of DMSO, since the β-keto sulfoxide produced can easily be reduced to a methyl ketone (p. 624). The methylsulfonyl carbanion ($CH_3SO_2CH_2^-$), the conjugate base of dimethyl sulfone, behaves similarly,[2034] and the product can be similarly reduced. Certain carboxylic esters, acyl halides, and DMF will acylate 1,3-dithianes[2035] (see **10-71**) to give, after oxidative hydrolysis with NBS or NCS, α-keto aldehydes or

[2030]Popik, V.V.; Nikolaev, V.A. *J. Org. Chem. USSR* ***1989***, *25*, 1636.
[2031]Mander, L.N.; Sethi, P. *Tetrahedron Lett.* ***1983***, *24*, 5425.
[2032]Hellou, J.; Kingston, J.F.; Fallis, A.G. *Synthesis* ***1984***, 1014.
[2033]See Durst, T. *Adv. Org. Chem.* ***1969***, *6*, 285, pp. 296–301.
[2034]Schank, K.; Hasenfratz, H.; Weber, A. *Chem. Ber.* ***1973***, *106*, 1107, House, H.O.; Larson, J.K. *J. Org. Chem.* ***1968***, *33*, 61.
[2035]Corey, E.J.; Seebach, D. *J. Org. Chem.* ***1975***, *40*, 231

α-diketones,[254] for example,



As in **10-67**, a ketone attacks with its second most acidic position if 2 equivalents of base are used. Thus, β-diketones have been converted to 1,3,5-triketones.[2036]

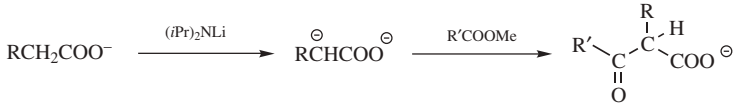


Side reactions are condensation of the ketone with itself (**16-34**), of the ester with itself, and of the ketone with the ester, but with the ester supplying the a position (**16-36**). The mechanism is the same as in **16-85**.[2037]

OS **I**, 238; **II**, 126, 200, 287, 487, 531; **III**, 17, 251, 291, 387, 829; **IV**, 174, 210, 461, 536; **V**, 187, 198, 439, 567, 718, 747; **VI**, 774; **VII**, 351.

16-87 Acylation of Carboxylic Acid Salts

α-Carboxyalkyl-de-alkoxy-substitution



We have previously seen (**10-70**) that dianions of carboxylic acids can be alkylated in the α position. These ions can also be acylated on treatment with a carboxylic ester[2038] to give salts of β-keto acids. As in **10-70**, the carboxylic acid can be of the form RCH_2COOH or $RR^2CHCOOH$. Since β-keto acids are so easily converted to ketones (**12-40**), this is also a method for the preparation of ketones $R'COCH_2R$ and $R'COCHRR^2$, where R′ can be primary, secondary, or tertiary alkyl, or aryl. If the ester is ethyl formate, an α-formyl carboxylate salt (R′ = H) is formed, which on acidification spontaneously decarboxylates into an aldehyde.[2039] This method accomplishes the conversion $RCH_2COOH \rightarrow RCH_2CHO$, and is an alternative to the reduction methods discussed in **19-39**. When the carboxylic acid is of the form RR″CHCOOH, better yields are obtained by acylating with acyl halides rather than esters.[2040]

[2036]Miles, M.L.; Harris, T.M.; Hauser, C.R. *J. Org. Chem.* ***1965***, *30*, 1007.
[2037]Hill, D.G.; Burkus, T.; Hauser, C.R. *J. Am. Chem. Soc.* ***1959***, *81*, 602.
[2038]Kuo, Y.; Yahner, J.A.; Ainsworth, C. *J. Am. Chem. Soc.* ***1971***, *93*, 6321; Angelo, B. *C.R. Seances Acad. Sci. Ser. C* ***1973***, *276*, 293.
[2039]Pfeffer, P.E.; Silbert, L.S. *Tetrahedron Lett.* ***1970***, 699; Koch, G.K.; Kop, J.M.M. *Tetrahedron Lett.* ***1974***, 603.
[2040]Krapcho, A.P.; Kashdan, D.S.; Jahngen, Jr., E.G.E.; Lovey, A.J. *J. Org. Chem.* ***1977***, *42*, 1189; Lion, C.; Dubois, J.E. *J. Chem. Res. (S)* ***1980***, 44.

16-88 Preparation of Acyl Cyanides

Cyano-de-halogenation

$$RCOX + CuCN \longrightarrow RCOCN$$

Acyl cyanides[2041] can be prepared by treatment of acyl halides with copper cyanide. The mechanism could be free-radical or nucleophilic substitution. The reaction has also been accomplished with thallium(I) cyanide,[2042] with Me_3SiCN and an $SnCl_4$ catalyst,[2043] and with Bu_3SnCN,[2044] but these reagents are successful only when R = aryl or tertiary alkyl. KCN has also been used, along with ultrasound,[2045] as has NaCN with phase-transfer catalysts.[2046]

OS **III**, 119.

16-89 Preparation of Diazo Ketones

Diazomethyl-de-halogenation

$$RCOX + CH_2N_2 \longrightarrow RCOCHN_2$$

The reaction between acyl halides and diazomethane is of wide scope and is the best way to prepare diazo ketones.[2047] Diazomethane must be present in excess or the HX produced will react with the diazo ketone (**10-52**). This reaction is the first step of the *Arndt–Eistert synthesis* (**18-8**). Diazo ketones can also be prepared directly from a carboxylic acid and diazomethane or diazoethane in the presence of DCC.[2048]

OS **III**, 119; **VI**, 386, 613; **VIII**, 196.

16-90 Ketonic Decarboxylation[2049]

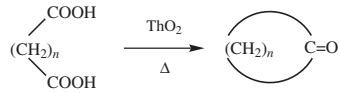
Alkyl-de-hydroxylation

$$2\ RCOOH \xrightarrow[ThO_2]{400\text{–}500^\circ C} RCOR + CO_2$$

[2041]For a review of acyl cyanides, see Hünig, S.; Schaller, R. *Angew. Chem. Int. Ed.* ***1982***, *21*, 36.
[2042]Taylor, E.C.; Andrade, J.G.; John, K.C.; McKillop, A. *J. Org. Chem.* ***1978***, *43*, 2280.
[2043]Olah, G.A.; Arvanaghi, M.; Prakash, G.K.S. *Synthesis* ***1983***, 636.
[2044]Tanaka, M. *Tetrahedron Lett.* ***1980***, *21*, 2959. See also Tanaka, M.; Koyanagi, M. *Synthesis* ***1981***, 973.
[2045]Ando, T.; Kawate, T.; Yamawaki, J.; Hanafusa, T. *Synthesis* ***1983***, 637.
[2046]Koenig, K.E.; Weber, W.P. *Tetrahedron Lett.* ***1974***, 2275. See also, Sukata, K. *Bull. Chem. Soc. Jpn.* ***1987***, *60*, 1085.
[2047]For reviews, see Fridman, A.L.; Ismagilova, G.S.; Zalesov, V.S.; Novikov, S.S. *Russ. Chem. Rev.* ***1972***, *41*, 371; Ried, W.; Mengler, H. *Fortshr. Chem. Forsch.*, ***1965***, *5*, 1.
[2048]Hodson, D.; Holt, G.; Wall, D.K. *J. Chem. Soc. C* ***1970***, 971.
[2049]For a review, see Kwart, H.; King, K., in Patai, S. *The Chemistry of Carboxylic Acids and Esters*, Wiley, NY, ***1969***, pp. 362–370.

Carboxylic acids can be converted to symmetrical ketones by pyrolysis in the presence of thorium oxide. In a mixed reaction, formic acid and another acid heated over thorium oxide give aldehydes. Mixed alkyl aryl ketones have been prepared by heating mixtures of ferrous salts.[2050] When the R group is large, the methyl ester rather than the acid can be decarbmethoxylated over thorium oxide to give the symmetrical ketone.

The reaction has been performed on dicarboxylic acids, whereupon cyclic ketones are obtained:



This process, called *Ruzicka cyclization*, is good for the preparation of rings of six and seven members and, with lower yields, of C_8 and C_{10}–C_{30} cyclic ketones.[2051]

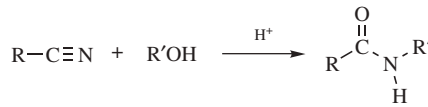
Not much work has been done on the mechanism of this reaction. However, a free-radical mechanism has been suggested on the basis of a thorough study of all the side products.[2052]

OS **I**, 192; **II**, 389; **IV**, 854; **V**, 589. Also see, OS **IV**, 55, 560.

REACTIONS IN WHICH CARBON ADDS TO THE HETEROATOM

A. Oxygen Adding to the Carbon

16-91 The Ritter Reaction
***N*-Hydro,*N*-alkyl-*C*-oxo-biaddition**



Alcohols can be added to nitriles in an entirely different manner from that of reaction **16-9**. In this reaction, the alcohol is converted by a strong acid to a carbocation, which is attacked by the nucleophilic nitrogen atom to give **117**. Subsequent addition of water to the electrophilic carbon atom leads to the enol form of the amide (see **118**), which tautomerizes (p. 98) to the *N*-alkyl amide.

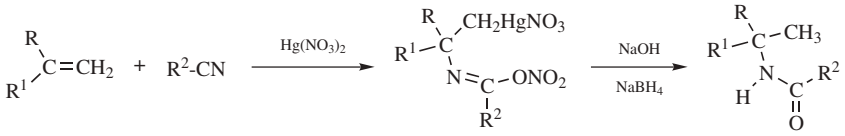
117 **118**

[2050]Granito, C.; Schultz, H.P. *J. Org. Chem.* ***1963***, *28*, 879.
[2051]See, for example, Ruzicka, L.; Stoll, M.; Schinz, H. *Helv. Chim. Acta* ***1926***, *9*, 249; ***1928***, *11*, 1174; Ruzicka, L.; Brugger, W.; Seidel, C.F.; Schinz, H. *Helv. Chim. Acta* ***1928***, *11*, 496.
[2052]Hites, R.A.; Biemann, K. *J. Am. Chem. Soc.* ***1972***, *94*, 5772. See also, Bouchoule, C.; Blanchard, M.; Thomassin, R. *Bull. Soc. Chim. Fr.* ***1973***, 1773.

Only alcohols that give rise to fairly stable carbocations react (secondary, tertiary, benzylic, etc.); non-benzylic primary alcohols do not give the reaction. The carbocation need not be generated from an alcohol, but may come from protonation of an alkene or from other sources. In any case, the reaction is called the *Ritter reaction*.[2053] Lewis acids, such as $Mg(HSO_4)_2$, have been used to promote the reaction.[2054] Highly sterically hindered nitriles have been converted to *N*-methyl amides by heating with methanol and sulfuric acid.[2055] HCN also gives the reaction, the product being a formamide. Trimethylsilyl cyanide has also been used.[2056]

Since the amides (especially the formamides) are easily cleaved under hydrolysis conditions to amines, the Ritter reaction provides a method for achieving the conversions $R'OH \rightarrow R'NH_2$ (see **10-32**) and alkene $\rightarrow R'NH_2$ (see **15-8**) in those cases where R′ can form a relatively stable carbocation. The reaction is especially useful for the preparation of tertiary alkyl amines because there are few alternate ways of preparing these compounds. The reaction can be extended to primary alcohols by treatment with triflic anhydride[2057] or Ph_2CCl^+ $SbCl_6^-$ or a similar salt[2058] in the presence of the nitrile.

Alkenes of the form $RCH{=}CHR'$ and $RR'C{=}CH_2$ add to nitriles in the presence of mercuric nitrate to give, after treatment with $NaBH_4$, the same amides that would be obtained by the Ritter reaction.[2059] This method has the advantage of avoiding strong acids.



Benzylic compounds, such as ethylbenzene, react with alkyl nitriles, ceric ammonium nitrate, and a catalytic amount of *N*-hydroxysuccinimide to give the Ritter product, the amide.[2060]

The Ritter reaction can be applied to cyanamides RNHCN to give ureas RNHCONHR′.[2061]

OS **V**, 73, 471.

[2053]Ritter, J.J.; Minieri, P.P. *J. Am. Chem. Soc.* ***1948***, *70*, 4045. For reviews, see Krimen, L.I.; Cota, D.J. *Org. React.* ***1969***, *17*, 213; Beckwith, A.L.J., in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 125–130; Johnson, F.; Madroñero, R. *Adv. Heterocycl. Chem.* ***1966***, *6*, 95; Tongco, E.C.; Prakash, G.K.S.; Olah, G.A. *Synlett* ***1997***, 1193.

[2054]Salehi, P.; Khodaei, M.M.; Zolfigol, M.A.; Keyvan, A. *Synth. Commun.* ***2001***, *31*, 1947.

[2055]Lebedev, M.Y.; Erman, M.B. *Tetrahedron Lett.* ***2002***, *43*, 1397.

[2056]Chen, H.G.; Goel, O.P.; Kesten, S.; Knobelsdorf, J. *Tetrahedron Lett.* ***1996***, *37*, 8129.

[2057]Martinez, A.G.; Alvarez, R.M.; Vilar, E.T.; Fraile, A.G.; Hanack, M.; Subramanian, L.R. *Tetrahedron Lett.* ***1989***, *30*, 581.

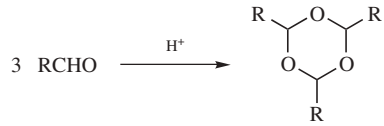
[2058]Barton, D.H.R.; Magnus, P.D.; Garbarino, J.A.; Young, R.N. *J. Chem. Soc. Perkin Trans. 1* ***1974***, 2101. See also, Top, S.; Jaouen, G. *J. Org. Chem.* ***1981***, *46*, 78.

[2059]Sokolov, V.I.; Reutov, O.A. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1968***, 225; Brown, H.C.; Kurek, J.T. *J. Am. Chem. Soc.* ***1969***, *91*, 5647; Chow, D.; Robson, J.H.; Wright, G.F. *Can. J. Chem.* ***1965***, *43*, 312; Fry, A.J.; Simon, J.A. *J. Org. Chem.* ***1982***, *47*, 5032.

[2060]Sakaguchi, S.; Hirabayashi, T.; Ishii, Y. *Chem. Commun.* ***2002***, 516.

[2061]Anatol, J.; Berecoechea, J. *Bull. Soc. Chim. Fr.* ***1975***, 395; *Synthesis* ***1975***, 111.

16-92 The Addition of Aldehydes to Aldehydes



When catalyzed by acids, low-molecular-weight aldehydes add to each other to give cyclic acetals, the most common product being the trimer.[2062] The cyclic trimer of formaldehyde is called *trioxane*,[2063] and that of acetaldehyde is known as *paraldehyde*. Under certain conditions, it is possible to get tetramers[2064] or dimers. Aldehydes can also polymerize to linear polymers, but here a small amount of water is required to form hemiacetal groups at the ends of the chains. The linear polymer formed from formaldehyde is called *paraformaldehyde*. Since trimers and polymers of aldehydes are acetals, they are stable to bases, but can be hydrolyzed by acids. Because formaldehyde and acetaldehyde have low boiling points, it is often convenient to use them in the form of their trimers or polymers.

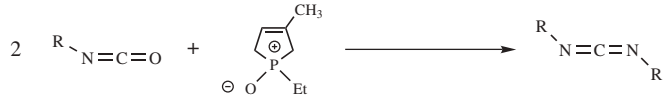
Aryl aldehydes condense with aliphatic aldehydes in the presence of benzoylformate decarboxylase and thiamin diphosphate to give an α-hydroxy ketone with god enantioselectivity.[2065]

A slightly related reaction involves nitriles, which can be trimerized with various acids, bases, or other catalysts to give triazines (see OS **III**, 71).[2066] Here HCl is most often used. Most nitriles with an α hydrogen do not give the reaction.

B. Nitrogen Adding to the Carbon

16-93 The Addition of Isocyanates to Isocyanates (Formation of Carbodiimides)

Alkylimino-de-oxo-bisubstitution



119

The treatment of isocyanates with 3-methyl-1-ethyl-3-phospholene-1-oxide (**119**) is a useful method for the synthesis of carbodiimides[2067] in good

[2062]For a review, see Bevington, J.C. *Q. Rev. Chem. Soc.* ***1952***, *6*, 141.

[2063]For a synthesis of trioxanes using bentonitic earth catalysts, see Camarena, R.; Cano, A.C.; Delgado, F.; Zúñiga, N.; Alvarez, C. *Tetrahedron Lett.* ***1993***, *34*, 6857.

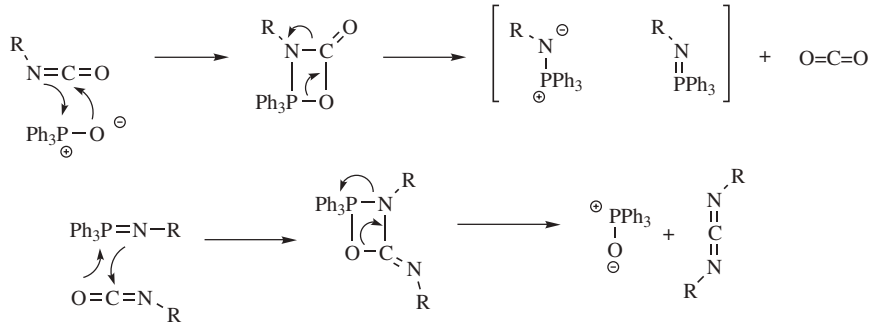
[2064]Barón, M.; de Manderola, O.B.; Westerkamp, J.F. *Can. J. Chem.* ***1963***, *41*, 1893.

[2065]Dünnwald, T.; Demir, A.S.; Siegert, P.; Pohl, M.; Müller, M. *Eur. J. Org. Chem.* ***2000***, 2161.

[2066]For a review, see Martin, D.; Bauer, M.; Pankratov, V.A. *Russ. Chem. Rev.* ***1978***, *47*, 975. For a review with respect to cyanamides RNH–CN, see Pankratov, V.A.; Chesnokova, A.E. *Russ. Chem. Rev.* ***1989***, *58*, 879. For reviews of the chemistry of carb.

[2067]For reviews of the chemistry of carbodiimides, see Williams, A.; Ibrahim, I.T. *Chem. Rev.* ***1981***, *81*, 589; Mikołajczyk, M.; Kiełbasiński, P. *Tetrahedron* ***1981***, *37*, 233; Kurzer, F.; Douraghi-Zadeh, K. *Chem. Rev.* ***1967***, *67*, 107.

yields.[2068] The mechanism does not simply involve the addition of one molecule of isocyanate to another, since the kinetics are first order in isocyanate and first order in catalyst. The following mechanism has been proposed (the catalyst is here represented as $R_3P^+—O^-$:[2069]



According to this mechanism, one molecule of isocyanate undergoes addition to C=O, and the other addition to C=N. Evidence is that ^{18}O labeling experiments have shown that each molecule of CO_2 produced contains one oxygen atom derived from the isocyanate and one from **119**,[2070] precisely what is predicted by this mechanism. Certain other catalysts are also effective.[2071] High-load, soluble oligomeric carbodiimides have been prepared.[2072]

OS **V**, 501.

16-94 The Conversion of Carboxylic Acid Salts to Nitriles

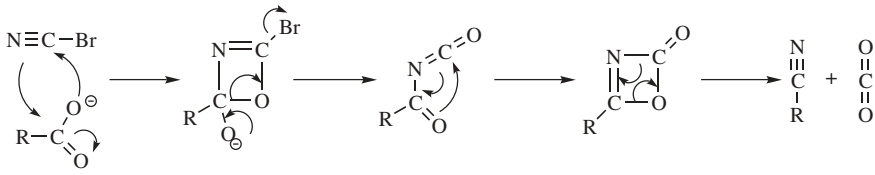
Nitrilo-de-oxido,oxo-tersubstitution

$$RCOO^- + BrCN \xrightarrow{250–300°C} RCN + CO_2$$

Salts of aliphatic or aromatic carboxylic acids can be converted to the corresponding nitriles by heating with BrCN or ClCN. Despite appearances, this is not a substitution reaction. When $R^{14}COO^-$ was used, the label appeared in the nitrile, not in the CO_2,[2073] and optical activity in R was retained.[2074] The acyl isocyanate RCON=C=O could be isolated from the reaction mixture; hence the

[2068]Campbell, T.W.; Monagle, J.J.; Foldi, V.S. *J. Am. Chem. Soc.* ***1962***, *84*, 3673.
[2069]Monagle, J.J.; Campbell, T.W.; McShane Jr., H.F. *J. Am. Chem. Soc.* ***1962***, *84*, 4288.
[2070]Monagle, J.J.; Mengenhauser, J.V. *J. Org. Chem.* ***1966***, *31*, 2321.
[2071]Monagle, J.J. *J. Org. Chem.* ***1962***, *27*, 3851; Appleman, J.O.; DeCarlo, V.J. *J. Org. Chem.* ***1967***, *32*, 1505; Ulrich, H.; Tucker, B.; Sayigh, A.A.R. *J. Org. Chem.* ***1967***, *32*, 1360; *Tetrahedron Lett.* ***1967***, 1731; Ostrogovich, G.; Kerek, F.; Buzás, A.; Doca, N. *Tetrahedron* ***1969***, *25*, 1875.
[2072]Zhang, M.; Vedantham, P.; Flynn, D.L.; Hanson, P.R. *J. Org. Chem.* ***2004***, *69*, 8340.
[2073]Douglas, D.E.; Burditt, A.M. *Can. J. Chem.* ***1958***, *36*, 1256.
[2074]Barltrop, J.A.; Day, A.C.; Bigley, D.B. *J. Chem. Soc.* ***1961***, 3185.

following mechanism was proposed:[2073]

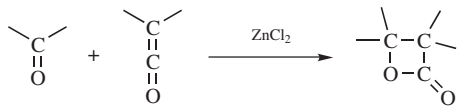


C. Carbon Adding to the Carbon.

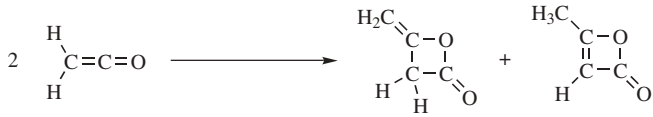
The reactions in this group are cycloadditions.

16-95 The Formation of β-Lactones and Oxetanes

(2+2)*OC*,*CC-cyclo*-[oxoethylene]-1/2/addition



Aldehydes, ketones, and quinones react with ketenes to give β-lactones,[2075] diphenylketene being used most often.[2076] The reaction is catalyzed by Lewis acids, and without them most ketenes do not give adducts because the adducts decompose at the high temperatures necessary when no catalyst is used. When ketene was added to chloral (Cl_3CCHO) in the presence of the chiral catalyst (+)-quinidine, one enantiomer of the β-lactone was produced with excellent enantioselectivity.[2077] The use of a chiral aluminum catalyst also led to β-lactones with good syn selectivity and good enantioselectivity.[2078] Other di- and trihalo aldehydes and ketones also give the reaction enantioselectively, with somewhat lower enantioselectivity.[2079] Ketene adds to another molecule of itself:



This dimerization is so rapid that ketene does not form β-lactones with aldehydes or ketones, except at low temperatures. Other ketenes dimerize more slowly. In

[2075]See Nelson, S.G.; Wan, Z.; Peclen, Y.J.; Spencer, K.L. *Tetrahedron Lett.* ***1999***, *40*, 6535; Cortez, G.S.; Tennyson, R.L.; Romo, D. *J. Am. Chem. Soc.* ***2001***, *123*, 7945.

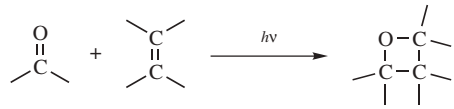
[2076]For reviews, see Muller, L.L.; Hamer, J. *1,2-Cycloaddition Reactions*, Wiley, NY, ***1967***, pp. 139–168; Ulrich, H. *Cycloaddition Reactions of Heterocumulenes*; Academic Press, NY, ***1967***, pp. 39–45, 64–74.

[2077]Wynberg, H.; Staring, E.G.J. *J. Am. Chem. Soc.* ***1982***, *104*, 166; *J. Chem. Soc., Chem. Commun.* ***1984***, 1181.

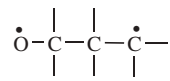
[2078]Nelson, S.G.; Zhu, C.; Shen, X. *J. Am. Chem. Soc.* ***2004***, *126*, 14.

[2079]Wynberg, H.; Staring, E.G.J. *J. Org. Chem.* ***1985***, *50*, 1977.

these cases, the major dimerization product is not the β-lactone, but a cyclobutanedione (see **15-63**). However, the proportion of ketene that dimerizes to β-lactone can be increased by the addition of catalysts, such as triethylamine or triethyl phosphite.[2080] Ketene acetals $R_2C{=}C(OR')_2$ add to aldehydes and ketones in the presence of $ZnCl_2$ to give the corresponding oxetanes.[2081]



Ordinary aldehydes and ketones can add to alkenes, under the influence of *UV* light, to give oxetanes. Quinones also react to give spirocyclic oxetanes.[2082] This reaction, called the *Paterno–Büchi reaction*,[2083] is similar to the photochemical dimerization of alkenes discussed at **15-63**. In general, the mechanism consists of the addition of an excited state of the carbonyl compound to the ground state of the alkene. Both singlet (S_1)[2084] and n,π^* triplet[2085] states have been shown to add to alkenes to give oxetanes. A diradical intermediate[2086]



has been detected by spectroscopic methods.[2087] Yields in the Paterno–Büchi reaction are variable, ranging from very low to fairly high (90%). The reaction can be

[2080]Farnum, D.G.; Johnson, J.R.; Hess, R.E.; Marshall, T.B.; Webster, B. *J. Am. Chem. Soc.* ***1965***, *87*, 5191; Elam, E.U. *J. Org. Chem.* ***1967***, *32*, 215.

[2081]Aben, R.W.; Hofstraat, R.; Scheeren, J.W. *Recl. Trav. Chim. Pays-Bas* ***1981***, *100*, 355. For a discussion of oxetane cycloreversion, see Miranda, M.A.; Izquierdo, M.A.; Galindo, F. *Org. Lett.* ***2001***, *3*, 1965.

[2082]Ciufolini, M.A.; Rivera-Fortin, M.A.; Byrne, N.E. *Tetrahedron Lett.* ***1993***, *34*, 3505.

[2083]For reviews, see Ninomiya, I.; Naito, T. *Photochemical Synthesis*, Academic Press, NY, ***1989***, pp. 138–152; Carless, H.A.J., in Coyle, J.D. *Photochemistry in Organic Synthesis*, Royal Society of Chemistry, London, ***1986***, pp. 95–117; Carless, H.A.J., in Horspool, W.M. *Synthetic Organic Photochemistry*, Plenum, NY, ***1984***, pp. 425–487; Jones II, M. *Org. Photochem.* ***1981***, *5*, 1; Arnold, D.R. *Adv. PhotoChem.* ***1968***, *6*, 301–423; Chapman, O.L.; Lenz, G. *Org. Photochem.* ***1967***, *1*, 283, pp. 283–294; Muller, L.L.; Hamer, J. *1,2-Cycloaddition Reactions*, Wiley, NY, ***1967***, pp. 111–139. Also see, Bosch, E.; Hubig, S.M.; Kochi, J.K. *J. Am. Chem. Soc.* ***1998***, *120*, 386; Bach, T.; Jödicke, K.; Kather, K.; Frölich, R. *J. Am. Chem. Soc.* ***1997***, *119*, 2437; Hu, S.; Neckers, D.C. *J. Org. Chem.* ***1997***, *62*, 564.

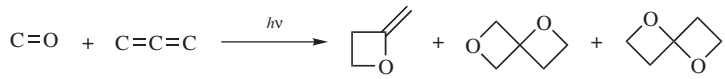
[2084]See, for example, Turro, N.J. *Pure Appl. Chem.* ***1971***, *27*, 679; Yang, N.C.; Kimura, M.; Eisenhardt, W. *J. Am. Chem. Soc.* ***1973***, *95*, 5058; Singer, L.A.; Davis, G.A.; Muralidharan, V.P. *J. Am. Chem. Soc.* ***1969***, *91*, 897; Barltrop, J.A.; Carless, H.A.J. *J. Am. Chem. Soc.* ***1972***, *94*, 1951, 8761.

[2085]Arnold, D.R.; Hinman, R.L.; Glick, A.H. *Tetrahedron Lett.* ***1964***, 1425; Yang, N.C.; Nussim, M.; Jorgenson, M.J.; Murov, S. *Tetrahedron Lett.* ***1964***, 3657.

[2086]For other evidence for these diradical intermediates, see references cited in Griesbeck, A.G.; Stadmüller, S. *J. Am. Chem. Soc.* ***1990***, *112*, 1281. See also, Kutateladze, A.G. *J. Am. Chem. Soc.* ***2001***, *123*, 9279.

[2087]Freilich, S.C.; Peters, K.S. *J. Am. Chem. Soc.* ***1981***, *103*, 6255; ***1985***, *107*, 3819. For a review, see Griesbeck, A.G.; Mauder, H.; Stadmüller, S. *Accts. Chem. Res.* ***1994***, *27*, 70.

highly diastereoselective,[2088] and allylic alcohols were shown to react with aldehydes to give an oxetane with syn selectivity.[2089] There are several side reactions. When the reaction proceeds through a triplet state, it can in general be successful only when the alkene possesses a triplet energy comparable to, or higher than, the carbonyl compound; otherwise energy transfer from the excited carbonyl group to the ground-state alkene can take place (triplet-triplet photosensitization, see p. 340).[2090] In most cases, quinones react normally with alkenes, giving oxetane products, but other α,β-unsaturated ketones usually give preferential cyclobutane formation (**15-63**). Aldehydes and ketones also add photochemically to allenes to give the corresponding alkylideneoxetanes and dioxaspiro compounds:[2091] Aldehydes add to silyl enol ethers.[2092] An intramolecular reaction of ketones was reported to give a bicyclic oxetane via photolysis on the solid state.[2093]



OS **III**, 508; **V**, 456. For the reverse reaction, see OS **V**, 679.

16-96 The Formation of β-Lactams

(2+2)*NC*,*CC*-*cyclo*-[oxoethylene]-1/2/addition

Ketenes add to imines to give β-lactams.[2094] The reaction is generally carried out with ketenes of the form $R_2C{=}C{=}O$. It has not been successfully applied to

[2088]Bach, T.; Jödicke, K.; Wibbeling, B. *Tetrahedron* ***1996***, *52*, 10861; Fleming, S.A.; Gao, J.J. *Tetrahedron Lett.* ***1997***, *38*, 5407; Vasudevan, S.; Brock, C.P.; Watt, D.S.; Morita, H. *J. Org. Chem.* ***1994***, *59*, 4677; Adam, W.; Stegmann, V.R.; Weinkötz, S. *J. Am. Chem. Soc.* ***2001***, *123*, 2452; Adam, W.; Stegmann, V.R. *J. Am. Chem. Soc.* ***2002***, *124*, 3600. For a discussion of the origins of regioselectivity, see Ciufolini, M.A.; Rivera-Fortin, M.A.; Zuzukin, V.; Whitmire, K.H. *J. Am. Chem. Soc.* ***1994***, *116*, 1272.

[2089]Greisbeck, A.G.; Bondock, S. *J. Am. Chem. Soc.* ***2001***, *123*, 6191. See also, Adam, W.; Stegmann, V.R. *Synthesis* ***2001***, 1203.

[2090]For a spin-directed reaction, see Griesbeck, A.G.; Fiege, M.; Bondock, S.; Gudipati, M.S. *Org. Lett.* ***2000***, *2*, 3623.

[2091]Howell, A.R.; Fan, R.; Truong, A. *Tetrahedron Lett.* ***1996***, *37*, 8651. For a review of the formation of heterocycles by cycloadditions of allenes, see Schuster, H.F.; Coppola, G.M. *Allenes in Organic Synthesis*, Wiley, NY, ***1984***, pp. 317–326.

[2092]Abe, M.; Tachibana, K.; Fujimoto, K.; Nojima, M. *Synthesis* ***2001***, 1243.

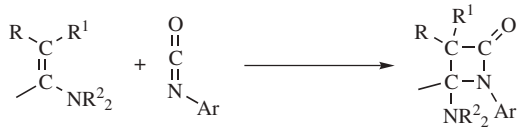
[2093]Kang, T.; Scheffer, J.R. *Org. Lett.* ***2001***, *3*, 3361.

[2094]For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1919–1921. For reviews of the formation of β-lactams, see Brown, M.J. *Heterocycles* ***1989***, *29*, 2225; Isaacs, N.S. *Chem. Soc. Rev.* ***1976***, *5*, 181; Mukerjee, A.K.; Srivastava, R.C. *Synthesis* ***1973***, 327; Muller, L.L.; Hamer, J. *1,2-Cycloaddition Reactions*, Wiley, NY, ***1967***, pp. 173–206; Ulrich, H. *Cycloaddition Reactions of Heterocumulenes*, Academic Press, NY, ***1967***, pp. 75–83, 135–152; Anselme, J., in Patai, S. *The Chemistry of the Carbon–Nitrogen Double Bond*, Wiley, NY, ***1970***, pp. 305–309. For a review of cycloaddition reactions of imines, see Sandhu, J.S.; Sain, B. *Heterocycles* ***1987***, *26*, 777.

RCH=C=O, except when these are generated *in situ* by decomposition of a diazo ketone (the Wolff rearrangement, **18-8**) in the presence of the imine. It has been done with ketene, but the more usual course with this reagent is an addition to the enamine tautomer of the substrate. Thioketenes[2095] ($R_2C{=}C{=}S$) give β-thiolactams.[2096] Imines also form β-lactams when treated with (*1*) zinc (or another metal[2097]) and an α-bromo ester (Reformatsky conditions, **16-28**),[2098] or (*2*) the chromium carbene complexes $(CO)_5Cr{=}C(Me)OMe$.[2099] The latter method has been used to prepare optically active β-lactams.[2100] Ketenes have also been added to certain hydrazones (e.g., $PhCH{=}NNMe_2$) to give *N*-amino β-lactams.[2101] A polymer-bound pyridinium salt facilitates β-lactam formation from carboxylic acids and imines.[2102]

N-Tosyl imines react with ketenes, Proton Sponge (p. 365) and a chiral amine to give the *N*-tosyl β-lactam with good enantioselectivity.[2103] A chiral ferrocenyl catalyst also gives good enantioselectivity,[2104] and chiral ammonium salts have been used as catalysts.[2105] A catalytic amount of benzoyl quinine gives β-lactams with good enantioselectivity.[2106] An intramolecular version of this ketene-imine reaction is known.[2107]

Like the similar cycloaddition of ketenes to alkenes (**15-63**), most of these reactions probably take place by the diionic mechanism *c* (p. 1224).[2108] β-Lactams have also been prepared in the opposite manner: by the addition of enamines to isocyanates:[2109]



[2095]For a review of thioketenes, see Schaumann, E. *Tetrahedron* ***1988***, *44*, 1827.
[2096]Schaumann, E. *Chem. Ber.* ***1976***, *109*, 906.
[2097]With In: Banik, B.K.; Ghatak, A.; Becker, F.F. *J. Chem. Soc., Perkin Trans. 1* ***2000***, 2179.
[2098]For a review, see Hart, D.J.; Ha, D. *Chem. Rev.* ***1989***, *89*, 1447.
[2099]Hegedus, L.S.; McGuire, M.A.; Schultze, L.M.; Yijun, C.; Anderson, O.P. *J. Am. Chem. Soc.* ***1984***, *106*, 2680; Hegedus, L.S.; McGuire, M.A.; Schultze, L.M. *Org. Synth. 65*, 140.
[2100]Hegedus, L.S.; Imwinkelried, R.; Alarid-Sargent, M.; Dvorak, D.; Satoh, Y. *J. Am. Chem. Soc.* ***1990***, *112*, 1109.
[2101]Sharma, S.D.; Pandhi, S.B. *J. Org. Chem.* ***1990***, *55*, 2196.
[2102]Donati, D.; Morelli, C.; Porcheddu, A.; Taddei, M. *J. Org. Chem.* ***2004***, *69*, 9316.
[2103]Taggi, A.E.; Hafez, A.M.; Wack, H.; Young, B.; Drury III, W.J.; Lectka, T. *J. Am. Chem. Soc.* ***2000***, *122*, 7831.
[2104]Hodous, B.L.; Fu, G.C. *J. Am. Chem. Soc.* ***2002***, *124*, 1578.
[2105]Taggi, A.E.; Hafez, A.M.; Wack, H.; Young, B.; Ferraris, D.; Lectka, T. *J. Am. Chem. Soc.* ***2002***, *124*, 6626.
[2106]Shah, M.H.; France, S.; Lectka, T. *Synlett* ***2003***, 1937.
[2107]Clark, A.J.; Battle, G.M.; Bridge, A. *Tetrahedron Lett.* ***2001***, *42*, 4409.
[2108]See Moore, H.W.; Hernandez Jr., L.; Chambers, R. *J. Am. Chem. Soc.* ***1978***, *100*, 2245; Pacansky, J.; Chang, J.S.; Brown, D.W.; Schwarz, W. *J. Org. Chem.* ***1982***, *47*, 2233; Brady, W.T.; Shieh, C.H. *J. Org. Chem.* ***1983***, *48*, 2499.
[2109]For example, see Perelman, M.; Mizsak, S.A. *J. Am. Chem. Soc.* ***1962***, *84*, 4988; Opitz, G.; Koch, J. *Angew. Chem. Int. Ed.* ***1963***, *2*, 152.

The reactive compound chlorosulfonyl isocyanate ($ClSO_2NCO$)[2110] forms β-lactams even with unactivated alkenes,[2111] as well as with imines,[2112] allenes,[2113] conjugated dienes,[2114] and cyclopropenes.[2115] With microwave irradiation, alkyl isocyanates also react.[2116]

α-Diazo ketones react with imines and microwave irradiation to give β-lactams.[2117] Allylic phosphonate esters react with imines, in the presence of a palladium catalyst, to give β-lactams.[2118] Alkynyl reagents, such as $BuC{\equiv}CO{-}Li^+$, react with imines to form β-lactams.[2119] Imines and benzylic halides react to give β-lactams in the presence of CO and a palladium catalyst.[2120] Conjugated amides react with NBS and 20% sodium acetate to give an α-bromo β-lactam.[2121] A different approach to β-lactams heated aziridines with CO and a cobalt catalyst.[2122] Aziridines also react with CO and a dendrimer catalyst to go a β-lactam.[2123]

OS **V**, 673; **VIII**, 3, 216.

ADDITION TO ISOCYANIDES[2124]

Addition to $R{-}{}^+N{\equiv}C^-$ is not a matter of a species with an electron pair adding to one atom and a species without a pair adding to the other, as is addition to the other types of double and triple bonds in this chapter and Chapter 15. In these additions, the electrophile and the nucleophile *both add to the carbon*. No species

[2110]For reviews of this compound, see Kamal, A.; Sattur, P.B. *Heterocycles* ***1987***, *26*, 1051; Szabo, W.A. *Aldrichimica Acta* ***1977***, *10*, 23; Rasmussen, J.K.; Hassner, A. *Chem. Rev.* ***1976***, *76*, 389; Graf, R. *Angew. Chem. Int. Ed.* ***1968***, *7*, 172.

[2111]Graf, R. *Liebigs Ann. Chem.* ***1963***, *661*, 111; Bestian, H. *Pure Appl. Chem.* ***1971***, *27*, 611. See also, Barrett, A.G.M.; Betts, M.J.; Fenwick, A. *J. Org. Chem.* ***1985***, *50*, 169.

[2112]McAllister, M.A.; Tidwell, T.T. *J. Chem. Soc. Perkin Trans. 2* ***1994***, 2239; Sordo, J.A.; González, J.; Sordo, T.L. *J. Am. Chem. Soc.* ***1992***, *114*, 6249.

[2113]Moriconi, E.J.; Kelly, J.F. *J. Org. Chem.* ***1968***, *33*, 3036. See also, Martin, J.C.; Carter, P.L.; Chitwood, J.L. *J. Org. Chem.* ***1971***, *36*, 2225.

[2114]Moriconi, E.J.; Meyer, W.C. *J. Org. Chem.* ***1971***, *36*, 2841; Malpass, J.R.; Tweddle, N.J. *J. Chem. Soc. Perkin Trans. 1* ***1977***, 874.

[2115]Moriconi, E.J.; Kelly, J.F.; Salomone, R.A. *J. Org. Chem.* ***1968***, *33*, 3448.

[2116]Taguchi, Y.; Tsuchiya, T.; Oishi, A.; Shibuya, I. *Bull. Chem. Soc. Jpn.* ***1996***, *69*, 1667.

[2117]Linder, M.R.; Podlech, J. *Org. Lett.* ***2001***, *3*, 1849.

[2118]Torii, S.; Okumoto, H.; Sadakane, M.; Hai, A.K.M.A.; Tanaka, H. *Tetrahedron Lett.* ***1993***, *34*, 6553.

[2119]Shindo, M.; Oya, S.; Sato, Y.; Shishido, K. *Heterocycles* ***1998***, *49*, 113.

[2120]Cho, C.S.; Jiang, L.H.; Shim, S.C. *Synth. Commun.* ***1999***, *29*, 2695.

[2121]Naskar, D.; Roy, S. *J. Chem. Soc., Perkin Trans. 1* ***1999***, 2435.

[2122]Davoli, P.; Forni, A.; Moretti, I.; Prati, F.; Torre, G. *Tetrahedron* ***2001***, *57*, 1801; Davoli, P.; Prati, F. *Heterocycles* ***2000***, *53*, 2379.

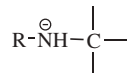
[2123]Lu, S.-M.; Alper, H. *J. Org. Chem.* ***2004***, *69*, 3558.

[2124]For a monograph, see Ugi, I. *Isonitrile Chemistry*, Academic Press, NY, ***1971***. For reviews, see Walborsky, H.M.; Periasamy, M.P., in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C*, pt. 2, Wiley, NY, ***1983***, pp. 835–887; Hoffmann, P.; Marquarding, D.; Kliimann, H.; Ugi, I., in Rappoport, Z. *The Chemistry of the Cyano Group*, Wiley, NY, ***1970***, pp. 853–883.

add to the

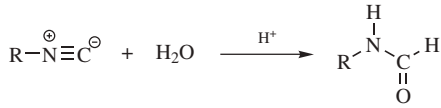
120

nitrogen, which, however, loses its positive charge by obtaining as an unshared pair one of the triple-bond pairs of electrons to give **120**. In most of the reactions considered below, **120** undergoes a further reaction, so the product is of the form.

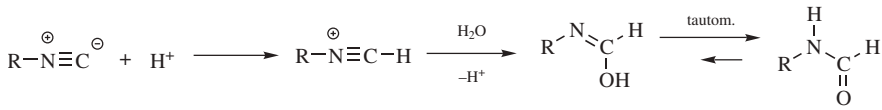


16-97 The Addition of Water to Isocyanides

1/*N*,2/*C*-Dihydro-2/*C*-oxo-biaddition



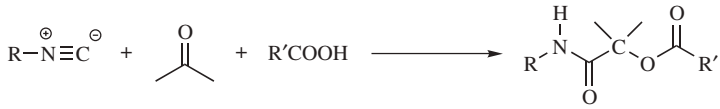
Formamides can be prepared by the acid-catalyzed addition of water to isocyanides. The mechanism is probably[2125]



The reaction has also been carried out under alkaline conditions, with hydroxide in aqueous dioxane.[2126] The mechanism here involves nucleophilic attack by hydroxide at the carbon atom. An intramolecular addition of an alkyne (in an ortho alkynyl phenyl isonitrile) to the carbon of an isonitrile occurred with heating in methanol to give quinoline derivatives.[2127]

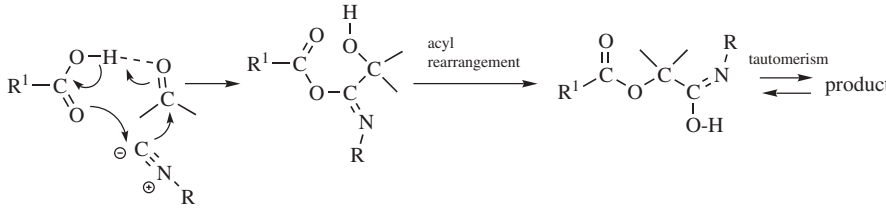
16-98 The Passerini and Ugi Reactions[2128]

1/*N*-Hydro-2/*C*-(α-acyloxyalkyl),2/*C*-oxo-biaddition

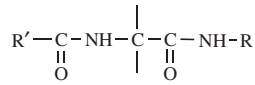


[2125]Drenth, W. *Recl. Trav. Chim. Pays-Bas* ***1962***, *81*, 319; Lim, Y.Y.; Stein, A.R. *Can. J. Chem.* ***1971***, *49*, 2455.
[2126]Cunningham, I.D.; Buist, G.J.; Arkle, S.R. *J. Chem. Soc. Perkin Trans. 2* ***1991***, 589.
[2127]Suginome, M.; Fukuda, T.; Ito, Y. *Org. Lett.* ***1999***, *1*, 1977.
[2128]For reviews, see Ugi, I. *Angew. Chem. Int. Ed.* ***1982***, *21*, 810; Marquarding, D.; Gokel, G.W.; Hoffmann, P.; Ugi, I. in Ugi, I. *Isonitrile Chemistry*, Academic Press, NY, ***1971***, pp. 133–143, Gokel, G.W.; Lüdke, G.; Ugi, I. in Ugi, I. Ref. 936, pp. 145–199, 252–254.

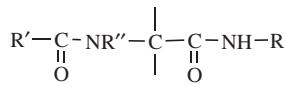
When an isocyanide is treated with a carboxylic acid and an aldehyde or ketone, an α-acyloxy amide is prepared. This is called the *Passerini reaction*. A $SiCl_4$-mediated reaction in the presence of a chiral bis-phosphoramide gives an α-hydroxy amide with good enantioselectivity.[2129] The following mechanism has been postulated for the basic reaction:[2130]



If ammonia or an amine is also added to the mixture (in which case the reaction is known as the *Ugi reaction*, or the *Ugi four-component condensation*, abbreviated 4 CC), the product is the corresponding bis(amide)



(from NH_3) or



(from a primary amine R^2NH_2).

Repetitive Ugi reactions are known.[2131] This product probably arises from a reaction between the carboxylic acid, the isocyanide, and the *imine* formed from the aldehyde or ketone and ammonia or the primary amine. The use of an *N*-protected amino acid[2132] or peptide as the carboxylic acid component and/or the use of an isocyanide containing a C-protected carboxyl group allows the reaction to be used for peptide synthesis.[2133]

[2129]Denmark, S.E.; Fan, Y. *J. Am. Chem. Soc.* ***2003***, *125*, 7825.

[2130]For the effect of high pressure of sterically hindered reactions, see Jenner, G. *Tetrahedron Lett.* ***2000***, *43*, 1235.

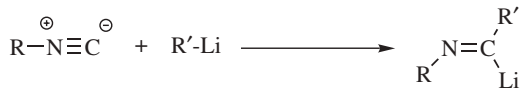
[2131]Constabel, F.; Ugi, I. *Tetrahedron* ***2001***, *57*, 5785.

[2132]See, for example, Godet, T.; Bovin, Y.; Vincent, G.; Merle, D.; Thozet, A.; Ciufolini, M.A. *Org. Lett.* ***2004***, *6*, 3281.

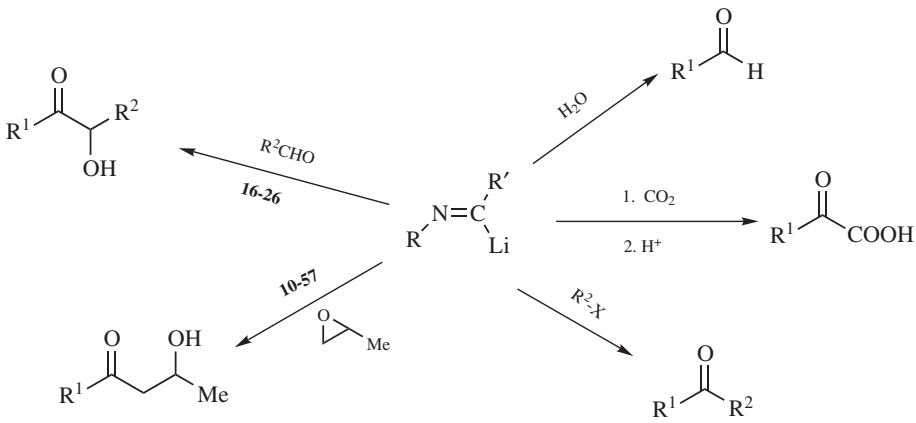
[2133]For reviews, see Ugi, I., in Gross, E.; Meienhofer, J. *The Peptides*, Vol. 2, Academic Press, NY, ***1980***, pp. 365–381, *Intra-Sci. Chem. Rep.* ***1971***, *5*, 229; *Rec. Chem. Prog.* ***1969***, *30*, 289; Gokel, G.W.; Hoffmann, P.; Kleimann, H.; Klusacek, H.; Lüdke, G.; Marquarding, D.; Ugi, I., in Ugi, I. *Isonitrile Chemistry*, Academic Press, NY, ***1971***, pp. 201–215. See also, Kunz, H.; Pfrengle, W. *J. Am. Chem. Soc.* ***1988***, *110*, 651.

16-99 The Formation of Metalated Aldimines

1/1/Lithio-alkyl-addition



Isocyanides that do not contain an α hydrogen react with alkyllithium compounds,[2134] as well as with Grignard reagents, to give lithium (or magnesium) aldimines.[2135] These metalated aldimines are versatile nucleophiles and react with various substrates as follows:



The reaction therefore constitutes a method for converting an organometallic compound R′M to an aldehyde R′CHO (see also, **12-33**), an α-keto acid,[2136] a ketone R′COR (see also, **12-33**), an α-hydroxy ketone, or a β-hydroxy ketone. In each case, the C=N bond is hydrolyzed to a C=O bond (**16-2**).

[2134]For a review of other metallation reactions of isocyanides, see Ito, Y.; Murakami, M. *Synlett* ***1990***, 245.

[2135]Niznik, G.E.; Morrison III, W.H.; Walborsky, H.M. *J. Org. Chem.* ***1974***, *39*, 600; Marks, M.J.; Walborsky, H.M. *J. Org. Chem.* ***1981***, *46*, 5405; ***1982***, *47*, 52. See also, Walborsky, H.M.; Ronman, P. *J. Org. Chem.* ***1978***, *43*, 731. For the formation of zinc aldimines, see Murakami, H.; Ito, H.; Ito, Y. *J. Org. Chem.* ***1988***, *53*, 4158.

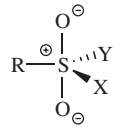
[2136]For a review of the synthesis and properties of α-keto acids, see Cooper, A.J.L.; Ginos, J.Z.; Meister, A. *Chem. Rev.* ***1983***, *83*, 321.

In a related reaction, isocyanides can be converted to aromatic aldimines by treatment with an iron complex followed by irradiation in benzene solution: $RNC + C_6H_6 \rightarrow PhCH{=}NR$.[2137]

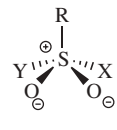
OS **VI**, 751.

NUCLEOPHILIC SUBSTITUTION AT A SULFONYL SULFUR ATOM[2138]

Nucleophilic substitution at RSO_2X is similar to attack at RCOX. Many of the reactions are essentially the same, though sulfonyl halides are less reactive than halides of carboxylic acids.[2139] The mechanisms[2140] are not identical, because a ''tetrahedral'' intermediate in this case (**121**) would have five groups on the central atom. This is possible since sulfur can accommodate up to 12 electrons in its valence shell, but it seems more likely that these mechanisms more closely resemble the S_N2 mechanism, with a trigonal-bipyramidal transition state (**122**). There are two major experimental results leading to this conclusion.



121



122

1. The stereospecificity of this reaction is more difficult to determine than that of nucleophilic substitution at a saturated carbon, where chiral compounds are relatively easy to prepare, but it may be recalled (p. 142) that optical activity is possible in a compound of the form RSO_2X if one oxygen is ^{16}O and the other ^{18}O. When a sulfonate ester possessing this type of chirality was converted to a sulfone with a Grignard reagent (**16-105**), inversion of configuration was found.[2141] This is not incompatible with an intermediate such as **121** but it is also in good accord with an S_N2-like mechanism with backside attack.

[2137]Jones, W.D.; Foster, G.P.; Putinas, J.M. *J. Am. Chem. Soc.* ***1987***, *109*, 5047.

[2138]For a review of mechanisms of nucleophilic substitutions at di-, tri-, and tetracoordinated sulfur atoms, see Ciuffarin, E.; Fava, A. *Prog. Phys. Org. Chem.* ***1968***, *6*, 81.

[2139]For a comparative reactivity study, see Hirata, R.; Kiyan, N.Z.; Miller, J. *Bull. Soc. Chim. Fr.* ***1988***, 694.

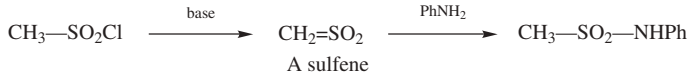
[2140]For a review of mechanisms of nucleophilic substitution at a sulfonyl sulfur, see Gordon, I.M.; Maskill, H.; Ruasse, M. *Chem. Soc. Rev.* ***1989***, *18*, 123.

[2141]Sabol, M.A.; Andersen, K.K. *J. Am. Chem. Soc.* ***1969***, *91*, 3603. See also, Jones, M.R.; Cram, D.J. *J. Am. Chem. Soc.* ***1974***, *96*, 2183.

2. More direct evidence against **121** (though still not conclusive) was found in an experiment involving acidic and basic hydrolysis of aryl arenesulfonates, where it has been shown by the use of ^{18}O that an intermediate like **121** is not reversibly formed, since ester recovered when the reaction was stopped before completion contained no ^{18}O when the hydrolysis was carried out in the presence of labeled water.[2142]

Other evidence favoring the S_N2-like mechanism comes from kinetics and substituent effects.[2143] However, evidence for the mechanism involving **121** is that the rates did not change much with changes in the leaving group[2144] and the ρ values were large, indicating that a negative charge builds up in the transition state.[2145]

In certain cases in which the substrate carries an α hydrogen, there is strong evidence[2146] that at least some of the reaction takes place by an elimination-addition mechanism (E1cB, similar to the one shown on p. 1406), going through a *sulfene* intermediate,[2147] for example, the reaction between methanesulfonyl chloride and aniline.



[2142]Christman, D.R.; Oae, S. *Chem. Ind. (London)* ***1959***, 1251; Oae, S.; Fukumoto, T.; Kiritani, R. *Bull. Chem. Soc. Jpn.* ***1963***, *36*, 346; Kaiser, E.T.; Zaborsky, O.R. *J. Am. Chem. Soc.* ***1968***, *90*, 4626.

[2143]See, for example, Robertson, R.E.; Rossall, B. *Can. J. Chem.* ***1971***, *49*, 1441; Rogne, O. *J. Chem. Soc. B* ***1971***, 1855; *J. Chem. Soc. Perkin Trans. 2* ***1972***, 489; Gnedin, B.G.; Ivanov, S.N.; Spryskov, A.A. *J. Org. Chem. USSR* ***1976***, *12*, 1894; Banjoko, O.; Okwuiwe, R. *J. Org. Chem.* ***1980***, *45*, 4966; Ballistreri, F.P.; Cantone, A.; Maccarone, E.; Tomaselli, G.A.; Tripolone, M. *J. Chem. Soc. Perkin Trans. 2* ***1981***, 438; Suttle, N.A.; Williams, A. *J. Chem. Soc. Perkin Trans. 2* ***1983***, 1563; D'Rozario, P.; Smyth, R.L.; Williams, A. *J. Am. Chem. Soc.* ***1984***, *106*, 5027; Lee, I.; Kang, H.K.; Lee, H.W. *J. Am. Chem. Soc.* ***1987***, *109*, 7472; Arcoria, A.; Ballistreri, F.P.; Spina, E.; Tomaselli, G.A.; Maccarone, E. *J. Chem. Soc. Perkin Trans. 2* ***1988***, 1793; Gnedin, B.G.; Ivanov, S.N.; Shchukina, M.V. *J. Org. Chem. USSR* ***1988***, *24*, 731.

[2144]Ciuffarin, E.; Senatore, L.; Isola, M. *J. Chem. Soc. Perkin Trans. 2* ***1972***, 468.

[2145]Ciuffarin, E.; Senatore, L. *Tetrahedron Lett.* ***1974***, 1635.

[2146]For a review, see Opitz, G. *Angew. Chem. Int. Ed.* ***1967***, *6*, 107. See also, King, J.F.; Lee, T.W.S. *J. Am. Chem. Soc.* ***1969***, *91*, 6524; Skrypnik, Yu.G.; Bezrodnyi, V.P. *Doklad. Chem.* ***1982***, *266*, 341; Farng, L.O.; Kice, J.L. *J. Am. Chem. Soc.* ***1981***, *103*, 1137; Thea, S.; Guanti, G.; Hopkins, A.; Williams, A. *J. Am. Chem. Soc.* ***1982***, *104*, 1128, *J. Org. Chem.* ***1985***, *50*, 5592; Bezrodnyi, V.P.; Skrypnik, Yu.G. *J. Org. Chem. USSR* ***1984***, *20*, 1660, 2349; King, J.F.; Skonieczny, S. *Tetrahedron Lett.* ***1987***, *28*, 5001; Pregel, M.J.; Buncel, E. *J. Chem. Soc. Perkin Trans. 2* ***1991***, 307.

[2147]For reviews of sulfenes, see King, J.F. *Acc. Chem. Res.* ***1975***, *8*, 10; Nagai, T.; Tokura, N. *Int. J. Sulfur Chem. Part B* ***1972***, 207; Truce, W.E.; Liu, L.K. *Mech. React. Sulfur Compd.* ***1969***, *4*, 145; Opitz, G. *Angew. Chem. Int. Ed.* ***1967***, *6*, 107; Wallace, T.J. *Q. Rev. Chem. Soc.* ***1966***, *20*, 67.

In the special case of nucleophilic substitution at a sulfonic ester RSO_2OR', where R′ is alkyl, R′—O cleavage is much more likely than S—O cleavage because the OSO_2R group is such a good leaving group (p. 497).[2148] Many of these reactions have been considered previously (e.g., **10-4**, **10-10**), because they are nucleophilic substitutions at an alkyl carbon atom and not at a sulfur atom. However, when R′ is aryl, then the S—O bond is much more likely to cleave because of the very low tendency aryl substrates have for nucleophilic substitution.[2149]

The order of nucleophilicity toward a sulfonyl sulfur has been reported as $OH^- > RNH_2 > N_3^- > F^- > AcO^- > Cl^- > H_2O > I^-$.[2150] This order is similar to that at a carbonyl carbon (p. $$$). Both of these substrates can be regarded as relatively hard acids, compared to a saturated carbon which is considerably softer and which has a different order of nucleophilicity (p. 494).

16-100 Attack by OH: Hydrolysis of Sulfonic Acid Derivatives

***S*-Hydroxy-de-chlorination**, etc.

$$RSO_2X \xrightarrow[H_2O + H^+]{H_2O \quad \text{or}} RSO_2OH \qquad (X = Cl, OR', NR'_2)$$

Sulfonyl chlorides as well as esters and amides of sulfonic acids can be hydrolyzed to the corresponding acids. Sulfonyl chlorides can by hydrolyzed with water or with an alcohol in the absence of acid or base. Basic catalysis is also used, though of course the salt is the product obtained. Esters are readily hydrolyzed, many with water or dilute alkali. This is the same reaction as **10-4**, and usually involves R′—O cleavage, except when R′ is aryl. However, in some cases retention of configuration has been shown at alkyl R′, indicating S—O cleavage in these cases.[2151] Sulfonamides are generally *not* hydrolyzed by alkaline treatment, not even with hot concentrated alkali. Acids, however, do hydrolyze sulfonamides, but less readily than they do sulfonyl halides or sulfonic esters. Of course, ammonia or the amine appears as the salt. However, sulfonamides can be hydrolyzed with base if the solvent is HMPA.[2152]

Magnesium in methanol has been used to convert sulfonate esters to the parent alcohol.[2153] Likewise, $CeCl_3 \cdot 7\,H_2O$—NaI in acetonitrile converted aryl tosylates to the parent phenol derivative.[2154]

[2148]A number of sulfonates in which R contains a branching, for example, $Ph_2C(CF_3)SO_2OR'$, can be used to ensure that there will be no S—O cleavage: Netscher, T.; Prinzbach, H. *Synthesis* ***1987***, 683.
[2149]See Tagaki, W.; Kurusu, T.; Oae, S. *Bull. Chem. Soc. Jpn.* ***1969***, *42*, 2894.
[2150]Kice, J.L.; Kasperek, G.J.; Patterson, D. *J. Am. Chem. Soc.* ***1969***, *91*, 5516; Rogne, O. *J. Chem. Soc. B* ***1970***, 1056; Kice, J.L.; Legan, E. *J. Am. Chem. Soc.* ***1973***, *95*, 3912.
[2151]Chang, F.C. *Tetrahedron Lett.* ***1964***, 305.
[2152]Cuvigny, T.; Larchevêque, M. *J. Organomet. Chem.* ***1974***, *64*, 315.
[2153]Sridhar, M.; Kumar, B.A.; Narender, R. *Tetrahedron Lett.* ***1998***, *39*, 2847.
[2154]Reddy, G.S.; Mohan, G.H.; Iyengar, D.S. *Synth. Commun.* ***2000***, *30*, 3829.

OS **I**, 14; **II**, 471; **III**, 262; **IV**, 34; **V**, 406; **VI**, 652, 727. Also see, OS **V**, 673; **VI**, 1016.

16-101 Attack by OR. Formation of Sulfonic Esters

***S*-Alkoxy-de-chlorination**, and so on

$$RSO_2Cl + R'OH \xrightarrow{\text{base}} RSO_2OR'$$

$$RSO_2NR_2'' + R'OH \xrightarrow{\text{base}} RSO_2OR' + NHR_2''$$

Sulfonic esters are most frequently prepared by treatment of the corresponding sulfonyl halides with alcohols in the presence of a base. This procedure is the most common method for the conversion of alcohols to tosylates, brosylates, and similar sulfonic esters. Both R and R′ may be alkyl or aryl. The base is often pyridine, which functions as a nucleophilic catalyst,[2155] as in the similar alcoholysis of carboxylic acyl halides (**16-61**). Propylenediamines have also been used to facilitate tosylation of an alcohol.[2156] Silver oxide has been used, in conjunction with KI.[2157] Primary alcohols react the most rapidly, and it is often possible to sulfonate selectively a primary OH group in a molecule that also contains secondary or tertiary OH groups. The reaction with sulfonamides has been much less frequently used and is limited to *N*,*N*-disubstituted sulfonamides; that is, R— may not be hydrogen. However, within these limits it is a useful reaction. The nucleophile in this case is actually RO^-. However, R′ may be hydrogen (as well as alkyl) if the nucleophile is a phenol, so that the product is RSO_2OAr. Acidic catalysts are used in this case.[2158] Sulfonic acids have been converted directly to sulfonates by treatment with triethyl or trimethyl orthoformate, $HC(OR)_3$, without catalyst or solvent;[2159] and with a trialkyl phosphite, $P(OR)_3$.[2160]

Mono-tosylation of a 1,2-diol was achieved using tosyl chloride and triethylamine, with a tin oxide catalyst.[2161]

OS **I**, 145; **III**, 366; **IV**, 753; **VI**, 56, 482, 587, 652; **VII**, 117; **66**, 1; **68**, 188. Also see, OS **IV**, 529; **VI**, 324, 757; **VII**, 495; **VIII**, 568.

[2155]Rogne, O. *J. Chem. Soc. B* ***1971***, 1334. See also, Litvinenko, M.; Shatskaya, V.A.; Savelova, V.A. *Doklad. Chem.* ***1982***, *265*, 199.
[2156]Yoshida, Y; Shimonishi, K.; Sakakura, Y.; Okada, S.; Aso, N.; Tanabe, Y. *Synthesis* ***1999***, 1633.
[2157]Bouzide, A.; LeBerre, N.; Sauvé, G. *Tetrahedron Lett.* ***2001***, *42*, 8781.
[2158]Klamann, D.; Fabienke, E. *Chem. Ber.* ***1960***, *93*, 252.
[2159]Padmapriya, A.A.; Just, G.; Lewis, N.G. *Synth. Commun.* ***1985***, *15*, 1057.
[2160]Karaman, R.; Leader, H.; Goldblum, A.; Breuer, E. *Chem. Ind. (London)* ***1987***, 857.
[2161]Martinelli, M.J.; Vaidyanathan, R.; Khau, V.V. *Tetrahedron Lett.* ***2000***, *41*, 3773; Bucher, B.; Curran, D.P. *Tetrahedron Lett.* ***2000***, *41*, 9617.

16-102 Attack by Nitrogen: Formation of Sulfonamides

S-Amino-de-chlorination

$$RSO_2Cl + NH_3 \longrightarrow RSO_2NH_2$$

The treatment of sulfonyl chlorides with ammonia or amines is the usual way of preparing sulfonamides. Primary amines give *N*-alkyl sulfonamides, and secondary amines give *N*,*N*-dialkyl sulfonamides. The reaction is the basis of the *Hinsberg test* for distinguishing between primary, secondary, and tertiary amines. *N*-Alkyl sulfonamides, having an acidic hydrogen, are soluble in alkali, while *N*,*N*-dialkyl sulfonamides are not. Since tertiary amines are usually recovered unchanged, primary, secondary, and tertiary amines can be told apart. However, the test is limited for at least two reasons.[2162] (*1*) Many *N*-alkyl sulfonamides in which the alkyl group has six or more carbons are insoluble in alkali, despite their acidic hydrogen,[2163] so that a primary amine may appear to be a secondary amine. (*2*) If the reaction conditions are not carefully controlled, tertiary amines may not be recovered unchanged.[2160]

A primary or a secondary amine can be protected by reaction with phenacylsulfonyl chloride, ($PhCOCH_2SO_2Cl$), to give a sulfonamide, $RNHSO_2CH_2COPh$ or $R_2NSO_2CH_2COPh$.[2164] The protecting group can be removed when desired with zinc and acetic acid. Sulfonyl chlorides react with azide ion to give sulfonyl azides (RSO_2N_3).[2165] Chlorothioformates, ROC(=S)Cl, react with triethylamine to give the *N*,*N*-diethylthioamide.[2166]

A quite different synthesis of sulfonamides treated allyltributyltin with PhI=NTs, in the presence of copper (II) triflate.[2167] another alternative method treats silyl enol ethers with sulfur dioxide, and subsequent and reaction with a secondary amine gave the β-sulfonamido ester.[2168]

OS **IV**, 34, 943; **V**, 39, 179, 1055; **VI**, 78, 652; **VII**, 501; **VIII**, 104. See also, OS **VI**, 788.

16-103 Attack by Halogen: Formation of Sulfonyl Halides

S-Halo-de-hydroxylation

$$RSO_2OH + PCl_5 \longrightarrow RSO_2Cl$$

[2162]For directions for performing and interpreting the Hinsberg test, see Gambill, C.R.; Roberts, T.D.; Shechter, H. *J. Chem. Educ.* ***1972***, *49*, 287.
[2163]Fanta, P.E.; Wang, C.S. *J. Chem. Educ.* ***1964***, *41*, 280.
[2164]Hendrickson, J.B.; Bergeron R. *Tetrahedron Lett.* ***1970***, 345.
[2165]For an example, see Regitz, M.; Hocker, J.; Liedhegener, A. *Org. Synth.* ***V***, 179.
[2166]Milan, D.S.; Prager, R.H. *Aust. J. Chem.* ***1999***, *52*, 841.
[2167]Kim, D.Y.; Kim. H.S.; Choi, Y.J.; Mang, J.Y.; Lee, K. *Synth. Commun.* ***2001***, *31*, 2463.
[2168]Bouchez, L.C.; Dubbaka, S.R.; Urks, M.; Vogel, P. *J. Org. Chem.* ***2004***, *69*, 6413.

This reaction, parallel with **16-79**, is the standard method for the preparation of sulfonyl halides. Also used are PCl_3 and $SOCl_2$, and sulfonic acid salts can also serve as substrates. Cyanuric acid (2,4,6-trichloro[1,3,5]triazene) also serves as a chlorinating agent.[2169] Sulfonyl bromides and iodides have been prepared from sulfonyl hydrazides ($ArSO_2NHNH_2$, themselves prepared by **16-102**) by treatment with bromine or iodine.[2170] Sulfonyl fluorides are generally prepared from the chlorides, by halogen exchange.[2171]

OS **I**, 84; **IV**, 571, 693, 846, 937; **V**, 196. See also, OS **VII**, 495.

16-104 Attack by Hydrogen: Reduction of Sulfonyl Chlorides

_S_-Hydro-de-chlorination or **_S_-Dechlorination**

$$2\ RSO_2Cl + Zn \longrightarrow (RSO_2)_2Zn \xrightarrow{H+} 2\ RSO_2H$$

Sulfinic acids can be prepared by reduction of sulfonyl chlorides. Though mostly done on aromatic sulfonyl chlorides, the reaction has also been applied to alkyl compounds. Besides zinc, sodium sulfite, hydrazine, sodium sulfide, and other reducing agents have been used. For reduction of sulfonyl chlorides to thiols, see **19-78**.

OS **I**, 7, 492; **IV**, 674.

16-105 Attack by Carbon: Preparation of Sulfones

_S_-Aryl-de-chlorination

$$ArSO_2Cl + Ar'MgX \longrightarrow ArSO_2Ar'$$

Grignard reagents convert aromatic sulfonyl chlorides or aromatic sulfonates to sulfones. Organolithium reagents react with sulfonyl fluorides at −78°C to give the corresponding sulfone.[2172] Aromatic sulfonates have also been converted to sulfones with organolithium compounds,[2173] with aryltin compounds,[2174] and with alkyl halides and Zn metal.[2175] Vinylic and allylic sulfones have been prepared by treatment of sulfonyl chlorides with a vinylic or allylic stannane and a palladium complex catalyst.[2176] Alkynyl sulfones can be prepared by treatment of sulfonyl chlorides with trimethylsilylalkynes, with an $AlCl_3$ catalyst.[2177] Note that

[2169]Blotny, G. *Tetrahedron Lett.* ***2003***, *44*, 1499.
[2170]Poshkus, A.C.; Herweh, J.E.; Magnotta, F.A. *J. Org. Chem.* ***1963***, *28*, 2766; Litvinenko, L.M.; Dadali, V.A.; Savelova, V.A.; Krichevtsova, T.I. *J. Gen. Chem. USSR* ***1964***, *34*, 3780.
[2171]See Bianchi, T.A.; Cate, L.A. *J. Org. Chem.* ***1977***, *42*, 2031, and references cited therein.
[2172]Frye, L.L.; Sullivan, E.L.; Cusack, K.P.; Funaro, J.M. *J. Org. Chem*, ***1992***, *57*, 697.
[2173]Baarschers, W.H. *Can. J. Chem.* ***1976***, *54*, 3056.
[2174]Neumann, W.P.; Wicenec, C. *Chem. Ber.* ***1993***, *126*, 763.
[2175]Sun, X.; Wang, L.; Zhang, Y. *Synth. Commun.* ***1998***, *28*, 1785.
[2176]Labadie, S.S. *J. Org. Chem.* ***1989***, *54*, 2496.
[2177]See Waykole, L.; Paquette, L.A. *Org. Synth. 67*, 149.

trifluoromethylsulfones were converted to methyl sulfones by reaction with methylmagneisum bromide.[2178]

Arylboronic acids (p. 815) react with sulfonyl chlorides in the presence of $PdCl_2$ to give the corresponding sulfone.[2179] arylboronic acids also react with sulfinate anions (RSO_2Na) in the presence of $Cu(OAc)_2$ to give the sulfone.[2180]

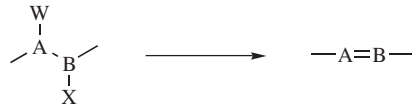
OS **VIII**, 281.

[2178]Steensma, R.W.; Galabi, S.; Tagat, J.R.; McCombie, S.W. *Tetrahedron Lett.* ***2001***, *42*, 2281.
[2179]Bandgar, B.P.; Bettigeri, S.V.; Phopase, J. *Org. Lett.* ***2004***, *6*, 2105.
[2180]Beaulieu, C.; Guay, D.; Wang, Z.; Evans, D.A. *Tetrahedron Lett.* ***2004***, *45*, 3233.

CHAPTER 17

Eliminations

When two groups are lost from adjacent atoms so that a new double[1]



(or triple) bond is formed the reaction is called β-*elimination*; one atom is the α, the other the β atom. In an α elimination, both groups are lost from the same atom to give a carbene (or a nitrene):

In a γ elimination, a three-membered ring is formed:

Some of these processes were discussed in Chapter 10. Another type of elimination involves the expulsion of a fragment from within a chain or ring (X–Y–Z → X–Z + Y). Such reactions are called *extrusion reactions*. This chapter discusses β-elimination and (beginning on p. 1553) extrusion reactions; however, β-elimination in which both X and W are hydrogens are oxidation reactions and are treated in Chapter 19.

[1]See Williams, J.M.J. *Preparation of Alkenes, A Practical Approach*, Oxford University Press, Oxford, ***1996***.

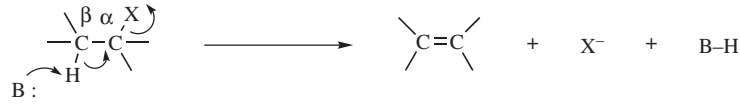
March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Sixth Edition, by Michael B. Smith and Jerry March

MECHANISMS AND ORIENTATION

β-Elimination reactions may be divided into two types; one type taking place largely in solution, the other (pyrolytic eliminations) mostly in the gas phase. In the reactions in solution, one group leaves with its electrons and the other without, the latter most often being hydrogen. In these cases, we refer to the former as the leaving group or nucleofuge. For pyrolytic eliminations, there are two principal mechanisms, one pericyclic and the other a free-radical pathway. A few photochemical eliminations are also known (the most important is Norrish type II cleavage of ketones, p. 344), but these are not generally of synthetic importance[2] and will not be discussed further. In most β-eliminations the new bonds are C=C or C≡C; our discussion of mechanisms is largely confined to these cases.[3] Mechanisms in solution (E2, E1)[4] and E1cB are discussed first.

The E2 Mechanism

In the E2 mechanism (elimination, bimolecular), the two groups depart simultaneously, with the proton being pulled off by a base:



The mechanism thus takes place in one step and kinetically is second order: first order in substrate and first order in base. An *ab initio* study has produced a model for the E2 transition state geometry.[5] The IUPAC designation is $A_{xH}D_HD_N$, or more generally (to include cases where the electrofuge is not hydrogen), $A_nD_ED_N$. It is analogous to the S_N2 mechanism (p. 426) and often competes with it. With respect

[2]For synthetically useful examples of Norrish type II cleavage, see Neckers, D.C.; Kellogg, R.M.; Prins, W.L.; Schoustra, B. *J. Org. Chem.* ***1971***, *36*, 1838.

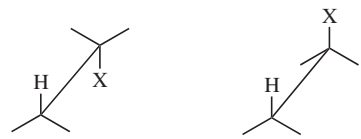
[3]For a monograph on elimination mechanisms, see Saunders, Jr., W.H.; Cockerill, A.F. *Mechanisms of Elimination Reactions*, Wiley, NY, ***1973***. For reviews, see Gandler, J.R., in Patai, S. *Supplement A: The Chemistry of Double-Bonded Functional Groups*, Vol. 2, pt. 1, Wiley, NY, ***1989***, pp. 733–797; Aleskerov, M.A.; Yufit, S.S.; Kucherov, V.F. *Russ. Chem. Rev.* ***1978***, *47*, 134; Cockerill, A.F.; Harrison, R.G., in Patai, S. *The Chemistry of Functional Groups, Supplement A* pt. 1, Wiley, NY, ***1977***, pp. 153–221; Willi, A.V. *Chimia*, ***1977***, *31*, 93; More O'Ferrall, R.A., in Patai, S. *The Chemistry of the Carbon-Halogen Bond*, pt. 2, Wiley, NY, ***1973***, pp. 609–675; Cockerill, A.F., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9, Elsevier, NY, ***1973***, pp. 163–372; Saunders, Jr., W.H. *Acc. Chem. Res.* ***1976***, *9*, 19; Stirling, C.J.M. *Essays Chem.* ***1973***, *5*, 123; Bordwell, F.G. *Acc. Chem. Res.* ***1972***, *5*, 374; Fry, A. *Chem. Soc. Rev.* ***1972***, *1*, 163; LeBel, N.A. *Adv. Alicyclic Chem.* ***1971***, *3*, 195; Bunnett, J.F. *Surv. Prog. Chem.* ***1969***, *5*, 53; in Patai, S. *The Chemistry of Alkenes*, Vol. 1, Wiley, NY, ***1964***, the articles by Saunders, Jr., W.H. pp. 149–201 (eliminations in solution); and by Maccoll, A. pp. 203–240 (pyrolytic eliminations); Köbrich, G. *Angew. Chem. Int. Ed.* ***1965***, *4*, 49, pp. 59–63 (for the formation of triple bonds).

[4]Thibblin, A. *Chem. Soc. Rev.* ***1993***, *22*, 427.

[5]Schrøder, S.; Jensen, F. *J. Org. Chem.* ***1997***, *62*, 253.

to the substrate, the difference between the two pathways is whether the species with the unshared pair attacks the carbon (and thus acts as a nucleophile) or the hydrogen (and thus acts as a base). As in the case of the S_N2 mechanism, the leaving group may be positive or neutral and the base may be negatively charged or neutral.

Among the evidence for the existence of the E2 mechanism are (*1*) the reaction displays the proper second-order kinetics; (*2*) when the hydrogen is replaced by deuterium in second-order eliminations, there is an isotope effect of from 3 to 8, consistent with breaking of this bond in the rate-determining step.[6] However, neither of these results alone could prove an E2 mechanism, since both are compatible with other mechanisms also (e.g., see E1cB p. 1488). The most compelling evidence for the E2 mechanism is found in stereochemical studies.[7] As will be illustrated in the examples below, the E2 mechanism is stereospecific: The five atoms involved (including the base) in the transition state must be in one plane. There are two ways for this to happen. The H and X may be



A **B**

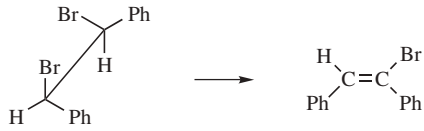
trans to one another (**A**) with a dihedral angle of 180°, or they may be cis (**B**) with a dihedral angle of 0°.[8] Conformation **A** is called *anti-periplanar*, and this type of elimination, in which H and X depart in opposite directions, is called *anti-elimination*. Conformation **B** is *syn-periplanar*, and this type of elimination, with H and X leaving in the same direction, is called *syn-elimination*. Many examples of both kinds have been discovered. In the absence of special effects (discussed below) anti-elimination is usually greatly favored over syn-elimination, probably because **A** is a staggered conformation (p. 199) and the molecule requires less energy to reach this transition state than it does to reach the eclipsed transition state **B**. A few of the many known examples of predominant or exclusive anti-elimination follow.

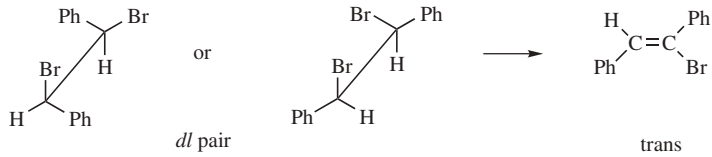
[6]See, for example, Saunders, Jr., W.H.; Edison, D.H. *J. Am. Chem. Soc.* ***1960***, *82*, 138; Shiner, Jr., V.J.; Smith, M.L. *J. Am. Chem. Soc.* ***1958***, *80*, 4095; ***1961***, *83*, 593. For a review of isotope effects in elimination reactions, see Fry, A. *Chem. Soc. Rev.* ***1972***, *1*, 163.

[7]For reviews, see Bartsch, R.A.; Závada, J. *Chem. Rev.* ***1980***, *80*, 453; Coke, J.L. *Sel. Org. Transform.* ***1972***, *2*, 269; Sicher, J. *Angew. Chem. Int. Ed.* ***1972***, *11*, 200; *Pure Appl. Chem.* ***1971***, *25*, 655; Saunders, Jr., W.H.; Cockerill, A.F. *Mechanisms of Elimination Reactions*, Wiley, NY, ***1973***, pp. 105–163; Cockerill, A.F., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9, Elsevier, NY, ***1973***, pp. 217–235; More O'Ferrall, R.A., in Patai, S. *The Chemistry of the Carbon–Halogen Bond*, pt. 2, Wiley, NY, ***1973***, pp. 630–640.

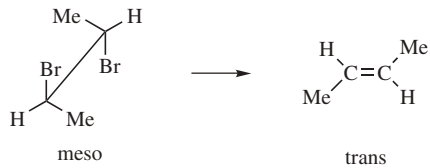
[8]DePuy, C.H.; Morris, G.F.; Smith, J.S.; Smat, R.J. *J. Am. Chem. Soc.* ***1965***, *87*, 2421.

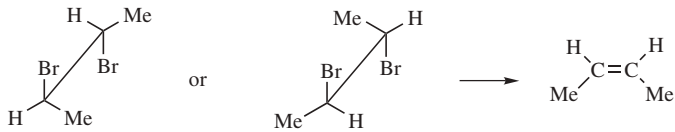
1. Elimination of HBr from *meso*-1,2-dibromo-1,2-diphenylethane gave *cis*-2-bromostilbene, while the (+) or (−) isomer gave the trans alkene. This stereospecific result, which





was obtained in 1904,[9] demonstrates that in this case elimination is anti. Many similar examples have been discovered since. Obviously, this type of experiment need not be restricted to compounds that have a meso form. Anti-elimination requires that an erythro *dl* pair (or either isomer) give the cis alkene, and the threo *dl* pair (or either isomer) give the trans isomer, and this has been found many times. Anti-elimination has also been demonstrated in cases where the electrofuge is not hydrogen. In the reaction of 2,3-dibromobutane with iodide ion, the two bromines are removed (**17-22**). In this case, the meso compound gave the trans alkene and the *dl* pair the cis:[10]

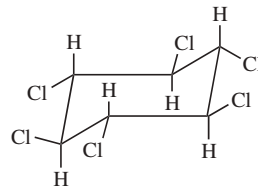




2. In open-chain compounds, the molecule can usually adopt that conformation in which H and X are anti-periplanar. However, in cyclic systems this is not always the case. There are nine stereoisomers of 1,2,3,4,5,6-hexachlorocyclohexane: seven meso forms and a *dl* pair (see p. 165). Four of the meso compounds and the *dl* pair (all that were then known) were subjected to

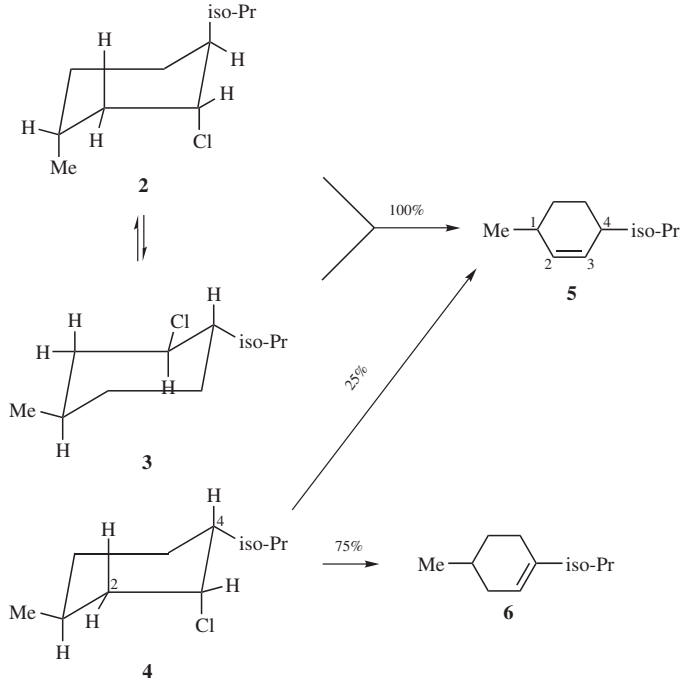
[9]Pfeiffer, P. *Z. Phys. Chem.* ***1904***, *48*, 40.
[10]Winstein, S.; Pressman, D.; Young, W.G. *J. Am. Chem. Soc.* ***1939***, *61*, 1645.

elimination of HCl. Only one of these (**1**) has no Cl trans to an H. Of the other isomers, the fastest elimination rate was about three times as fast as the slowest, but the rate for **1** was 7000 times slower than that of the slowest of the other isomers.[11] This result demonstrates that with these compounds anti elimination is greatly favored over syn elimination, although the latter must be taking place on **1**, very slowly, to be sure.



1

3. The preceding result shows that elimination of HCl in a six-membered ring proceeds best when the H and X are trans to each other. However, there is an additional restriction. Adjacent trans groups on a six-membered ring can be diaxial or diequatorial (p. 204) and the molecule is generally free to adopt either conformation, although one may have a higher energy than the other. Anti-periplanarity of the leaving groups requires that they be diaxial, even if this is the conformation of higher energy. The results with menthyl and neomenthyl chlorides are easily



2 **3** **4** **5** **6**

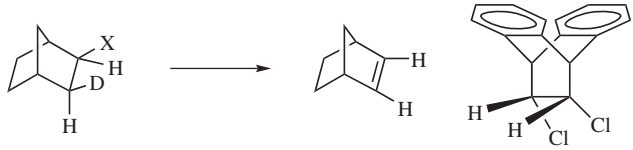
[11]Cristol, S.J.; Hause, N.L.; Meek, J.S. *J. Am. Chem. Soc.* ***1951***, *73*, 674.

interpretable on this basis. Menthyl chloride has two chair conformations, **2** and **3**. Compound **3**, in which the three substituents are all equatorial, is the more stable. The more stable chair conformation of neomenthyl chloride is **4**, in which the chlorine is axial; there are axial hydrogens on both C-2 and C-4. The results are: neomenthyl chloride gives rapid E2 elimination and the alkene produced is predominantly **6** (**6/5** ratio is 3:1) in accord with Zaitsev's rule (p. 767). Since an axial hydrogen is available on both sides, this factor does not control the direction of elimination and Zaitsev's rule is free to operate. However, for menthyl chloride, elimination is much slower and the product is entirely the anti-Zaitsev, **5**. It is slow because the unfavorable conformation **2** has to be achieved before elimination can take place, and the product is **5** because only on this side is there an axial hydrogen.[12]

4. That anti-elimination also occurs in the formation of triple bonds is shown by elimination from *cis*- and *trans*-HOOC–CH=C(Cl)COOH. In this case, the product in both cases is HOOCC≡CCOOH, but the trans isomer reacts ∼50 times faster than the cis compound.[13]

Some examples of syn-elimination have been found in molecules where H and X could not achieve an anti-periplanar conformation.

1. The deuterated norbornyl bromide (**7**, X = Br) gave 94% of the product containing no deuterium.[14] Similar results were obtained with other leaving groups and with bicyclo[2.2.2] compounds.[15] In these cases the exo X group cannot achieve a dihedral angle of 180° with the endo β hydrogen because of the rigid structure of the molecule. The dihedral angle here is ∼120°. These leaving groups prefer syn-elimination with a dihedral angle of ∼0° to anti-elimination with an angle of ∼120°.



7 **8**

[12]Hughes, E.D.; Ingold, C.K.; Rose, J.B. *J. Chem. Soc.* ***1953***, 3839.

[13]Michael, A. *J. Prakt. Chem.* ***1895***, *52*, 308. See also, Marchese, G.; Naso, F.; Modena, G. *J. Chem. Soc. B* ***1968***, 958.

[14]Kwart, H.; Takeshita, T.; Nyce, J.L. *J. Am. Chem. Soc.* ***1964***, *86*, 2606.

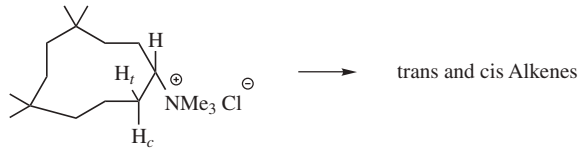
[15]For example, see Bird, C.W.; Cookson, R.C.; Hudec, J.; Williams, R.O. *J. Chem. Soc.* ***1963***, 410; Stille, J.K.; Sonnenberg, F.M.; Kinstle, T.H. *J. Am. Chem. Soc.* ***1966***, *88*, 4922; Coke, J.L.; Cooke, Jr., M.P. *J. Am. Chem. Soc.* ***1967***, *89*, 6701; DePuy, C.H.; Naylor, C.G.; Beckman, J.A. *J. Org. Chem.* ***1970***, *35*, 2750; Brown, H.C.; Liu, K. *J. Am. Chem. Soc.* ***1970***, *92*, 200; Sicher, J.; Pánkova, M.; Závada, J.; Kniežo, L.; Orahovats, A. *Collect. Czech. Chem. Commun.* ***1971***, *36*, 3128; Bartsch, R.A.; Lee, J.G. *J. Org. Chem.* ***1991***, *56*, 212, 2579.

2. Molecule **8** is a particularly graphic example of the need for a planar transition state. In **8**, each Cl has an adjacent hydrogen trans to it, and if planarity of leaving groups were not required, anti-elimination could easily take place. However, the crowding of the rest of the molecule forces the dihedral angle to be ~120°, and elimination of HCl from **8** is much slower than from corresponding nonbridged compounds.[16] (Note that syn elimination from **8** is even less likely than anti-elimination.) Syn-elimination can take place from the trans isomer of **8** (dihedral angle ~0°); this isomer reacted about eight times faster than **8**.[16]

The examples so far given illustrate two points. (*1*) Anti-elimination *requires* a dihedral angle of 180°. When this angle cannot be achieved, anti-elimination is greatly slowed or prevented entirely. (*2*) For the simple systems so far discussed syn-elimination is not found to any significant extent unless anti elimination is greatly diminished by failure to achieve the 180° angle.

As noted in Chapter 4 (p. 223), six-membered rings are the only ones among rings of 4–13 members in which strain-free anti-periplanar conformations can be achieved. It is not surprising, therefore, that syn elimination is least common in six-membered rings. Cooke and Coke subjected cycloalkyltrimethylammonium hydroxides to elimination (**17-7**) and found the following percentages of syn-elimination with ring size: four-membered, 90%; five-membered, 46%; six-membered, 4% seven-membered, 31 to 37%.[17] Note that the NMe_3^+ group has a greater tendency to syn-elimination than do other common leaving groups, such as OTs, Cl, and Br.

Other examples of syn-elimination have been found in medium-ring compounds, where both cis and trans alkenes are possible (p. 184). As an illustration, we can look at experiments performed by, Svoboda, and Sicher.[18] These workers subjected 1,1,4,4-tetramethyl-7-cyclodecyltrimethylammonium chloride (**9**) to



9

elimination and obtained mostly *trans*-, but also some *cis*-tetramethylcyclodecenes as products. (Note that *trans*-cyclodecenes, although stable, are less stable than the cis isomers). In order to determine the stereochemistry of the reaction, they repeated the elimination, this time using deuterated substrates. They found that

[16]Cristol, S.J.; Hause, N.L. *J. Am. Chem. Soc*. ***1952***, *74*, 2193.
[17]Cooke, Jr., M.P.; Coke, J.L. *J. Am. Chem. Soc*. ***1968***, *90*, 5556. See also, Coke, J.L.; Smith, G.D.; Britton, Jr., G.H. *J. Am. Chem. Soc*. ***1975***, *97*, 4323.
[18]Závada, J.; Svoboda, M.; Sicher, J. *Tetrahedron Lett*. ***1966***, 1627; *Collect. Czech. Chem. Commun*. ***1968***, *33*, 4027.

when **9** was deuterated in the trans position ($H_t = D$), there was a substantial isotope effect in the formation of *both* cis and trans alkenes, but when **9** was deuterated in the cis position ($H_c = D$), there was *no* isotope effect in the formation of either alkene. Since an isotope effect is expected for an E2 mechanism,[19] these results indicated that *only* the trans hydrogen (H_t) was lost, whether the product was the cis or the trans isomer.[20] This in turn means that *the cis isomer must have been formed by anti-elimination and the trans isomer by syn-elimination*. (Anti-elimination could take place from approximately the conformation shown, but for syn elimination the molecule must twist into a conformation in which the C–H_t and C–NMe_3^+ bonds are syn-periplanar.) This remarkable result, called the *syn–anti dichotomy*, has also been demonstrated by other types of evidence.[21] The fact that syn-elimination in this case predominates over anti (as indicated by the formation of trans isomer in greater amounts than cis) has been explained by conformational factors.[22] The syn–anti dichotomy has also been found in other medium-ring systems (8–12 membered),[23] although the effect is greatest for 10-membered rings. With leaving groups,[24] the extent of this behavior decreases in the order $^+NMe_3 > OTs > Br > Cl$, which parallels steric requirements. When the leaving group is uncharged, syn-elimination is favored by strong bases and by weakly ionizing solvents.[25]

Syn-elimination and the syn—anti dichotomy have also been found in open-chain systems, although to a lesser extent than in medium-ring compounds. For example, in the conversion of 3-hexyl-4-*d*-trimethylammonium ion to 3-hexene with potassium *sec*-butoxide, ~67% of the reaction followed the syn–anti dichotomy.[26] In general syn-elimination in open-chain systems is only important in cases where certain types of steric effect are present. One such type is compounds in which substituents are found on both the β′ and the γ carbons (the unprimed letter refers to the branch in which the elimination takes place). The factors that cause these results are not

[19]Other possible mechanisms, such as E1cB (p. 1488) or α′,β elimination (p. 1524), were ruled out in all these cases by other evidence.

[20]This conclusion has been challenged by Coke, J.L. *Sel. Org. Transform* ***1972***, *2*, 269.

[21]Sicher, J.; Závada, J. *Collect. Czech. Chem. Commun*. ***1967***, *32*, 2122; Závada, J.; Sicher, J. *Collect. Czech. Chem. Commun*. ***1967***, *32*, 3701. For a review, see Bartsch, R.A.; Závada, J. *Chem. Rev*. ***1980***, *80*, 453.

[22]For discussions, see Bartsch, R.A.; Závada, J. *Chem. Rev*. ***1980***, *80*, 453; Coke, J.L. *Sel. Org. Transform*. ***1972***, *2*, 269; Sicher, J. *Angew. Chem. Int. Ed*. ***1972***, *11*, 200; *Pure Appl. Chem*. ***1971***, *25*, 655.

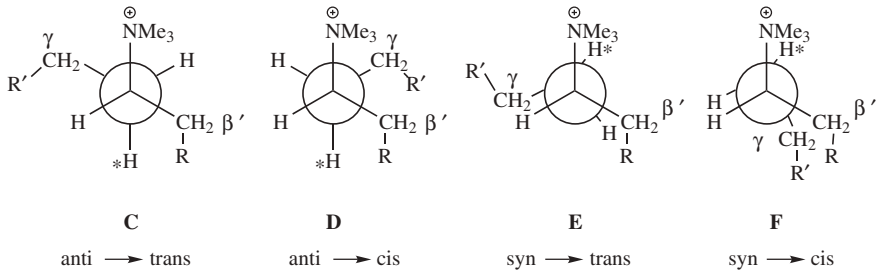
[23]For example, see Coke, J.L.; Mourning, M.C. *J. Am. Chem. Soc*. ***1968***, *90*, 5561, where the experiment was performed on cyclooctyltrimethylammonium hydroxide, and *trans*-cyclooctene was formed by a 100% syn mechanism, and *cis*-cyclooctene by a 51% syn and 49% anti mechanism.

[24]For examples with other leaving groups, see Sicher, J.; Jan, G.; Schlosser, M. *Angew. Chem. Int. Ed*. ***1971***, *10*, 926; Závada, J.; Pánková, M. *Collect. Czech. Chem. Commun*. ***1980***, *45*, 2171, and references.cited therein.

[25]See, for example, Sicher, J.; Závada, J. *Collect. Czech. Chem. Commun*. ***1968***, *33*, 1278.

[26]Bailey, D.S.; Saunders Jr., W.H. *J. Am. Chem. Soc*. ***1970***, *92*, 6904. For other examples of syn-elimination and the syn-anti dichotomy in open-chain systems, see Pánková, M.; Vítek, A.; Vasíšková, S.; Řeřicha, R.; Závada, J. *Collect. Czech. Chem. Commun*. ***1972***, *37*, 3456; Schlosser, M.; An, T.D. *Helv. Chim. Acta* ***1979***, *62*, 1194; Sugita, T.; Nakagawa, J.; Nishimoto, K.; Kasai, Y.; Ichikawa, K. *Bull. Chem. Soc. Jpn*. ***1979***, *52*, 871; Pánková, M.; Kocián, O.; Krupička, J.; Závada, J. *Collect. Czech. Chem. Commun*. ***1983***, *48*, 2944.

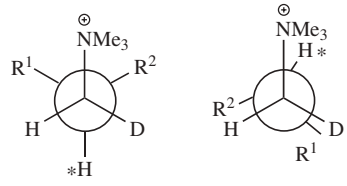
completely understood, but the following conformational effects have been proposed as a partial explanation.[27] The two anti- and two syn-periplanar conformations are, for a quaternary ammonium salt:



C **D** **E** **F**

anti → trans anti → cis syn → trans syn → cis

In order for an E2 mechanism to take place, a base must approach the proton marked *. In **C**, this proton is shielded on both sides by R and R′. In **D**, the shielding is on only one side. Therefore, when anti-elimination does take place in such systems, it should give more cis product than trans. Also, when the normal anti elimination pathway is hindered sufficiently to allow the syn pathway to compete, the anti → trans route should be diminished more than the anti → cis route. When syn-elimination begins to appear, it seems clear that **E**, which is less eclipsed than **F**, should be the favored pathway and syn-elimination should generally give the trans isomer. In general, deviations from the syn–anti dichotomy are greater on the trans side than on the cis. Thus, trans alkenes are formed partly or mainly by syn-elimination, but cis alkenes are formed entirely by anti-elimination. Predominant syn-elimination has also been found in compounds of the form $R^1R^2CHCHDNMe_3^+$, where R^1 and R^2 are both bulky.[28] In this case, the conformation leading to syn-elimination (**H**) is also less strained than **G**, which gives anti-elimination. The **G** compound has three bulky groups (including NMe_3^+) in the *gauche* position to each other.

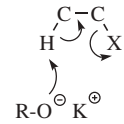


G **H**

It was mentioned above that weakly ionizing solvents promote syn-elimination when the leaving group is uncharged. This is probably caused by ion pairing, which

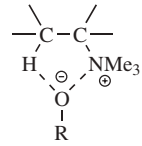
[27]Bailey, D.S.; Saunders, Jr., W.H. *J. Am. Chem. Soc.* ***1970***, *92*, 6904; Chiao, W.; Saunders, Jr., W.H. *J. Am. Chem. Soc.* ***1977***, *99*, 6699.
[28]Dohner, B.R.; Saunders Jr., W.H. *J. Am. Chem. Soc.* ***1986***, *108*, 245.

is greatest in nonpolar solvents.[29] Ion pairing can



10

cause syn-elimination with an uncharged leaving group by means of the transition state shown in **10**. This effect was graphically illustrated by elimination from 1,1,4,4-tetramethyl-7-cyclodecyl bromide.[30] The ratio of syn-to-anti-elimination when this compound was treated with *t*-BuOK in the nonpolar benzene was 55.0. But when the crown ether dicyclohexano-18-crown-6 was added (this compound selectively removes K^+ from the *t*-BuO^- K^+ ion pair and thus leaves *t*-BuO^- as a free ion), the syn/anti ratio decreased to 0.12. Large decreases in the syn/anti ratio on addition of the crown ether were also found with the corresponding tosylate and with other nonpolar solvents.[31] However, with positively charged leaving groups the effect is reversed. Here, ion pairing *increases* the amount of anti-elimination.[32] In this case, a relatively free base (e.g., PhO^-) can be attracted to the leaving group, putting it in a favorable position for attack on the syn β hydrogen, while ion pairing would reduce this attraction.



We can conclude that anti-elimination is generally favored in the E2 mechanism, but that steric (inability to form the anti-periplanar transition state), conformational, ion pairing, and other factors cause syn-elimination to intervene (and even predominate) in some cases.

[29]For reviews of ion pairing in this reaction, see Bartsch, R.A.; Závada, J. *Chem. Rev.* ***1980***, *80*, 453; Bartsch, R.A. *Acc. Chem. Res*. ***1975***, *8*, 239.

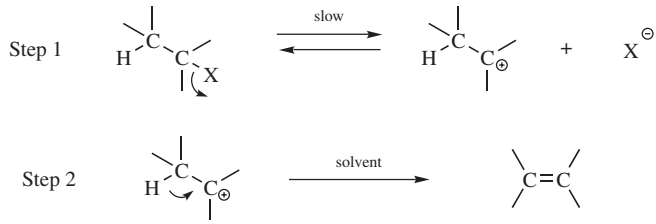
[30]Svoboda, M.; Hapala, J.; Závada, J. *Tetrahedron Lett*. ***1972***, 265.

[31]For other examples of the effect of ion pairing, see Bayne, W.F.; Snyder, E.I. *Tetrahedron Lett*. ***1971***, 571; Bartsch, R.A.; Wiegers, K.E. *Tetrahedron Lett*. ***1972***, 3819; Fiandanese, V.; Marchese, G.; Naso, F.; Sciacovelli, *O. J. Chem. Soc. Perkin Trans. 2* ***1973***, 1336; Borchardt, J.K.; Swanson, J.C.; Saunders, Jr., W.H. *J. Am. Chem. Soc*. ***1974***, *96*, 3918; Mano, H.; Sera, A.; Maruyama, K. *Bull. Chem. Soc. Jpn*. ***1974***, *47*, 1758; Závada, J.; Pánková, M.; Svoboda, M. *Collect. Czech. Chem. Commun*. ***1976***, *41*, 3778; Baciocchi, E.; Ruzziconi, R.; Sebastiani, G.V. *J. Org. Chem*. ***1979***, *44*, 3718; Croft, A.P.; Bartsch, R.A. *Tetrahedron Lett*. ***1983***, *24*, 2737; Kwart, H.; Gaffney, A.H.; Wilk, K.A. *J. Chem. Soc. Perkin Trans. 2* ***1984***, 565.

[32]Borchardt, J.K.; Saunders Jr., W.H. *J. Am. Chem. Soc*. ***1974***, *96*, 3912.

The E1 Mechanism

The E1 mechanism is a two-step process in which the rate-determining step is ionization of the substrate to give a carbocation that rapidly loses a β proton to a base, usually the solvent:

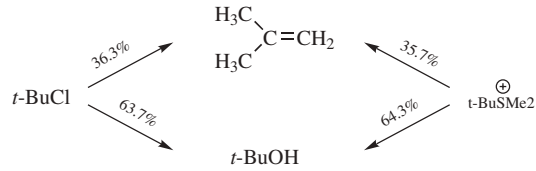


The IUPAC designation is $D_N + D_E$ (or $D_N + D_H$). This mechanism normally operates without an *added* base. Just as the E2 mechanism is analogous to and competes with the S_N2, so is the E1 mechanism related to the S_N1. In fact, the first step of the E1 is exactly the same as that of the S_N1 mechanism. The second step differs in that the solvent pulls a proton from the β carbon of the carbocation rather than attacking it at the positively charged carbon, as in the S_N1 process. In a pure E1 reaction (without ion pairs, etc.), the product should be completely nonstereospecific, since the carbocation is free to adopt its most stable conformation before giving up the proton.

Some of the evidence for the E1 mechanism is as follows:

1. The reaction exhibits first-order kinetics (in substrate) as expected. Of course, the solvent is not expected to appear in the rate equation, even if it were involved in the rate-determining step (p. 316), but this point can be easily checked by adding a small amount of the conjugate base of the solvent. It is generally found that such an addition does not increase the rate of the reaction. If this more powerful base does not enter into the rate-determining step, it is unlikely that the solvent does. An example of an E1 mechanism with a rate-determining second step (proton transfer) has been reported.[33]
2. If the reaction is performed on two molecules that differ only in the leaving group (e.g., *t*-BuCl and *t*-$BuSMe_2^+$), the rates should obviously be different, since they depend on the ionizing ability of the molecule. However, once the carbocation is formed, if the solvent and the temperature are the same, it should suffer the same fate in both cases, since the nature of the leaving group does not affect the second step. This means that *the ratio of elimination to substitution should be the same*. The compounds mentioned in the example were solvolyzed at 65.3°C in 80% aqueous ethanol with the following results:[34]

[33]Baciocchi, E.; Clementi, S.; Sebastiani, G.V.; Ruzziconi, R. *J. Org. Chem.* ***1979***, *44*, 32.
[34]Cooper, K.A.; Hughes, E.D.; Ingold, C.K.; MacNulty, B.J. *J. Chem. Soc.* ***1948***, 2038.



Although the rates were greatly different (as expected with such different leaving groups), the product ratios were the same, within 1%. If this had taken place by a second-order mechanism, the nucleophile would not be expected to have the same ratio of preference for attack at the β hydrogen compared to attack at a *neutral* chloride as for attack at the β hydrogen compared to attack at a *positive* SMe_2 group.

3. Many reactions carried out under first-order conditions on systems where E2 elimination is anti proceed quite readily to give alkenes where a cis hydrogen must be removed, often in preference to the removal of a trans hydrogen. For example, menthyl chloride (**2**, p. 1482), which by the E2 mechanism gave only **5**, under E1 conditions gave 68% **6** and 32% **5**, since the steric nature of the hydrogen is no longer a factor here, and the more stable alkene (Zaitsev's rule, p. 1482) is predominantly formed.

4. If carbocations are intermediates, we should expect rearrangements with suitable substrates. These have often been found in elimination reactions performed under E1 conditions.

E1 reactions can involve ion pairs, just as is true for S_N1 reactions (p. 437).[35] This effect is naturally greatest for nondissociating solvents: It is least in water, greater in ethanol, and greater still in acetic acid. It has been proposed that the ion-pair mechanism (p. 439) extends to elimination reactions too, and that the S_N1, S_N2, E1, and E2 mechanisms possess in common an ion-pair intermediate, at least occasionally.[36]

The E1cB Mechanism[37]

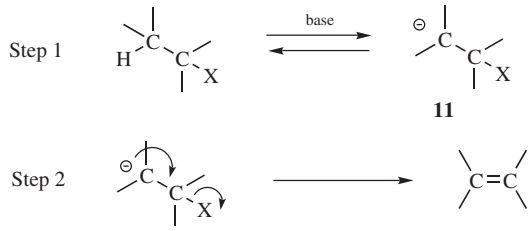
In the E1 mechanism, X leaves first and then H. In the E2 mechanism, the two groups leave at the same time. There is a third possibility: The H leaves first,

[35]Cocivera, M.; Winstein, S. *J. Am. Chem. Soc*. ***1963***, *85*, 1702; Smith, S.G.; Goon, D.J.W. *J. Org. Chem*. ***1969***, *34*, 3127; Bunnett, J.F.; Eck, D.L. *J. Org. Chem*. ***1971***, *36*, 897; Sridharan, S.; Vitullo, V.P. *J. Am. Chem. Soc*. ***1977***, *99*, 8093; Seib. R.C.; Shiner Jr., V.J.; Sendijarević, V.; Humski, K. *J. Am. Chem. Soc*. ***1978***, *100*, 8133; Jansen, M.P.; Koshy, K.M.; Mangru, N.N.; Tidwell, T.T. *J. Am. Chem. Soc*. ***1981***, *103*, 3863; Coxon, J.M.; Simpson, G.W.; Steel, P.J.; Whiteling, S.C. *Tetrahedron* ***1984***, *40*, 3503; Thibblin, A. *J. Am. Chem. Soc*. ***1987***, *109*, 2071; *J. Phys. Org. Chem*. ***1989***, *2*, 15.

[36]Sneen, R.A. *Acc. Chem. Res*. ***1973***, *6*, 46; Thibblin, A.; Sidhu, H. *J. Chem. Soc. Perkin Trans. 2* ***1994***, 1423. See, however, McLennan, D.J. *J. Chem. Soc. Perkin Trans. 2* ***1972***, 1577.

[37]For reviews, see Cockerill, A.F.; Harrison, R.G., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9, Elsevier, NY, ***1973***, pp. 158–178; Hunter, D.H. *Intra-Sci. Chem. Rep*. ***1973***, *7(3)*, 19; McLennan, D.J. *Q. Rev. Chem. Soc*. ***1967***, *21*, 490. For a general discussion, see Koch, H.F. *Acc. Chem. Res*. ***1984***, *17*, 137.

and then the X. This is a two-step process, called the E1cB *mechanism*,[38] or the *carbanion mechanism*, since the intermediate is a carbanion:



11

The name E1cB comes from the fact that it is the conjugate base of the substrate that is giving up the leaving group (see the S_N1cB mechanism, p. 521). The IUPAC designation is $A_nD_E + D_N$ or $A_{xh}D_H + D_N$ (see p. 420). We can distinguish three limiting cases: (*1*) The carbanion returns to starting material faster than it forms product: step 1 is reversible; step 2 is slow. (*2*) Step 1 is the slow step, and formation of product is faster than return of the carbanion to starting material. In this case, step 1 is essentially irreversible. (*3*) Step 1 is rapid, and the carbanion goes slowly to product. This case occurs only with the most stable carbanions. Here, too, step 1 is essentially irreversible. These cases have been given the designations: (*1*) $(E1cB)_R$, (*2*) $(E1cB)_I$ (or $E1cB_{irr}$), and (*3*) $(E1)_{anion}$. Their characteristics are listed in Table 17.1.[39] Investigations of the reaction order are generally not very useful (except for case 3, which is first order), because cases 1 and 2 are second order and thus difficult or impossible to distinguish from the E2 mechanism by this procedure.[40] We would expect the greatest likelihood of finding the E1cB mechanism in substrates that have (a) a poor nucleofuge and (b) an acidic hydrogen, and most investigations have concerned such substrates. The following is some of the evidence in support of the E1cB mechanism:

1. The first step of the $(E1cB)_R$ mechanism involves a reversible exchange of protons between the substrate and the base. In that case, if deuterium is present in the base, recovered starting material should contain deuterium. This was found to be the case in the treatment of $Cl_2C{=}CHCl$ with NaOD to give $ClC{\equiv}CCl$. When the reaction was stopped before completion, there *was*

[38]For a discussion, see Ryberg, P.; Matsson, O. *J. Org. Chem.* ***2002***, *67*, 811.

[39]This table, which appears in Cockerill, A.F.; Harrison, R.G. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9, Elsevier, NY, ***1973***, p. 161, was adapted from a longer one, in Bordwell, F.G. *Acc. Chem. Res.* ***1972***, *5*, 374, see p. 375.

[40]$(E1cB)_I$ cannot be distinguished from E2 by this means, because it has the identical rate law: Rate = k[substrate][B^-]. The rate law for $(E1cB)_R$ is different: Rate = k[substrate][B^-]/[BH], but this is often not useful because the only difference is that the rate is also dependent (inversely) on the concentration of the conjugate acid of the base, and this is usually the solvent, so that changes in its concentration cannot be measured.

TABLE 17.1. Kinetic Predictions for Base-Induced β-Eliminations[39]

Mechanism	Kinetic[a] Order	β-Hydrogen Exchange Faster Than Elimination	General or Specific Base Catalysis	k_H/k_D	Electron Withdrawal at Cβ[d]	Electron release at Cα[d]	Leaving-Group Isotope Effect or Element Effect
$(E1)_{anion}$	1	Yes	General[c]	1.0	Rate decrease	Rate increase	Substantial
$(E1cB)_R$	2	Yes	Specific	1.0	Small rate increase	Small rate increase	Substantial
$(E1cB)_{ip}$	2	No	General[e]	1.0 → 1.2	Small rate increase	Small rate increase	Substantial
$(E1cB)_I$	2	No	General	2 → 8	Rate increase	Little effect	Small to negligible
E2[b]	2	No	General	2 → 8	Rate increase	Small rate increase	Small

[a]All mechanism exhibit first-order kinetics in substrate.
[b]Only transition states with considerable carbanion character considered in this table.
[c]Specific base catalysis predicted if extent of substrate ionization reduced from almost complete.
[d]Effect on rate assuming no change in mechanism is caused; steric factors upon substitution at Cα and rise to Cβ have not been considered. The rate reductions are geared to substituent effects such as those giving rise to Hammett reaction constants on β- and α-aryl substitution.
[e]Depends on whether an ion pair assists in removal of leaving group.

deuterium in the recovered alkene.[41] A similar result was found for pentahaloethanes.[42] These substrates are relatively acidic. In both cases the electron-withdrawing halogens increase the acidity of the hydrogen, and in the case of trichloroethylene there is the additional factor that a hydrogen on an sp^2 carbon is more acidic than one on an sp^3 carbon (p. 388). Thus, the E1cB mechanism is more likely to be found in eliminations yielding triple bonds than in those giving double bonds. Another likely place for the E1cB mechanism should be in reaction of a substrate like $PhCH_2CH_2Br$, since the carbanion is stabilized by resonance with the phenyl group. Nevertheless, no deuterium exchange was found here.[43] If this type of evidence is a guide, then it may be inferred that the $(E1cB)_R$ mechanism is quite rare, at least for eliminations with common leaving groups such as Br, Cl, or OTs, which yield C=C double bonds.

[41]Houser, J.J.; Bernstein, R.B.; Miekka, R.G.; Angus, J.C. *J. Am. Chem. Soc.* ***1955***, *77*, 6201.
[42]Hine, J.; Wiesboeck, R.; Ghirardelli, R.G. *J. Am. Chem. Soc.* ***1961***, *83*, 1219; Hine, J.; Wiesboeck, R.; Ramsay, O.B. *J. Am. Chem. Soc.* ***1961***, *83*, 1222.
[43]Skell, P.S.; Hauser, C.R. *J. Am. Chem. Soc.* ***1945***, *67*, 1661.

2. When the reaction

was carried out in water containing acetohydroxamate buffers, a plot of the rate against the buffer concentration was curved and the rate leveled off at high buffer concentrations, indicating a change in rate-determining step.[44] This rules out an E2 mechanism, which has only one step.[45] When D_2O was used instead of H_2O as solvent, there was an initial inverse solvent isotope effect of 7.7 (the highest inverse solvent isotope effect yet reported).

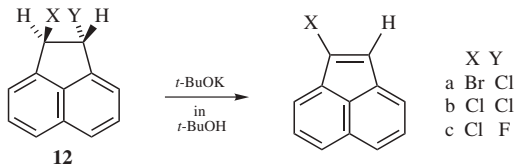
That is, the reaction took place faster in D_2O than in H_2O. This is compatible only with an E1cB mechanism in which the proton-transfer step is not entirely rate determining. The isotope effect arises from a partitioning of the carbanion intermediate **11**. This intermediate either can go to product or it can revert to starting compound, which requires taking a proton from the solvent. In D_2O, the latter process is slower (because the O–D bond of D_2O cleaves less easily than the O–H bond of H_2O), reducing the rate at which **11** returns to starting compound. With the return reaction competing less effectively, the rate of conversion of **11** to product is increased.

3. We have predicted that the E1cB mechanism would most likely be found with substrates containing acidic hydrogens and poor leaving groups. Compounds of the type ZCH_2CH_2OPh, where Z is an electron-withdrawing group (e.g., NO_2, SMe_2^+, $ArSO_2$, CN, COOR), belong to this category, because OPh is a very poor leaving group (p. 438). There is much evidence to show that the mechanism here is indeed E1cB.[46] Isotope effects, measured for $MeSOCD_2CH_2OPh$ and $Me_2S^+CD_2CH_2OPh$ with NaOD in D_2O, are ~0.7. This is compatible with an $(E1cB)_R$ mechanism, but not with an E2 mechanism for which an isotope effect of perhaps 5 might be expected (of course, an E1 mechanism is precluded by the extremely poor nucleofugal ability of OPh). The fact that k_H/k_D is less than the expected value of 1 is attributable to solvent and secondary isotope effects. Among other evidence for an E1cB mechanism in these systems is that changes in the identity of Z had a dramatic effect on the relative rates: a span of 10^{11} between NO_2 and COO^-. Note that elimination from substrates of the type $RCOCH_2CH_2Y$ is the reverse of Michael-type addition to C=C bonds. We have seen (p. $$$) that such addition involves initial attack by a nucleophile Y and subsequent attack by a proton. Thus the initial loss of a proton from substrates of this type (i.e., an E1cB mechanism) is in accord with the principle of microscopic

[44]Keeffe, J.R.; Jencks, W.P. *J. Am. Chem. Soc.* ***1983***, *105*, 265.
[45]For a borderline E1cB–E2 mechanism, see Jia, Z.S.; Rudziń sci, J.; Panethy, P.; Thibblin, A. *J. Org. Chem.* ***2002***, *67*, 177.
[46]Cann, P.F.; Stirling, C.J.M. *J. Chem. Soc. Perkin Trans. 2* ***1974***, 820. For other examples; see Fedor, L.R. *J. Am. Chem. Soc.* ***1969***, *91*, 908; More O'Ferrall, R.A.; Slae, S. *J. Chem. Soc. B* ***1970***, 260; Kurzawa, J.; Leffek, K.T. *Can. J. Chem.* ***1977***, *55*, 1696.

reversibility.[47] It may also be recalled that benzyne formation (p. 859) can occur by such a process. It has been suggested that all base-initiated eliminations wherein the proton is activated by a strong electron-withdrawing group are E1cB reactions,[48] but there is evidence that this is not the case that when there is a good nucleofuge, the mechanism is E2 even when strong electron-withdrawing groups are present.[49] On the other hand, Cl^- has been found to be a leaving group in an E1cB reaction.[50]

Of the three cases of the E1cB mechanism, the one most difficult to distinguish from E2 is $(E1cB)_I$. One way to make this distinction is to study the effect of a change in leaving group. This was done in the case of the three acenaphthylenes **12**, where it was found that (*1*) the three rates were fairly similar, the largest being only about



12

four times that of the smallest, and (*2*) in compound *c* (X = Cl, Y = F), the only product contained Cl and no F, that is, only the poorer nucleofuge F departed while Cl remained.[51] Result (*1*) rules out all the E1cB mechanisms except $(E1cB)_I$, because the others should all have considerable leaving group effects (Table 17.1). An ordinary E2 mechanism should also have a large leaving group effect, but an E2 mechanism with substantial carbanionic character (see the next section) might not. However, no E2 mechanism can explain result (*2*), which can be explained by the fact that an a Cl is more effective than an a F in stabilizing the planar carbanion that remains when the proton is lost. Thus (as in the somewhat similar case of aromatic nucleophilic substitution, see p. 868), when X^- leaves in the second step, the one that leaves is not determined by which is the better nucleofuge, but by which has had its β hydrogen removed.[52] Additional evidence for the existence of the

[47]Patai, S.; Weinstein, S.; Rappoport, Z. *J. Chem. Soc.* ***1962***, 1741. See also, Hilbert, J.M.; Fedor, L.R. *J. Org. Chem.* ***1978***, *43*, 452.

[48]Bordwell, F.G.; Vestling, M.M.; Yee, K.C. *J. Am. Chem. Soc.* ***1970***, *92*, 5950; Bordwell, F.G. *Acc. Chem. Res.* ***1972***, *5*, 374.

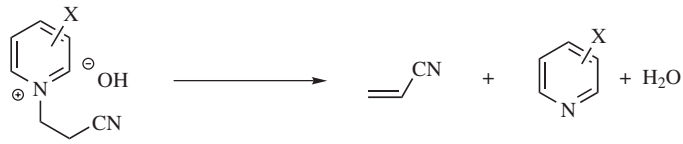
[49]Marshall, D.R.; Thomas, P.J.; Stirling, C.J.M. *J. Chem. Soc. Perkin Trans. 2* ***1977***, 1898, 1914; Banait, N.S.; Jencks, W.P. *J. Am. Chem. Soc.* ***1990***, *112*, 6950.

[50]Ölwegård, M.; McEwen, I.; Thibblin, A.; Ahlberg, P. *J. Am. Chem. Soc.* ***1985***, *107*, 7494.

[51]Baciocchi, E.; Ruzziconi, R.; Sebastiani, G.V. *J. Org. Chem.* ***1982***, *47*, 3237.

[52]For other evidence for the existence of the $(E1cB)_I$ mechanism, see Bordwell, F.G.; Vestling, M.M.; Yee, K.C. *J. Am. Chem. Soc.* ***1970***, *92*, 5950; Fedor, L.R.; Glave, W.R. *J. Am. Chem. Soc.* ***1971***. *93*, 985; Redman, R.P.; Thomas, P.J.; Stirling, C.J.M. *J. Chem. Soc. Perkin Trans. 2* ***1978***. 1135; Thibblin, A. *Chem. Scr.* ***1980***, *15*, 121; Carey, E.; More O'Ferrall, R.A.; Vernon, N.M. *J. Chem. Soc. Perkin Trans. 2* ***1982*** 1581; Baciocchi, E.; Ruzziconi, R. *J. Org. Chem.* ***1984***, *49*, 3395; Jarczewski, A.; Waligorska, M.; Leffek, K.T. *Can. J Chem.* ***1985***, *63*, 1194; Gula, M.J.; Vitale, D.E.; Dostal, J.M.; Trometer, J.D.; Spencer, T.A. *J. Am. Chem. Soc.* ***1988*** *110*, 4400; Garay, R.O.; Cabaleiro, M.C. *J. Chem. Res. (S)*, ***1988***, 388; Gandler, J.R.; Storer, J.W.; Ohlberg, D.A.A. *J. Am. Chem. Soc.* ***1990***, *112*, 7756.

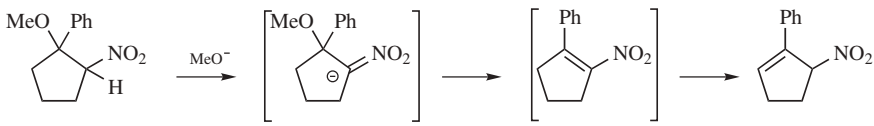
$(E1cB)_I$ mechanism was the observation of a change in the rate-determining step in the elimination reaction of *N*-(2-cyanoethyl)pyridinium



13

ions **13**, treated with base, when X was changed.[53] Once again, the demonstration that two steps are involved precludes the one-step E2 mechanism.

4. An example of an $(E1)_{anion}$ mechanism has been found with the substrate **14**, which when treated with methoxide ion undergoes elimination to **16**, which is unstable under the reaction conditions and rearranges as

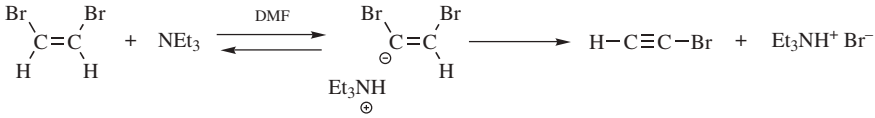


14 **15** **16**

shown.[54] Among the evidence for the proposed mechanism in this case were kinetic and isotope-effect results, as well as the spectral detection of **15**.[55]

5. In many eliminations to form C=O and C≡N bonds the initial step is loss of a positive group (normally a proton) from the oxygen or nitrogen. These may also be regarded as E1cB processes.

There is evidence that some E1cB mechanisms can involve carbanion ion pairs, for example,[56]



This case is designated $(E1cB)_{ip}$; its characteristics are shown in Table 17.1.

[53]Bunting, J.W.; Toth, A.; Heo, C.K.M.; Moors, R.G. *J. Am. Chem. Soc.* ***1990***, *112*, 8878. See also, Bunting, J.W.; Kanter, J.P. *J. Am. Chem. Soc.* ***1991***, *113*, 6950.

[54]Bordwell, F.G.; Yee, K.C.; Knipe, A.C. *J. Am. Chem. Soc.* ***1970***, *92*, 5945.

[55]For other examples of this mechanism, see Berndt, A. *Angew. Chem. Int. Ed.* ***1969***, *8*, 613; Albeck, M.; Hoz, S.; Rappoport, Z. *J. Chem. Soc. Perkin Trans. 2* ***1972***, 1248; ***1975***, 628.

[56]Kwok, W.K.; Lee, W.G.; Miller, S.I. *J. Am. Chem. Soc.* ***1969***, *91*, 468. See also Lord, E.; Naan, M.P.; Hall, C.D. *J. Chem. Soc. B* ***1971***, 220; Rappoport, Z.; Shohamy, E. *J. Chem. Soc. B* ***1971***, 2060; Fiandanese, V.; Marchese, G.; Naso, F. *J. Chem. Soc., Chem. Commun.* ***1972***, 250; Koch, H.F.; Dahlberg, D.B.; Toczko, A.G.; Solsky, R.L. *J. Am. Chem. Soc.* ***1973***, *95*, 2029; Hunter, D.H.; Shearing, D.J. *J. Am. Chem. Soc.* ***1973***, *95*, 8333; Thibblin, A.; Ahlberg, P. *J. Am. Chem. Soc.* ***1979***, *101*, 7311; Petrillo, G.; Novi, M.; Garbarino, G.; Dell'Erba, C.; Mugnoli, A. *J. Chem. Soc. Perkin Trans. 2* ***1985***, 1291.

The E1-E2-E1cB Spectrum

In the three mechanisms so far considered, the similarities are greater than the differences. In each case, there is a leaving group that comes off with its pair of electrons and another group (usually hydrogen) that comes off without them. The only difference is in the order of the steps. It is now generally accepted that there is a spectrum of mechanisms ranging from one extreme, in which the leaving group departs well before the proton (pure E1), to the other extreme, in which the proton comes off first and then, after some time, the leaving group follows (pure E1cB). The *pure* E2 case would be somewhere in the middle, with both groups leaving simultaneously. However, most E2 reactions are not exactly in the middle, but somewhere to one side or the other. For example, the nucleofuge might depart just before the proton. This case may be described as an E2 reaction with a small amount of E1 character. The concept can be expressed by the question: In the transition state, which bond (C–H or C–X) has undergone more cleavage?[57]

One way to determine just where a given reaction stands on the E1-E2-E1cB spectrum is to study isotope effects, which ought to tell something about the behavior of bonds in the transition state.[58] For example, $CH_3CH_2NMe_3^+$ showed a nitrogen isotope effect (k^{14}/k^{15}) of 1.017, while $PhCH_2CH_2NMe_3^+$ gave a corresponding value of 1.009.[59] It would be expected that the phenyl group would move the reaction toward the E1cB side of the line, which means that for this compound the C–N bond is not as greatly broken in the transition state as it is for the unsubstituted one. The isotope effect bears this out, for it shows that in the phenyl compound, the mass of the nitrogen has less effect on the reaction rate than it does in the unsubstituted compound. Similar results have been obtained with SR_2^+ leaving groups by the use of $^{32}S/^{34}S$ isotope effects[60] and with Cl ($^{35}Cl/^{37}Cl$).[61] The position of reactions along the spectrum has also been studied from the other side of the newly forming double bond by the use of H/D and H/T isotope effects,[62] although interpretation of these results is clouded by the fact that β hydrogen isotope effects are expected to change smoothly from small to large to small again as the degree of transfer of the

[57]For discussions, see Cockerill, A.F.; Harrison, R.G., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9, Elsevier, NY, ***1973***, pp. 178–189; Saunders, Jr., W.H. *Acc. Chem. Res*. ***1976***, *9*, 19; Bunnett, J.F. *Surv. Prog. Chem*. ***1969***, *5*, 53; Saunders, Jr., W.H.; Cockerill, A.F. *Mechanisms of Elimination Reactions*, Wiley, NY, ***1973***, pp. 47–104; Bordwell, F.G. *Acc. Chem. Res*. ***1972***, *5*, 374.

[58]For a review, see Fry, A. *Chem. Soc. Rev*. ***1972***, *1*, 163. See also Hasan, T.; Sims, L.B.; Fry, A. *J. Am. Chem. Soc*. ***1983***, *105*, 3967; Pulay, A.; Fry, A. *Tetrahedron Lett*. ***1986***, *27*, 5055.

[59]Ayrey, G.; Bourns, A.N.; Vyas, V.A. *Can. J. Chem*. ***1963***, *41*, 1759. Also see, Simon, H.; Müllhofer, G. *Chem. Ber*. ***1963***, *96*, 3167; ***1964***, *97*, 2202; *Pure Appl. Chem*. ***1964***, *8*, 379, 536; Smith, P.J.; Bourns, A.N. *Can. J. Chem*. ***1970***, *48*, 125.

[60]Wu, S.; Hargreaves, R.T.; Saunders Jr., W.H. *J. Org. Chem*. ***1985***, *50*, 2392, and references cited therein.

[61]Grout, A.; McLennan, D.J.; Spackman, I.H. *J. Chem. Soc. Perkin Trans. 2* ***1977***, 1758.

[62]For example, see Hodnett, E.M.; Sparapany, J.J. *Pure Appl. Chem*. ***1964***, *8*, 385, 537; Finley, K.T.; Saunders, Jr., W.H. *J. Am. Chem. Soc*. ***1967***, *89*, 898; Ghanbarpour, A.; Willi, A.V. *Liebigs Ann. Chem*. ***1975***, 1295; Simon, H.; Müllhofer, G. *Chem. Ber*. ***1964***, *97*, 2202; Thibblin, A. *J. Am. Chem. Soc*. ***1988***, *110*, 4582; Smith, P.J.; Amin, M. *Can. J. Chem*. ***1989***, *67*, 1457.

β hydrogen from the β carbon to the base increases[63] (recall, p. $$$, that isotope effects are greatest when the proton is half-transferred in the transition state), by the possibility of secondary isotope effects (e.g., the presence of a β deuterium or tritium may cause the leaving group to depart more slowly), and by the possibility of tunneling.[64] Other isotope-effect studies have involved labeled a or β carbon, labeled a hydrogen, or labeled base.[58]

Another way to study the position of a given reaction on the spectrum involves the use of β-aryl substitution. Since a positive Hammet ρ value is an indication of a negatively charged transition state, the ρ value for substituted β-aryl groups should increase as a reaction moves from E1- to E1cB-like along the spectrum. This has been shown to be the case in a number of studies;[65] for example, ρ values of $ArCH_2CH_2X$ increase as the leaving-group ability of X decreases. A typical set of ρ values was X = I, 2.07; Br, 2.14; Cl, 2.61; SMe_2^+, 2.75; F, 3.12.[66] As we have seen, decreasing leaving-group ability correlates with increasing E1cB character.

Still another method measures volumes of activation.[67] These are negative for E2 and positive for E1cB mechanisms. Measurement of the activation volume therefore provides a continuous scale for deciding just where a reaction lies on the spectrum.

The E2C Mechanism[68]

Certain alkyl halides and tosylates undergo E2 eliminations faster when treated with such weak bases as Cl^- in polar aprotic solvents or PhS^- than with the usual E2 strong bases, such as RO^- in ROH.[69] In order to explain these results, Parker

[63]There is controversy as to whether such an effect has been established in this reaction: See Cockerill, A.F. *J. Chem. Soc. B* ***1967***, 964; Blackwell, L.F. *J. Chem. Soc. Perkin Trans. 2* ***1976***, 488.

[64]For examples of tunneling in elimination reactions, see Miller, D.J.; Saunders, Jr., W.H. *J. Org. Chem.* ***1981***, *46*, 4247 and previous papers in this series. See also, Shiner, Jr., V.J.; Smith, M.L. *J. Am. Chem. Soc.* ***1961***, *83*, 593; McLennan, D.J. *J. Chem. Soc. Perkin Trans. 2* ***1977***, 1753; Fouad, F.M.; Farrell, P.G. *Tetrahedron Lett.* ***1978***, 4735; Koth, H.F.; McLennan, D.J.; Koch, J.G.; Tumas, W.; Dobson, B.; Koch, J.G. *J. Am. Chem. Soc.* ***1983***, *105*, 1930; Kwart, H.; Wilk, K.A. *J. Org. Chem.* ***1985***, *50*, 817; Amin, M.; Price, R.C.; Saunders, Jr., W.H. *J. Am. Chem. Soc.* ***1990***, *112*, 4467.

[65]Saunders Jr., W.H.; Bushman, D.G.; Cockerill, A.F. *J. Am. Chem. Soc.* ***1968***, *90*, 1775; Yano, Y.; Oae, S. *Tetrahedron* ***1970***, *26*, 27, 67; Blackwell, L.F.; Buckley, P.D.; Jolley, K.W.; MacGibbon, A.K.H. *J. Chem. Soc. Perkin Trans. 2* ***1973***, 169; Smith, P.J.; Tsui, S.K. *J. Am. Chem. Soc.* ***1973***, *95*, 4760; *Can. J. Chem.* ***1974***, *52*, 749.

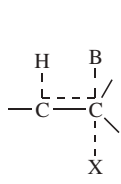
[66]DePuy, C.H.; Froemsdorf, D.H. *J. Am. Chem. Soc.* ***1957***, *79*, 3710; DePuy, C.H.; Bishop, C.A. *J. Am. Chem. Soc.* ***1960***, *82*, 2532, 2535.

[67]Brower, K.R.; Muhsin, M.; Brower, H.E. *J. Am. Chem. Soc.* ***1976***, *98*, 779. For a review, see van Eldik, R.; Asano, T.; le Noble, W.J. *Chem. Rev.* ***1989***, *89*, 549.

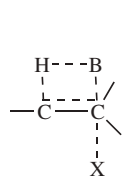
[68]For reviews, see McLennan, D.J. *Tetrahedron* ***1975***, *31*, 2999; Ford, W.T. *Acc. Chem. Res.* ***1973***, *6*, 410; Parker, A.J. *CHEMTECH* ***1971***, 297.

[69]For example; see Winstein, S.; Darwish, D.; Holness, N.J. *J. Am. Chem. Soc.* ***1956***, *78*, 2915; de la Mare, P.B.D.; Vernon, C.A. *J. Chem. Soc.* ***1956***, 41; Eliel, E.L.; Ro, R.S. *Tetrahedron* ***1958***, *2*, 353; Bunnett, J.F.; Davis, G.T.; Tanida, H. *J. Am. Chem. Soc.* ***1962***, *84*, 1606; McLennan, D.J. *J. Chem. Soc. B* ***1966***, 705, 709; Hayami, J.; Ono, N.; Kaji, A. *Bull. Chem. Soc. Jpn.* ***1971***, *44*, 1628.

and co-workers proposed[70] that there is a spectrum[71] of E2 transition states in which the base can interact in the transition state with the α carbon, as well as with the β hydrogen. At one end of this spectrum is



E2C



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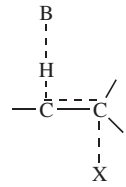
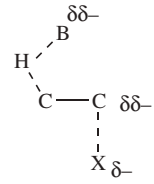


E2H



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a mechanism (called E2C) in which, in the transition state, the base interacts mainly with the carbon. The E2C mechanism is characterized by strong nucleophiles that are weak bases. At the other extreme is the normal E2 mechanism, here called E2H to distinguish it from E2C, characterized by strong bases. Transition state **17** represents a transition state between these extremes. Additional evidence[72] for the E2C mechanism is derived from Brønsted equation considerations (p. 373), from substrate effects, from isotope effects, and from the effects of solvents on rates.

However, the E2C mechanism has been criticized, and it has been contended that all the experimental results can be explained by the normal E2 mechanism.[73] McLennan has suggested that the transition state is that shown as **18**.[74] An ion-pair mechanism has also been proposed.[75] Although the actual mechanisms involved may be a matter of controversy, there is no doubt that a class of elimination reactions exists that is characterized by second-order attack by weak bases.[76] These reactions also have the following general characteristics:[77] (*1*) they are favored by good leaving groups; (*2*) they are favored by polar aprotic solvents;

[70]Parker, A.J.; Ruane, M.; Biale, G.; Winstein, S. *Tetrahedron Lett*. ***1968***, 2113.

[71]This is apart from the E1-E2-E1cB spectrum.

[72]Lloyd, D.J.; Parker, A.J. *Tetrahedron Lett*. ***1968***, 5183; ***1970***, 5029; Alexander, R.; Ko, E.C.F.; Parker, A.J.; Broxton, T.J. *J. Am. Chem. Soc*. ***1968***, *90*, 5049; Ko, E.C.F.; Parker, A.J. *J. Am. Chem. Soc*. ***1968***, *90*, 6447; Parker, A.J.; Ruane, M.; Palmer, D.A.; Winstein, S. *J. Am. Chem. Soc*. ***1972***, *94*, 2228; Biale, G.; Parker, A.J.; Stevens, I.D.R.; Takahashi, J.; Winstein, S. *J. Am. Chem. Soc*. ***1972***, *94*, 2235; Cook, D. *J. Org. Chem*. ***1976***, *41*, 2173, and references cited therein; Muir, D.M.; Parker, A.J. *Aust. J. Chem*. ***1983***, *36*, 1667; Kwart, H.; Wilk, K.A. *J. Org. Chem*. ***1985***, *50*, 3038.

[73]McLennan, D.J.; Wong, R.J. *J. Chem. Soc. Perkin Trans. 2* ***1974***, 1818, and references cited therein; Ford, W.T.; Pietsek, D.J.J. *J. Am. Chem. Soc*. ***1975***, *97*, 2194; Loupy, A. *Bull. Soc. Chim. Fr*. ***1975***, 2662; Miller, D.J.; Saunders Jr., W.H. *J. Am. Chem. Soc*. ***1979***, *101*, 6749; Bordwell, F.G.; Mrozack, S.R. *J. Org. Chem*. ***1982***, *47*, 4813; Bunnett, J.F.; Migdal, C.A. *J. Org. Chem*. ***1989***, *54*, 3037, 3041, and references cited therein.

[74]McLennan, D.J.; Lim, G. *Aust. J. Chem*. ***1983***, *36*, 1821. For an opposing view, see Kwart, H.; Gaffney, A. *J. Org. Chem*. ***1983***, *48*, 4502.

[75]Ford, W.T. *Acc. Chem. Res*. ***1973***, *6*, 410.

[76]For convenience, we will refer to this class of reactions as E2C reactions, though the actual mechanism is in dispute.

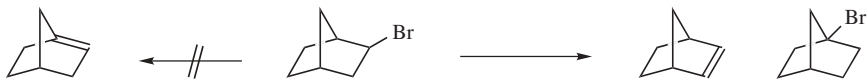
[77]Beltrame, P.; Biale, G.; Lloyd, D.J.; Parker, A.J.; Ruane, M.; Winstein, S. *J. Am. Chem. Soc*. ***1972***, *94*, 2240; Beltrame, P.; Ceccon, A.; Winstein, S. *J. Am. Chem. Soc*. ***1972***, *94*, 2315.

(*3*) the reactivity order is tertiary > secondary > primary, the opposite of the normal E2 order (p. 1503); (*4*) the elimination is always anti- (syn-elimination is not found), but in cyclohexyl systems, a diequatorial anti-elimination is about as favorable as a diaxial anti-elimination (unlike the normal E2 reaction, p. 1481); (*5*) they follow Zaitsev's rule (see below), where this does not conflict with the requirement for anti-elimination.

Regiochemistry of the Double Bond

With some substrates, a β hydrogen is present on only one carbon and (barring rearrangements) there is no doubt as to the identity of the product. For example, $PhCH_2CH_2Br$ can give only $PhCH{=}CH_2$. However, in many other cases two or three alkenyl products are possible. In the simplest such case, a *sec*-butyl compound can give either 1- or 2-butene. There are a number of rules that enable us to predict, in many instances, which product will predominantly form.[78]

1. No matter what the mechanism, a double bond does not go to a bridgehead carbon unless the ring sizes are large enough (Bredt's rule, see p. 229). This means, for example, not only that **19** gives only **20** and not **21** (indeed **21** is not a known compound), but also that **22** does not undergo elimination.



21 **19** **20** **22**

2. No matter what the mechanism, if there is a double bond (C=C or C=O) or an aromatic ring already in the molecule that can be in conjugation with the new double bond, the conjugated product usually predominates, sometimes even when the stereochemistry is unfavorable (for an exception, see p. 1501).
3. In the E1 mechanism the leaving group is gone before the choice is made as to which direction the new double bond takes. Therefore the direction is determined almost entirely by the relative stabilities of the two (or three) possible alkenes. In such cases, *Zaitsev's rule*[79] operates. This rule states that *the double bond goes mainly toward the most highly substituted carbon*. That is, a *sec*-butyl compound gives more 2-butene than 1-butene, and 3-bromo-2,3-dimethylpentane gives more 2,3-dimethyl-2-pentene than either 3,4-dimethyl-2-pentene or 2-ethyl-3-methyl-1-butene. Thus Zaitsev's rule predicts that the alkene predominantly formed will be the one with the largest possible number of alkyl groups on the C=C carbons, and in most cases this is what is found. From heat of combustion data (see p. 29) it is known that

[78]For a review of orientation in cycloalkyl systems, see Hückel, W.; Hanack, M. *Angew. Chem. Int. Ed.* ***1967***, *6*, 534.
[79]Often given the German spelling: Saytzeff.

alkene stability increases with alkyl substitution, although just why this should be is a matter of conjecture. The most common explanation is hyperconjugation. For E1 eliminations, Zaitsev's rule governs the orientation whether the leaving group is neutral or positive, since, as already mentioned, the leaving group is not present when the choice of direction is made. This statement does not hold for E2 eliminations, and it may be mentioned here, for contrast with later results, that E1 elimination of $Me_2CHCHMeSMe_2^+$ gave 91% of the Zaitsev product and 9% of the other.[80] However, there *are* cases in which the leaving group affects the direction of the double bond in E1-eliminations.[81] This may be attributed to ion pairs; that is, the leaving group is not completely gone when the hydrogen departs. Zaitsev's rule breaks down in cases where the non-Zaitsev product is more stable for steric reasons. For example, E1 or E1-like eliminations of 1,2-diphenyl-2-X-propanes $PhMeCXCH_2Ph$ were reported to give ~50% $CH_2{=}CPhCH_2Ph$, despite the fact that the double bond of the Zaitsev product ($PhMeC{=}CHPh$) is conjugated with two benzene rings.[82]

4. For the anti E2 mechanism a trans β proton is necessary; if this is available in only one direction, that is the way the double bond will form. Because of the free rotation in acyclic systems (except where steric hindrance is great), this is a factor only in cyclic systems. Where trans β hydrogens are available on two or three carbons, two types of behavior are found, depending on substrate structure and the nature of the leaving group. Some compounds follow Zaitsev's rule and give predominant formation of the most highly substituted alkene, but others follow *Hofmann's rule: The double bond goes mainly toward the least highly substituted carbon*. although many exceptions are known, the following general statements can be made: In most cases, compounds containing uncharged nucleofuges (those that come off as negative ions) follow Zaitsev's rule, just as they do in E1 elimination, no matter what the structure of the substrate. However, elimination from compounds with charged nucleofuges, for example, NR_3^+, SR_2^+ (those that come off as neutral molecules), follow Hofmann's rule if the substrate is acyclic,[83] but Zaitsev's rule if the leaving group is attached to a six-membered ring.[84]

Much work has been devoted to searching for the reasons for the differences in orientation. Since Zaitsev orientation almost always gives the

[80]de la Mare, P.B.D. *Prog. Stereochem*. ***1954***, *1*, 112.

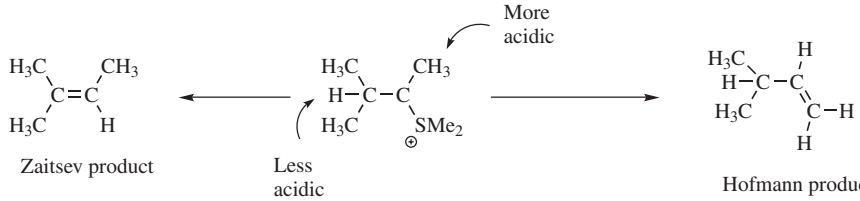
[81]Cram, D.J.; Sahyun, M.R.V. *J. Am. Chem. Soc*. ***1963***, *85*, 1257; Silver, M.S. *J. Am. Chem. Soc*. ***1961***, *83*, 3482.

[82]Ho, I.; Smith, J.G. *Tetrahedron* ***1970***, *26*, 4277.

[83]An example of an acyclic quaternary ammonium salt that follows Zaitsev's rule is found, in Feit, I.N.; Saunders, Jr., W.H. *J. Am. Chem. Soc*. ***1970***, *92*, 5615.

[84]For examples where Zaitsev's rule is followed with charged leaving groups in cyclohexyl systems, see Gent, B.B.; McKenna, J. *J. Chem. Soc*. ***1959***, 137; Hughes, E.D.; Wilby, J. *J. Chem. Soc*. ***1960***, 4094; Brownlee, T.H.; Saunders Jr., W.H. *Proc. Chem. Soc*. ***1961***, 314; Booth, H.; Franklin, N.C.; Gidley, G.C. *J. Chem. Soc. C* ***1968***, 1891. For a discussion of the possible reasons for this, see Saunders, Jr., W.H.; Cockerill, A.F. *Mechanisms of Elimination Reactions*, Wiley, NY, ***1973***, pp. 192–193.

thermodynamically more stable isomer, what needs to be explained is why in some cases the less stable Hofmann product predominates. Three explanations have been offered for the change in orientation in acyclic systems with a change from uncharged to charged nucleofuges. The first of these, by Hughes and Ingold,[85] is that Hofmann orientation is caused by the fact that the acidity of the β hydrogen is decreased by the presence of the electron-donating alkyl groups. For example, under E2 conditions $Me_2CHCHMeSMe_2^+$ gives more of the Hofmann product; it is the more acidic hydrogen that is removed by the base.



Of course, the CH_3 hydrogens would still be more acidic than the Me_2CH hydrogen even if a neutral leaving group were present, but the explanation of Hughes and Ingold is that acidity matters with charged and not with neutral leaving groups, because the charged groups exert a strong electron-withdrawing effect, making differences in acidity greater than they are with the less electron-withdrawing neutral groups.[85] The explanation of Bunnett[86] is similar. According to this, the change to a positive leaving group causes the mechanism to shift toward the E1cB end of the spectrum, where there is more C–H bond breaking in the rate-determining step and where, consequently, acidity is more important. In this view, when there is a neutral leaving group, the mechanism is more E1-like, C–X bond breaking is more important, and alkene stability determines the direction of the new double bond. The third explanation, by H.C. Brown, is completely different. In this picture, field effects are unimportant, and the difference in orientation is largely a steric effect caused by the fact that charged groups are usually larger than neutral ones. A CH_3 group is more open to attack than a CH_2R group and a CHR_2 group is still less easily attacked. Of course, these considerations also apply when the leaving group is neutral, but, according to Brown, they are much less important here because the neutral groups are smaller and do not block access to the hydrogens as much. Brown showed that Hofmann elimination increases with the size of the leaving group. Thus the percentage of 1-ene obtained from $CH_3CH_2CH_2CHXCH_3$ was as follows (X listed in order of increasing size): Br, 31%; I, 30%; OTs, 48%; SMe_2^+, 87%; SO_2Me, 89%;

[85]For summaries of this position, see Ingold, C.K. *Proc. Chem. Soc*. ***1962***, 265; Banthorpe, D.V.; Hughes, E.D.; Ingold, C.K. *J. Chem. Soc*. ***1960***, 4054.
[86]Bunnett, J.F. *Surv. Prog. Chem.* ***1969***, *5*, 53.

NMe_3^+, 98%.[87] Hofmann elimination was also shown to increase with increase in bulk of the substrate.[88] With large enough compounds, Hofmann orientation can be obtained even with halides, for example, *tert*-amyl bromide ogave 89% of the Hofmann product. Even those who believe in the acidity explanations concede that these steric factors operate in extreme cases.[89]

There is one series of results incompatible with the steric explanation E2 elimination from the four 2-halopentanes gave the following percentages of 1-pentene: F, 83%; Cl, 37%; Br, 25%; I, 20%.[90] The same order was found for the four-2-halohexanes.[91] Although there is some doubt about the relative steric requirements of Br, Cl, and I, there is no doubt that F is the smallest of the halogens, and if the steric explanation were the only valid one, the fluoroalkanes could not give predominant Hofmann orientation. Another result that argues against the steric explanation is the effect of changing the nature of the base. An experiment in which the effective size of the base was kept constant while its basicity was increased (by using as bases a series of $XC_6H_4O^-$ ions) showed that the percentage of Hofmann elimination increased with increasing base strength, although the size of the base did not change.[92] These results are in accord with the explanation of Bunnett, since an increase in base strength moves an E2 reaction closer to the E1cB end of the spectrum. In further experiments, a large series of bases of different kinds was shown to obey linear free-energy relationships between basicity and percentage of Hofmann elimination,[93] although certain very large bases (e.g., 2,6-di-*tert*-butyl-phenoxide) did not obey the relationships, steric effects becoming important in these cases. How large the base must be before steric effects are observed depends on the pattern of alkyl substitution in the substrate, but not on the nucleofuge.[94] One further result may be noted. In the gas phase, elimination of H and BrH^+ or H and ClH^+ using Me_3N as the base predominantly followed Hofmann's rule,[95] although BrH^+ and ClH^+ are not very large.

[87]Brown, H.C.; Wheeler, O.H. *J. Am. Chem. Soc.* ***1956***, *78*, 2199.

[88]Brown, H.C.; Moritani, I.; Nakagawa, M. *J. Am. Chem. Soc.* ***1956***, *78*, 2190; Brown, H.C.; Moritani, I. *J. Am. Chem. Soc.* ***1956***, *78*, 2203; Bartsch, R.A. *J. Org. Chem.* ***1970***, *35*, 1334. See also, Charton, M. *J. Am. Chem. Soc.* ***1975***, *97*, 6159.

[89]For example, see Banthorpe, D.V.; Hughes, E.D.; Ingold, C.K. *J. Chem. Soc.* ***1960***, 4054.

[90]Saunders, Jr., W.H.; Fahrenholtz, S.R.; Caress, E.A.; Lowe, J.P.; Schreiber, M.R. *J. Am. Chem. Soc.* ***1965***, *87*, 3401. Similar results were obtained by Brown, H.C.; Klimisch, R.L. *J. Am. Chem. Soc.* ***1966***, *88*, 1425.

[91]Bartsch, R.A.; Bunnett, J.F. *J. Am. Chem. Soc.* ***1968***, *90*, 408.

[92]Froemsdorf, D.H.; Robbins, M.D. *J. Am. Chem. Soc.* ***1967***, *89*, 1737. See also, Froemsdorf, D.H.; Dowd, W.; Leimer, K.E. *J. Am. Chem. Soc.* ***1966***, *88*, 2345; Bartsch, R.A.; Kelly, C.F.; Pruss, G.M. *Tetrahedron Lett.* ***1970***, 3795; Feit, I.N.; Breger, I.K.; Capobianco, A.M.; Cooke, T.W.; Gitlin, L.F. *J. Am. Chem. Soc.* ***1975***, *97*, 2477; Feit, I.N.; Suanders, Jr., W.H. *J. Am. Chem. Soc.* ***1970***, *92*, 5615.

[93]Bartsch, R.A.; Roberts, D.K.; Cho, B.R. *J. Org. Chem.* ***1979***, *44*, 4105.

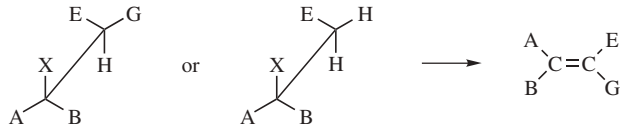
[94]Bartsch, R.A.; Read, R.A.; Larsen, D.T.; Roberts, D.K.; Scott, K.J.; Cho, B.R. *J. Am. Chem. Soc.* ***1979***, *101*, 1176.

[95]Angelini, G.; Lilla, G.; Speranza, M. *J. Am. Chem. Soc.* ***1989***, *111*, 7393.

5. Only a few investigations on the orientation of syn E2 eliminations have been carried out, but these show that Hofmann orientation is greatly favored over Zaitsev.[96]
6. In the E1cB mechanism the question of orientation seldom arises because the mechanism is generally found only where there is an electron-withdrawing group in the β position, and that is where the double bond goes.
7. As already mentioned, E2C reactions show a strong preference for Zaitsev orientation.[97] In some cases, this can be put to preparative use. For example, the compound $PhCH_2CHOTsCHMe_2$ gave ~98% $PhCH{=}CHCHMe_2$ under the usual E2 reaction conditions (*t*-BuOK in *t*-BuOH). In this case, the double bond goes to the side with more hydrogens because on that side it will be able to conjugate with the benzene ring. However, with the weak base $Bu_4N^+\ Br^-$ in acetone the Zaitsev product $PhCH_2CH{=}CMe_2$ was formed in 90% yield.[98]

Stereochemistry of the Double Bond

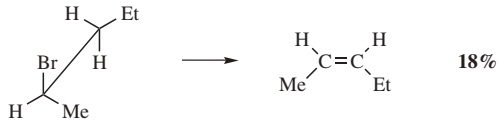
When elimination takes place on a compound of the form CH_3–CABX or CHAB–CGGX, the new alkene does not have cis–trans isomerism, but for compounds of the form CHEG–CABX (E and G *not* H) (**23**) and CH_2E–CABX (**24**), cis and trans isomers are possible. When the anti E2 mechanism is in operation, **23** gives the isomer



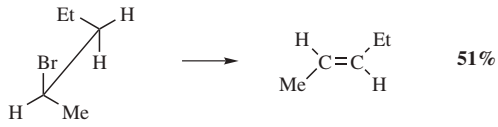
23 **24**

arising from trans orientation of X and H and, as we have seen before (p. 1478), an erythro compound gives the cis alkene and a threo compound the trans. For **24**, two conformations are possible for the transition state; these lead to different isomers and often both are obtained. However, the one that predominates is often determined by an eclipsing effect.[99] For example, Zaitsev elimination from 2-bromopentane can occur as follows:

[96]Sicher, J.; Svoboda, M.; Pánková, M.; Závada, J. *Collect. Czech. Chem. Commun.* ***1971***, *36*, 3633; Bailey, D.S.; Saunders, Jr., W.H. *J. Am. Chem. Soc.* ***1970***, *92*, 6904.
[97]For example; see Ono, N. *Bull. Chem. Soc. Jpn.* ***1971***, *44*, 1369; Bailey, D.S.; Saunders, Jr., W.H. *J. Org. Chem.* ***1973***, *38*, 3363; Muir, D.M.; Parker, A.J. *J. Org. Chem.* ***1976***, *41*, 3201.
[98]Lloyd, D.J.; Muir, D.M.; Parker, A.J. *Tetrahedron Lett.* ***1971***, 3015
[99]See Cram, D.J.; Greene, F.D.; DePuy, C.H. *J. Am. Chem. Soc.* ***1956***, *78*, 790; Cram, D.G., in Newman, M.S. *Steric Effects in Organic Chemistry*, Wiley, NY, ***1956***, pp. 338–345.



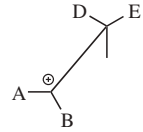
I



J

In conformation **I**, the ethyl group is between Br and Me, while in **J** it is between Br and H. This means that **J** is more stable, and most of the elimination should occur from this conformation. This is indeed what happens, and 51% of the trans isomer is formed (with KOEt) compared to 18% of the cis (the rest is the Hofmann product).[100] These effects become larger with increasing size of A, B, and E.

However, eclipsing effects are not the only factors that affect the cis/trans ratio in anti E2 eliminations. Other factors are the nature of the leaving group, the base, the solvent, and the substrate. Not all these effects are completely understood.[101]



(D may be H)

25

For E1 eliminations, if there is a free carbocation (**25**), it is free to rotate, and no matter what the geometry of the original compound, the more stable situation is the one where the larger of the D–E pair is opposite the smaller of the A–B pair and the corresponding alkene should form. If the carbocation is not completely free, then to that extent, E2-type products are formed. Similar considerations apply in E1cB eliminations.[102]

REACTIVITY

In this section, we examine the effects of changes in the substrate, base, leaving group, and medium on (*1*) overall reactivity, (*2*) E1 versus E2 versus E1cB,[103] and (*3*) elimination versus substitution.

[100]Brown, H.C.; Wheeler, O.H. *J. Am. Chem. Soc.* ***1956***, *78* 2199.
[101]For discussions, see Bartsch, R.A.; Bunnett, J.F. *J. Am. Chem. Soc.* ***1969***, *91*, 1376, 1382; Feit, I.N.; Saunders, Jr., W.H. *J. Am. Chem. Soc.* ***1970***, *92*, 1630, 5615; Alunni, S.; Baciocchi, E. *J. Chem. Soc. Perkin Trans. 2* ***1976***, 877; Saunders, Jr., W.H.; Cockerill, A.F. *Mechanisms of Elimination Reactions*, Wiley, NY, ***1973***, pp. 165–193.
[102]See, for example, Redman, R.P.; Thomas, P.J.; Stirling, C.J.M. *J. Chem. Soc., Chem. Commun.* ***1978***, 43.
[103]For discussions, see Cockerill, A.F.; Harrison, R.G., in Patai, S. *The Chemistry of Functional Groups*, Supplement A, pt. 1, Wiley, NY, ***1977***, pp. 178–189.

Effect of Substrate Structure

1. *Effect on Reactivity.* We refer to the carbon containing the nucleofuge (X) as the a carbon and to the carbon that loses the positive species as the β carbon. Groups attached to the α or β carbons can exert at least four kinds of influence:

a. They can stabilize or destabilize the incipient double bond (both α and β groups).
b. They can stabilize or destabilize an incipient negative charge, affecting the acidity of the proton (β groups only).
c. They can stabilize or destabilize an incipient positive charge (α groups only).
d. They can exert steric effects (e.g., eclipsing effects) (both α and β groups).

Effects a and d can apply in all three mechanisms, although steric effects are greatest for the E2 mechanism. Effect b does not apply in the E1 mechanism, and effect c does not apply in the E1cB mechanism. Groups, such as Ar and C=C, increase the rate by any mechanism, except perhaps when formation of the C=C bond is not the rate-determining step, whether they are α or β (effect a). Electron-withdrawing groups increase the acidity when in the β position, but have little effect in the a position unless they also conjugate with the double bond. Thus Br, Cl, CN, Ts, NO_2, CN, and SR in the β position all increase the rate of E2 eliminations.

2. *Effect on* E1 *versus* E2 *versus* E1cB. The α alkyl and α aryl groups stabilize the carbocation character of the transition state, shifting the spectrum toward the E1 end. β alkyl groups also shift the mechanism toward E1, since they *decrease* the acidity of the hydrogen. However, β aryl groups shift the mechanism the other way (toward E1cB) by stabilizing the carbanion. Indeed, as we have seen (p. $$$), all electron-withdrawing groups in the β position shift the mechanism toward E1cB.[104] α alkyl groups also increase the extent of elimination with weak bases (E2C reactions).

3. *Effect on Elimination versus Substitution*. Under second-order conditions, a branching increases elimination, to the point where tertiary substrates undergo few S_N2 reactions, as we saw in Chapter 10. For example, Table 17.2 shows results on some simple alkyl bromides. Similar results were obtained with SMe_2^+ as the leaving group.[105] Two reasons can be presented for this trend. One is statistical: As a branching increases, there are usually more hydrogens for the base to attack. The other is that a branching presents steric hindrance to attack of the base at the carbon. Under first-order conditions, increased a branching also increases the amount of elimination (E1 vs. S_N1), although not

[104]For a review of eliminations with COOH, COOR, $CONH_2$, and CN groups in the β position, see Butskus, P.F.; Denis, G.I. *Russ. Chem. Rev.* ***1966***, *35*, 839.
[105]Dhar, M.L.; Hughes, E.D.; Ingold, C.K.; Masterman, S. *J. Chem. Soc*. ***1948***, 2055.

TABLE 17.2. The Effect of α and β Branching on the Rate of E2 Elimination and the Amount of Alkene Formed[a]

Substrate	Temperature, °C	Alkene, %	Rate × 10^5 of E2 Reaction	Reference
CH_3CH_2Br	55	0.9	1.6	108
$(CH_3)_2CHBr$	24	80.3	0.237	109
$(CH_3)_3CBr$	25	97	4.17	107
$CH_3CH_2CH_2Br$	55	8.9	5.3	105
$(CH_3)_2CHCH_2Br$	55	59.5	8.5	105

[a]The reactions were between the alkyl bromide and ^-OEt The rate for isopropyl bromide was actually greater than that for ethyl bromide, if the temperature difference is considered. Neopentyl bromide, the next compound in the β-branching series, cannot be compared because it has no β-hydrogen and cannot give an elimination product without rearrangement.

so much, and usually the substitution product predominates. For example, solvolysis of *tert*-butyl bromide gave only 19% elimination[106] (cf. with Table 17.2). β Branching also increases the amount of E2 elimination with respect to S_N2 substitution (Table 17.2), not because elimination is faster, but because the S_N2 mechanism is so greatly slowed (p. 478). Under first-order conditions too, β branching favors elimination over substitution, probably for steric reasons.[107] However, E2 eliminations from compounds with charged leaving groups are slowed by β branching. This is related to Hofmann's rule (p. 1498). Electron-withdrawing groups in the β position not only increase the rate of E2 eliminations and shift the mechanisms toward the E1cB end of the spectrum, but also increase the extent of elimination as opposed to substitution.

Effect of the Attacking Base

1. *Effect on* E1 *versus* E2 *versus* E1cB. In the E1 mechanism, an external base is generally not required: The solvent acts as the base. Hence, when external bases are added, the mechanism is shifted toward E2. Stronger bases and higher base concentrations cause the mechanism to move toward the E1cB end of the E1-E2-E1cB spectrum.[110] However, weak bases in polar aprotic solvents can also be effective in elimination reactions with certain substrates (the E2C reaction). Normal E2 elimination has been accomplished with the following bases:[111] H_2O, NR_3, ^-OH, ^-OAc, ^-OR, ^-OAr, $^-NH_2$, CO_3^{2-},

[106]Dhar, M.L.; Hughes, E.D.; Ingold, C.K. *J. Chem. Soc.* ***1948***, 2058.
[107]Hughes, M.L.; Ingold, C.K.; Maw, G.A. *J. Chem. Soc.* ***1948***, 2065.
[108]Hughes, E.D.; Ingold, C.K.; Maw, G.A. *J. Chem. Soc.* ***1948***, 2072; Hughes, E.D.; Ingold, C.K.; Woolf, L.I. *J. Chem. Soc.* ***1948***, 2084.
[109]Brown, H.C.; Berneis, H.L. *J. Am. Chem. Soc.* ***1953***, *75*, 10.
[110]For a review, see Baciocchi, E. *Acc. Chem. Res.* ***1979***, *12*, 430. See also, Baciocchi, E.; Ruzziconi, R.; Sebastiani, G.V. *J. Org. Chem.* ***1980***, *45*, 827.
[111]This list is from Banthorpe, D.V. *Elimination Reactions*; Elsevier, NY, ***1963***, p. 4.

$LiAlH_4$, I^-, CN^-, and organic bases. However, the only bases of preparative importance in the normal E2 reaction are OH^-, OR^-, and NH_2^-, usually in the conjugate acid as solvent, and certain amines. Weak bases effective in the E2C reaction are Cl^-, Br^- F^-, ^-OAc, and RS^-. These bases are often used in the form of their R_4N^+ salts.

2. *Effect on Elimination versus Substitution*. Strong bases not only benefit E2 as against E1, but also benefit elimination as against substitution. With a high concentration of strong base in a non-ionizing solvent, bimolecular mechanisms are favored and E2 predominates over S_N2. At low base concentrations, or in the absence of base altogether, in ionizing solvents, unimolecular mechanisms are favored, and the S_N1 mechanism predominates over the E1. In Chapter 10, it was pointed out that some species are strong nucleophiles, but weak bases (p. 490). The use of these obviously favors substitution, except that, as we have seen, elimination can predominate if polar aprotic solvents are used. It has been shown for the base cyanide that in polar aprotic solvents, the less the base is encumbered by its counterion in an ion pair (i.e., the freer the base), the more substitution is favored at the expense of elimination.[112]

Effect of the Leaving Group

1. *Effect on Reactivity.* The leaving groups in elimination reactions are similar to those in nucleophilic substitution. The E2 eliminations have been performed with the following groups: NR_3^+, PR_3^+, SR_2^+, OHR^+, SO_2R, OSO_2R, OCOR, OOH, OOR, NO_2,[113] F, Cl, Br, I, and CN (*not* OH_2^+). The E1 eliminations have been carried out with: NR_3^+, SR_2^+, OH_2^+, OHR^+, OSO_2R, OCOR, Cl, Br, I, and N_2^+.[114] However, the major leaving groups for preparative purposes are OH_2^+ (always by E1) and Cl, Br, I, and NR_3^+ (usually by E2).
2. *Effect on* E1 *versus* E2 *versus* E1cB. Better leaving groups shift the mechanism toward the E1 end of the spectrum, since they make ionization easier. This effect has been studied in various ways. One way already mentioned was a study of ρ values (p. 1495). Poor leaving groups and positively charged leaving groups shift the mechanism toward the E1cB end of the spectrum because the strong electron-withdrawing field effects increase the acidity of the β hydrogen.[115] The E2C reaction is favored by good leaving groups.
3. *Effect on Elimination versus Substitution*. As we have already seen (p. 1487), for first-order reactions the leaving group has nothing to do with the

[112]Loupy, A.; Seyden-Penne, J. *Bull. Soc. Chim. Fr.* ***1971***, 2306.

[113]For a review of eliminations in which NO_2 is a leaving group, see Ono, N., in Feuer, H.; Nielsen, A.T. *Nitro Compounds; Recent Advances in Synthesis and Chemistry*, VCH, NY, ***1990***, pp. 1–135, 86–126.

[114]These lists are from Banthorpe, D.V. *Elimination Reactions*, Elsevier, NY, ***1963***, pp. 4, 7.

[115]For a discussion of leaving-group ability, see Stirling, C.J.M. *Acc. Chem. Res*. ***1979***, *12*, 198. See also, Varma, M.; Stirling, C.J.M. *J. Chem. Soc., Chem. Commun*. ***1981***, 553.

competition between elimination and substitution, since it is gone before the decision is made as to which path to take. However, where ion pairs are involved, this is not true, and results have been found where the nature of the leaving group does affect the product.[116] In second-order reactions, the elimination/substitution ratio is not greatly dependent on a halide leaving group, although there is a slight increase in elimination in the order I > Br > Cl. When OTs is the leaving group, there is usually much more substitution. For example, *n*-$C_{18}H_{37}$Br treated with *t*-BuOK gave 85% elimination, while *n*-$C_{18}H_{37}$OTs gave, under the same conditions, 99% substitution.[117] On the other hand, positively charged leaving groups increase the amount of elimination.

Effect of the Medium

1. *Effect of Solvent on* E1 *versus* E2 *versus* E1cB. With any reaction a more polar environment enhances the rate of mechanisms that involve ionic intermediates. For neutral leaving groups, it is expected that E1 and E1cB mechanisms will be aided by increasing polarity of solvent and by increasing ionic strength. With certain substrates, polar aprotic solvents promote elimination with weak bases (the E2C reaction).
2. *Effect of Solvent on Elimination versus Substitution*. Increasing polarity of solvent favors S_N2 reactions at the expense of E2. In the classical example, alcoholic KOH is used to effect elimination, while the more polar aqueous KOH is used for substitution. Charge-dispersal discussions, similar to those on p. 503,[118] only partially explain this. In most solvents, S_N1 reactions are favored over E1. The E1 reactions compete best in polar solvents that are poor nucleophiles, especially dipolar aprotic solvents.[119] A study made in the gas phase, where there is no solvent, has shown that when 1-bromopropane reacts with MeO^- only elimination takes place (no substitution) even with this primary substrate.[120]
3. *Effect of Temperature*. Elimination is favored over substitution by increasing temperature, whether the mechanism is first or second order.[121] The reason is that the activation energies of eliminations are higher than those of substitutions (because eliminations have greater changes in bonding).

[116]For example, see Skell, P.S.; Hall, W.L. *J. Am. Chem. Soc*. ***1963***, *85* 2851; Cocivera, M.; Winstein, S. *J. Am. Chem. Soc*. ***1963***, *85*, 1702; Feit, I.N.; Wright, D.G. *J. Chem. Soc., Chem. Commun*. ***1975***, 776. See, however, Cavazza, M. *Tetrahedron Lett*. ***1975***, 1031.

[117]Veeravagu, P.; Arnold, R.T.; Eigenmann, E.W. *J. Am. Chem. Soc*. ***1964***, *86*, 3072.

[118]Cooper, K.A.; Dhar, M.L.; Hughes, E.D.; Ingold, C.K.; MacNulty, B.J.; Woolf, L.I. *J. Chem. Soc*. ***1948***, 2043.

[119]Aksnes, G.; Stensland, P. *Acta Chem. Scand*. ***1989***, *43*, 893, and references cited therein.

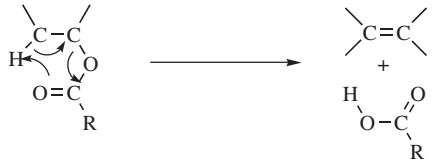
[120]Jones, M.E.; Ellison, G.B. *J. Am. Chem. Soc*. ***1989***, *111*, 1645. For a different result with other reactants, see Lum, R.C.; Grabowski, J.J. *J. Am. Chem. Soc*. ***1988***, *110*, 8568.

[121]Cooper, K.A.; Hughes, E.D.; Ingold, C.K.; Maw, G.A.; MacNulty, B.J. *J. Chem. Soc*. ***1948***, 2049.

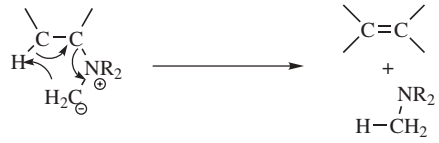
MECHANISMS AND ORIENTATION IN PYROLYTIC ELIMINATIONS

Mechanisms[122]

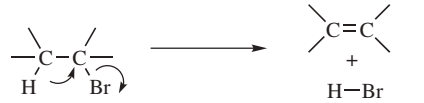
Several types of compound undergo elimination on heating, with no other reagent present. Reactions of this type are often run in the gas phase. The mechanisms are obviously different from those already discussed, since all those require a base (which may be the solvent) in one of the steps, and there is no base or solvent present in pyrolytic elimination. Two mechanisms have been found to operate. One involves a cyclic transition state, which may be four, five, or six membered. Examples of each size are



(17-4)

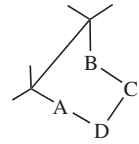


(17-8)



(17-13)

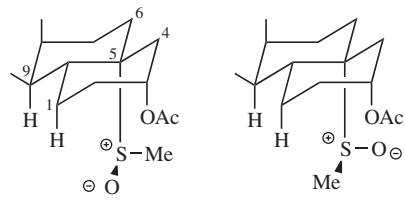
In this mechanism, the two groups leave at about the same time and bond to each other as they are doing so. The designation is E^i in the Ingold terminology and *cyclo*-$D_ED_NA_n$ in the IUPAC system. The elimination must be syn and, for the four- and five-membered transition states, the four or five atoms making up the ring must be coplanar. Coplanarity is not required for the six-membered transition state, since there is room for the outside atoms when the leaving atoms are staggered.



[122]For reviews, see Taylor, R., in Patai, S. *The Chemistry of Functional Groups, Supplement B*, pt. 2, Wiley, NY, ***1979***, pp. 860–914; Smith, G.G.; Kelly, F.W. *Prog. Phys. Org. Chem.* ***1971***, *8*, 75, pp. 76–143, 207–234; in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 5, Elsevier, NY, ***1972***, the articles by Swinbourne, E.S. pp. 149–233 (pp. 158–188), and by Richardson, W.H.; O'Neal, H.E. pp. 381–565 (pp. 381–446); Maccoll, A. *Adv. Phys. Org. Chem.* ***1965***, *3*, 91. For reviews of mechanisms in pyrolytic eliminations of halides, see Egger, K.W.; Cocks, A.T., in Patai's. *The Chemistry of the Carbon-Halogen Bond*, pt. 2, Wiley, NY, ***1973***, pp. 677–745; Maccoll, A. *Chem. Rev.* ***1969***, *69*, 33.

As in the E2 mechanism, it is not necessary that the C–H and C–X bond be equally broken in the transition state. In fact, there is also a spectrum of mechanisms here, ranging from a mechanism in which C–X bond breaking is a good deal more advanced than C–H bond breaking to one in which the extent of bond breaking is virtually identical for the two bonds. Evidence for the existence of the E^i mechanism is

1. The kinetics are first order, so only one molecule of the substrate is involved in the reaction (i.e., if one molecule attacked another, the kinetics would be second order in substrate).[123]
2. Free-radical inhibitors do not slow the reactions, so no free-radical mechanism is involved.[124]
3. The mechanism predicts exclusive syn elimination, and this behavior has been found in many cases.[125] The evidence is inverse to that for the anti E2 mechanism and generally involves the following facts: (*1*) an erythro isomer gives a trans alkene and a threo isomer gives a cis alkene; (*2*) the reaction takes place only when a cis β hydrogen is available; (*3*) if, in a cyclic compound, a cis hydrogen is available on only one side, the elimination goes in that direction. Another piece of evidence involves a pair of steroid molecules. In 3β-acetoxy-(*R*)-5α-methylsulfinylcholestane (**26** shows rings A and B of this compound) and in 3β-acetoxy-(*S*)-5α-methylsulfinylcholestane (**27:** rings A and B), the *only* difference is the configuration of



26 **27**

oxygen and methyl about the sulfur. Yet pyrolysis of **26** gave only elimination to the 4-side (86% 4-ene), while **27** gave predominant elimination to the 6-side (65% 5-ene and 20% 4-ene).[126] Models show that interference from the 1- and 9-hydrogens causes the two groups on the sulfur to lie *in front of it* with respect to the rings, rather than behind it. Since the sulfur is chiral, this

[123]O'Connor, G.L.; Nace, H.R. *J. Am. Chem. Soc*. ***1953***, *75*, 2118.
[124]Barton, D.H.R.; Head, A.J.; Williams, R.J. *J. Chem. Soc*. ***1953***, 1715.
[125]In a few instances anti or nonstereoselective elimination has been found; this behavior is generally ascribed to the intervention of other mechanisms. For example, see Bordwell, F.G.; Landis, P.S. *J. Am. Chem. Soc*. ***1958***, *80*, 2450, 6383; Briggs, W.S.; Djerassi, C. *J. Org. Chem*. ***1968***, *33*, 1625; Smissman, E.E.; Li, J.P.; Creese, M.W. *J. Org. Chem*. ***1970***, *35*, 1352.
[126]Jones, D.N.; Saeed, M.A. *Proc. Chem. Soc*. ***1964***, 81. See also, Goldberg, S.I.; Sahli, M.S. *J. Org. Chem*. ***1967***, *32*, 2059.

means that in **26** the oxygen is near the 4-hydrogen, while in **27** it is near the 6-hydrogen. This experiment is compatible only with syn-elimination.[127]

4. The ^{14}C isotope effects for the Cope elimination (**17-9**) show that both the C–H and C–N bonds have been extensively broken in the transition state.[128]
5. Some of these reactions have been shown to exhibit negative entropies of activation, indicating that the molecules are more restricted in geometry in the transition state than they are in the starting compound.

Where a pyrolytic elimination lies on the mechanistic spectrum seems to depend mostly on the leaving group. When this is halogen, all available evidence suggests that in the transition state the C–X bond is cleaved to a much greater extent than the C–H bond, that is, there is a considerable amount of carbocation character in the transition state. This is in accord with the fact that a completely nonpolar four-membered cyclic transition state violates the Woodward–Hoffmann rules (see the similar case of **15-63**). Evidence for the carbocation-like character of the transition state when halide is the leaving group is that relative rates are in the order $I > Br > Cl$[129] (see p. 496), and that the effects of substituents on reaction rates are in accord with such a transition state.[130] Rate ratios for pyrolysis of some alkyl bromides at 320°C were ethyl bromide, 1; isopropyl bromide, 280; *tert*-butyl bromide, 78,000. Also, α-phenylethyl bromide had about the same rate as *tert*-butyl bromide. On the other hand, β-phenylethyl bromide was only slightly faster than ethyl bromide.[131] This indicates that C–Br cleavage was much more important in the transition state than C–H cleavage, since the incipient carbocation was stabilized by a alkyl and α-aryl substitution, while there was no incipient carbanion to be stabilized by β-aryl substitution. These substituent effects, as well as those for other groups, are very similar to the effects found for the S_N1 mechanism and thus in very good accord with a carbocation-like transition state.

For carboxylic esters, the rate ratios were much smaller,[132] although still in the same order, so that this reaction is closer to a pure E^i mechanism, although the transition state still has some carbocationic character. Other evidence for a greater initial C–O cleavage with carboxylic esters is that a series of 1-arylethyl acetates followed σ^+ rather than σ, showing carbocationic character at the 1 position.[133]

[127]For other evidence for syn-elimination, see Curtin, D.Y.; Kellom, D.B. *J. Am. Chem. Soc*. ***1953***, *75*, 6011; Skell, P.S.; Hall, W.L. *J. Am. Chem. Soc*. ***1964***, *86*, 1557; Bailey, W.J.; Bird, C.N. *J. Org. Chem*. ***1977***, *42*, 3895.

[128]Wright, D.R.; Sims, L.B.; Fry, A. *J. Am. Chem. Soc*. ***1983***, *105*, 3714.

[129]Maccoll, A., in Patai, S. *The Chemistry of Alkenes*, Vol. 1, Wiley, NY, ***1964***, pp. 215–216.

[130]For reviews of such studies, see Maccoll, A. *Chem. Rev*. ***1969***, *69*, 33.

[131]For rate studies of pyrolysis of some β-alkyl substituted ethyl bromides, see Chuchani, G.; Rotinov, A.; Dominguez, R.M.; Martin, I. *Int. J. Chem. Kinet*. ***1987***, *19*, 781.

[132]For example, see Scheer, J.C.; Kooyman, E.C.; Sixma, F.L.J. *Recl. Trav. Chim. Pays-Bas* ***1963***, *82*, 1123. See also, Louw, R.; Vermeeren, H.P.W.; Vogelzang, M.W. *J. Chem. Soc. Perkin Trans. 2* ***1983***, 1875.

[133]Taylor, R.; Smith, G.G.; Wetzel, W.H. *J. Am. Chem. Soc*. ***1962***, *84*, 4817; Smith, G.G.; Jones, D.A.K.; Brown, D.F. *J. Org. Chem*. ***1963***, *28*, 403; Taylor, R. *J. Chem. Soc. Perkin Trans. 2* ***1978***, 1255. See also, Ottenbrite, R.M.; Brockington, J.W. *J. Org. Chem*. ***1974***, *39*, 2463; Jordan, E.A.; Thorne, M.P. *J. Chem. Soc. Perkin Trans. 2* ***1984***, 647; August, R.; McEwen, I.; Taylor, R. *J. Chem. Soc. Perkin Trans. 2* ***1987***, 1683, and other papers in this series; Al-Awadi, N.A. *J. Chem. Soc. Perkin Trans. 2* ***1990***, 2187.

The extent of E1 character in the transition state increases in the following order of ester types: acetate < phenylacetate < benzoate < carbamate < carbonate.[134] Cleavage of xanthates (**17-5**), cleavage of sulfoxides (**17-12**), the Cope reaction (**17-9**), and reaction **17-8** are probably very close to straight E^i mechanisms.[135]

The second type of pyrolysis mechanism is completely different and involves free radicals. Initiation occurs by pyrolytic homolytic cleavage. The remaining steps may vary, and a few are shown

$$\text{Initiation} \qquad R_2CHCH_2X \longrightarrow R_2CHCH_2\bullet + X\bullet$$

$$\text{Propagation} \qquad R_2CHCH_2X + X\bullet \longrightarrow R_2\overset{\bullet}{C}CH_2X + HX$$

$$R_2\overset{\bullet}{C}CH_2X \longrightarrow CH_2 = CH_2X\bullet$$

$$\text{Termination (disproportionation)} \qquad 2R_2\overset{\bullet}{C}CH_2X \longrightarrow R_2C = CH_2 + R_2CXCH_2X$$

Free-radical mechanisms are mostly found in pyrolyses of polyhalides and of primary monohalides,[136] although they also have been postulated in pyrolysis of certain carboxylic esters.[137] β-Elimination of tosyl radicals is known.[138] Much less is known about these mechanisms and we will not consider them further. Free-radical eliminations in solution are also known, but are rare.[139]

Orientation in Pyrolytic Eliminations

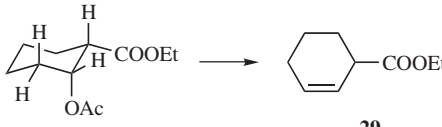
As in the E1-E2-E1cB mechanistic spectrum, Bredt's rule applies; and if a double bond is present, a conjugated system will be preferred, if sterically possible. Apart from these considerations, the following statements can be made for E^i eliminations:

1. In the absence of considerations mentioned below, orientation is statistical and is determined by the number of β hydrogens available (therefore *Hofmann's rule* is followed). For example, *sec*-butyl acetate gives 55–62%

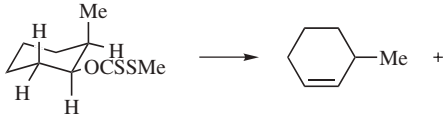
[134]Taylor, R. *J. Chem. Soc. Perkin Trans. 2* ***1975***, 1025.
[135]For a review of the mechanisms of **17-12**, **17-9**, and the pyrolysis of sulfilimines, see Oae, S.; Furukawa, N. *Tetrahedron* ***1977***, *33*, 2359.
[136]For example, see Barton, D.H.R.; Howlett, K.E. *J. Chem. Soc*. ***1949***, 155, 165.
[137]For example, see Rummens, F.H.A. *Recl. Trav. Chim. Pays-Bas* ***1964***, *83*, 901; Louw, R.; Kooyman, E.C. *Recl. Trav. Chim. Pays-Bas* ***1965***, *84*, 1511.
[138]Timokhin, V.I.; Gastaldi, S.; Bertrand, M.P.; Chatgilialoglu, C. *J. Org. Chem*. ***2003***, *68*, 3532.
[139]For examples; see Kampmeier, J.A.; Geer, R.P.; Meskin, A.J.; D'Silva, R.M. *J. Am. Chem. Soc*. ***1966***, *88*, 1257; Kochi, J.K.; Singleton, D.M.; Andrews, L.J. *Tetrahedron* ***1968***, *24*, 3503; Boothe, T.E.; Greene Jr., J.L.; Shevlin, P.B. *J. Org. Chem*. ***1980***, *45*, 794; Stark, T.J.; Nelson, N.T.; Jensen, F.R. *J. Org. Chem*. ***1980***, *45*, 420; Kochi, J.K. *Organic Mechanisms and Catalysis*, Academic Press, NY, ***1978***, pp. 346–349; Kamimura, A.; Ono, N. *J. Chem. Soc., Chem. Commun*. ***1988***, 1278.

1-butene and 38–45% 2-butene,[140] which is close to the 3:2 distribution predicted by the number of hydrogens available.[141]

2. A cis β hydrogen is required. Therefore in cyclic systems, if there is a cis hydrogen on only one side, the double bond will go that way. However, when there is a six-membered transition state, this does not necessarily mean that the leaving groups must be cis to each other, since such transition states need not be completely coplanar. If the leaving group is axial, then the hydrogen obviously must be equatorial (and consequently cis to the leaving group), since the transition state cannot be realized when the groups are both axial. But if the leaving group is equatorial, it can form a transition state with a β hydrogen that is either axial (hence, cis) or equatorial (hence, trans). Thus **28**, in which the leaving group is most likely axial, does not form a double bond in the



28 **29** **(17-4)**



30 **(17-5)**

direction of the carbethoxyl group, even although that would be conjugated, because there is no equatorial hydrogen on that side. Instead it gives 100% **29**.[142] On the other hand, **30**, with an equatorial leaving group, gives ~50% of each alkene, even although, for elimination to the 1-ene, the leaving group must go off with a trans hydrogen.[143]

3. In some cases, especially with cyclic compounds, the more stable alkene forms and Zaitsev's rule applies. For example, menthyl acetate gives 35% of the Hofmann product and 65% of the Zaitsev, even although a cis β hydrogen is present on both sides and the statistical distribution is the other way. A similar result was found for the pyrolysis of menthyl chloride.[144]

4. There are also steric effects. In some cases, the direction of elimination is determined by the need to minimize steric interactions in the transition state or to relieve steric interactions in the ground state.

[140]Froemsdorf, D.H.; Collins, C.H.; Hammond, G.S.; DePuy, C.H. *J. Am. Chem. Soc.* ***1959***, *81*, 643; Haag, W.O.; Pines, H. *J. Org. Chem.* ***1959***, *24*, 877.

[141]DePuy, C.H.; King, R.W. *Chem. Rev.* ***1960***, *60*, 431, have tables showing the product distribution for many cases.

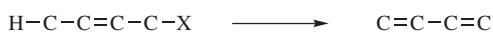
[142]Bailey, W.J.; Baylouny, R.A. *J. Am. Chem. Soc.* ***1959***, *81*, 2126.

[143]Botteron D.G.; Shulman, G.P. *J. Org. Chem.* ***1962***, *27*, 2007.

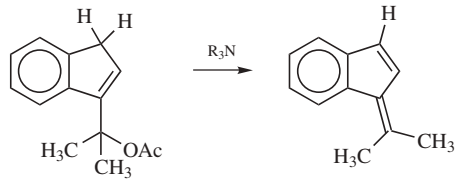
[144]Barton, D.H.R.; Head, A.J.; Williams, R.J. *J. Chem. Soc.* ***1952***, 453; Bamkole, T.; Maccoll, A. *J. Chem. Soc. B* ***1970***, 1159.

1,4 Conjugate Eliminations[145]

1,4-Eliminations of the type



are much rarer than conjugate additions (Chapter 15), but some examples are known.[146] One such is[147]



REACTIONS

First, we consider reactions in which a C=C or a C≡C bond is formed. From a synthetic point of view, the most important reactions for the formation of double bonds are **17-1** (usually by an E1 mechanism), **17-7**, **17-13**, and **17-22** (usually by an E2 mechanism), and **17-4**, **17-5**, and **17-9** (usually by an E^i mechanism). The only synthetically important method for the formation of triple bonds is **17-13**.[148] In the second section, we treat reactions in which C≡N bonds and C=N bonds are formed, and then eliminations that give C=O bonds and diazoalkanes. Finally, we discuss extrusion reactions.

REACTIONS IN WHICH C=C AND C≡C BONDS ARE FORMED

A. Reactions in which Hydrogen Is Removed from One Side

In **17-1**–**17-6**, the other leaving atom is oxygen. In **17-7**–**17-11**, it is nitrogen. For reactions in which hydrogen is removed from both sides, see **19-1**–**19-6**.

[145]Taylor, R., in Patai *The Chemistry of Functional Groups, Supplement B*, pt. 2, Wiley, NY, ***1979***, pp. 885–890; Smith, G.G.; Mutter, L.; Todd, G.P. *J. Org. Chem.* ***1977***, *42*, 44; Chuchani, G.; Dominguez, R.M. *Int. J. Chem. Kinet.* ***1981***, *13*, 577; Hernández, A.; Chuchani, G. *Int. J. Chem. Kinet.* ***1983***, *15*, 205.

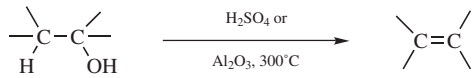
[146]For a review of certain types of 1,4- and 1,6-eliminations, see Wakselman, M. *Nouv. J. Chem.* ***1983***, *7*, 439.

[147]Thibblin, A. *J. Chem. Soc. Perkin Trans. 2* ***1986***, 321; Ölwegård, M.; Ahlberg, P. *Acta Chem. Scand.* ***1990***, *44*, 642. For studies of the stereochemistry of 1,4-eliminations, see Hill, R.K.; Bock, M.G. *J. Am. Chem. Soc.* ***1978***, *100*, 637; Moss, R.J.; Rickborn, B. *J. Org. Chem.* ***1986***, *51*, 1992; Ölwegård, M.; Ahlberg, P. *J. Chem. Soc., Chem. Commun.* ***1989***, 1279.

[148]For reviews of methods for preparing alkynes, see Friedrich, K., in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C*, pt. 2, Wiley, NY, ***1983***; pp. 1376–1384; Ben-Efraim, D.A., in Patai, S. *The Chemistry of the Carbon–Carbon Triple Bond*, pt. 2, Wiley, NY, ***1978***, pp. 755–790. For a comparative study of various methods, see Mesnard, D.; Bernadou, F.; Miginiac, L. *J. Chem. Res. (S)* ***1981***, 270, and references cited therein.

17-1 Dehydration of Alcohols

Hydro-hydroxy-elimination



Dehydration of alcohols can be accomplished in several ways. Both H_2SO_4 and H_3PO_4 are common reagents, but in many cases these lead to rearrangement products and to ether formation (**10-12**). If the alcohol can be evaporated, vapor-phase elimination over Al_2O_3 is an excellent method since side reactions are greatly reduced. This method has even been applied to such high-molecular-weight alcohols as 1-dodecanol.[149] Other metallic oxides (e.g., Cr_2O_3, TiO_2, WO_3) have also been used, as have been sulfides, other metallic salts, and zeolites. The presence of an electron-withdrawing group usually facilitates elimination of water, as in the aldol condensation (**16-35**). 2-Nitroalcohols, for example, give conjugated nitro compounds when heated with zeolite Y–Y.[150] Treating a 4-hydroxy lactam with DMAP (*N,N*-dimethylaminopyridine) and Boc anhydride leads to the conjugated lactam.[151] Elimination of serine derivatives to α-alkylidene amino acid derivatives was accomplished with $(EtO)_2POCl$.[152] Another method of avoiding side reactions is the conversion of alcohols to esters, and the pyrolysis of these (**17-4**–**17-6**). The ease of dehydration increases with α branching, and tertiary alcohols are dehydrated so easily with only a trace of acid that it sometimes happens even when the investigator desires otherwise. It may also be recalled that the initial alcohol products of many base-catalyzed condensations dehydrate spontaneously (Chapter 16) because the new double bond can be in conjugation with one already there. Many other dehydrating agents[153] have been used on occasion: P_2O_5, I_2, $ZnCl_2$, Ph_3BiBr_2/I_2,[154] PPh_3–I_2,[155] BF_3–etherate, DMSO, SiO_2–Cl/Me_3SiCl,[156] $KHSO_4$, anhydrous $CuSO_4$, and phthalic anhydride, among others. Secondary and tertiary alcohols can also be dehydrated, without rearrangements, simply on refluxing in HMPA.[157] With nearly all reagents, dehydration follows Zaitsev's rule.

[149]For example, see Spitzin, V.I.; Michailenko, I.E.; Pirogowa, G.N. *J. Prakt. Chem.* ***1964***, *[4] 25*, 160; Bertsch, H.; Greiner, A.; Kretzschmar, G.; Falk, F. *J. Prakt. Chem.* ***1964***, *[4] 25*, 184.

[150]Anbazhagan, M.; Kumaran, G.; Sasidharan, M. *J. Chem. Res. (S)* ***1997***, 336.

[151]Mattern, R.-H. *Tetrahedron Lett.* ***1996***, *37*, 291.

[152]Berti, F.; Ebert, C.; Gardossi, L. *Tetrahedron Lett.* ***1992***, *33*, 8145.

[153]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 291–294.

[154]Dorta, R.L.; Suárez, E.; Betancor, C. *Tetrahedron Lett.* ***1994***, *35*, 5035.

[155]Alvarez-Manzaneda, E.J.; Chahboun, R.; Torres, E.C.; Alvarez, E.; Alvarez-Manzaneda, R.; Haidour, A.; Ramos, J. *Tetrahedron Lett.* ***2004***, *45*, 4453.

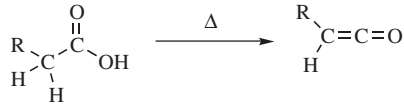
[156]Firouzabadi, H.; Iranpoor, N.; Hazarkhani, H.; Karimi, B. *Synth. Commun.* ***2003***, *33*, 3653.

[157]Monson, R.S. *Tetrahedron Lett.* ***1971***, 567; Monson, R.S.; Priest, D.N. *J. Org. Chem.* ***1971***, *36*, 3826; Lomas, J.S.; Sagatys, D.S.; Dubois, J.E. *Tetrahedron Lett.* ***1972***, 165.

An exception involves the passage of hot alcohol vapors over thorium oxide at 350–450°C, under which conditions Hofmann's rule is followed,[158] and the mechanism is probably different. Cyclobutanol derivatives can be opened in the presence of a palladium catalyst. 2-Phenylbicyclo[3.2.0]octan-2-ol, for example, reacted with a catalytic amount of palladium acetate in the presence of pyridine and oxygen to give phenyl methylenecyclohexane ketone.[159]

Transition metals can induce the dehydration of certain alcohols. β-Hydroxy ketones are converted to conjugated ketones by treatment with $CeCl_3$ and NaI.[160] In the presence of a palladium complex, alkyl cyclopropanols undergo a dehydration reaction to give a conjugated ketone.[161] A δ-hydroxy-α,β-unsaturated aldehyde was converted to a dienyl aldehyde with a hafnium catalyst.[162] β-Hydroxy esters are converted to conjugated esters when treated with 2 equivalents of SmI_2.[163] The reaction of a β-hydroxy nitrile with methylmagneisum chloride[164] or with MgO[165] leads to a conjugated nitrile. In another variation of the dehydration reaction, vicinal bromohydrins are converted to alkenes upon treatment with In, $InCl_3$, and a palladium catalyst.[166] Chlorohydrins react similarly when treated with samarium, and then diiodomethane.[167]

Carboxylic acids can be dehydrated by pyrolysis, the product being a ketene:



Ketene itself is commercially prepared in this manner. Carboxylic acids have also been converted to ketenes by treatment with certain reagents, among them TsCl,[168] dicyclohexylcarbodiimide,[169] and 1-methyl-2-chloropyridinium iodide (*Mukaiyama's reagent*).[170] Analogously, amides can be dehydrated with P_2O_5, pyridine,

[158]Lundeen, A.J.; Van Hoozer, R. *J. Am. Chem. Soc.* ***1963***, *85*, 2180; *J. Org. Chem.* ***1967***, *32*, 3386. See also, Davis, B.H. *J. Org. Chem.* ***1982***, *47*, 900; Iimori, T.; Ohtsuka, Y.; Oishi, T. *Tetrahedron Lett.* ***1991***, *32*, 1209.

[159]Nishimura, T.; Ohe, K.; Uemura, S. *J. Am. Chem. Soc.* ***1999***, *121*, 2645.

[160]Bartoli, G.; Bellucci, M.C.; Petrini, M.; Marcantoni, E.; Sambri, L.; Torregiani, E. *Org. Lett.* ***2000***, *2*, 1791.

[161]Okumoto, H.; Jinnai, T.; Shimizu, H.; Harada, Y.; Mishima, H.; Suzuki, A. *Synlett* ***2000***, 629.

[162]Saito, S.; Nagahara, T.; Yamamoto, H. *Synlett* ***2001***, 1690.

[163]Concellón, J.M.; Pérez-Andrés, J.A.; Rodríguez-Solla, H. *Angew. Chem. Int. Ed.* ***2000***, *39*, 2773.

[164]Fleming, F.F.; Shook, B.C. *Tetrahedron Lett.* ***2000***, *41*, 8847.

[165]Fleming, F.F.; Shook, B.C. *J. Org. Chem.* ***2002***, *67*, 3668.

[166]Cho, S.; Kang, S.; Keum, G.; Kang, S.B.; Han, S.-Y.; Kim, Y. *J. Org. Chem.* ***2003***, *68*, 180.

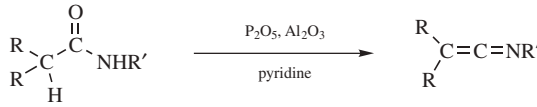
[167]Concellón, J.M.; Rodríguez-Solla, H.; Huerta, M..; Pérez-Andrés, J.A. *Eur. J. Org. Chem.* ***2002***, 1839.

[168]Brady, W.T.; Marchand, A.P.; Giang, Y.F.; Wu, A. *Synthesis* ***1987***, 395; *J. Org. Chem.* ***1987***, *52*, 3457.

[169]Olah, G.A.; Wu, A.; Farooq, O. *Synthesis* ***1989***, 568.

[170]Brady, W.T.; Marchand, A.P.; Giang, Y.F.; Wu, A. *J. Org. Chem.* ***1987***, *52*, 3457; Funk, R.L.; Abelman, M.M.; Jellison, K.M. *Synlett* ***1989***, 36.

and Al_2O_3 to give ketenimines:[171]



There is no way in which dehydration of alcohols can be used to prepare triple bonds: *gem*-diols and vinylic alcohols are not normally stable compounds and *vic*-diols[172] give either conjugated dienes or lose only 1 equivalent of water to give an aldehyde or ketone. Dienes can be prepared, however, by heating alkynyl alcohols with triphenyl phosphine.[173]

When proton acids catalyze alcohol dehydration, the mechanism is E1.[174] The principal process involves conversion of ROH to ROH_2^+ and cleavage of the latter to R^+ and H_2O, although with some acids a secondary process probably involves conversion of the alcohol to an inorganic ester and ionization of *this* (illustrated for H_2SO_4):

Note that these mechanisms are the reverse of those involved in the acid-catalyzed hydration of double bonds (**15-3**), in accord with the principle of microscopic reversibility. With anhydrides (e.g., P_2O_5, phthalic anhydride), as well as with some other reagents, such as HMPA,[175] it is likely that an ester is formed, and the leaving group is the conjugate base of the corresponding acid. In these cases, the mechanism can be E1 or E2. The mechanism with Al_2O_3 and other solid catalysts has been studied extensively, but is poorly understood.[176]

Magnesium alkoxides (formed by $ROH + Me_2Mg \rightarrow ROMgMe$) have been decomposed thermally, by heating at 195–340°C to give the alkene, CH_4, and MgO.[177] Syn-elimination is found and an E^i mechanism is likely. Similar decomposition of aluminum and zinc alkoxides has also been accomplished.[178,189]

[171]Stevens, C.L.; Singhal, G.H. *J. Org. Chem.* ***1964***, *29*, 34.

[172]For a review on the dehydration of 1,2- and 1,3-diols, see Bartók, M.; Molnár, A., in Patai, S. *The Chemistry of Functional Groups, Supplement E*, pt. 2, Wiley, NY, ***1980***, pp. 721–760.

[173]Guo, C.; Lu, X. *J. Chem. Soc., Chem. Commun*. ***1993***, 394.

[174]For reviews of dehydration mechanisms, see Vinnik, M.I.; Obraztsov, P.A. *Russ. Chem. Rev*. ***1990***, *59*, 63; Saunders, Jr., W.H.; Cockerill, A.F. *Mechanisms of Elimination Reactions*, Wiley, NY, ***1973***, pp. 221–274, 317–331; Knözinger, H., in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 2, Wiley, NY, ***1971***, pp. 641–718.

[175]See, for example, Kawanisi, M.; Arimatsu, S.; Yamaguchi, R.; Kimoto, K. *Chem. Lett*. ***1972***, 881.

[176]For reviews, see Beránek, L.; Kraus, M., in Bamford, C,H; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 20, Elsevier, NY, ***1978***, pp. 274–295; Pines, H. *Intra-Sci. Chem. Rep*. ***1972***, *6*(*2*), 1, pp. 17–21; Noller, H.; Andréu, P.; Hunger, M. *Angew. Chem. Int. Ed*. ***1971***, *10*, 172; Knözinger, H. *Angew. Chem. Int. Ed*. ***1968***, *7*, 791. See also, Berteau, P.; Ruwet, M.; Delmon, B. *Bull. Soc. Chim. Belg*. ***1985***, *94*, 859.

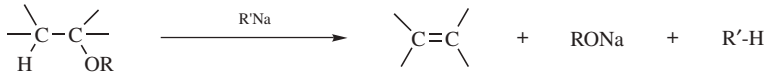
[177]Ashby, E.C.; Willard, G.F.; Goel, A.B. *J. Org. Chem*. ***1979***, *44*, 1221.

[178]Brieger, G.; Watson, S.W.; Barar, D.G.; Shene, A.L. *J. Org. Chem*. ***1979***, *44*, 1340.

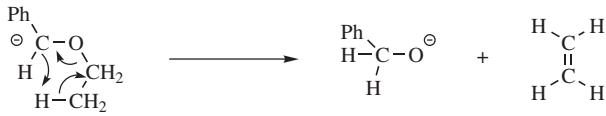
OS **I**, 15, 183, 226, 280, 345, 430, 473, 475; **II**, 12, 368, 408, 606; **III**, 22, 204, 237, 312, 313, 353, 560, 729, 786; **IV**, 130, 444, 771; **V**, 294; **VI**, 307, 901; **VII**, 210, 241, 363, 368, 396; **VIII**, 210, 444. See also, OS **VII**, 63; **VIII**, 306, 474. No attempt has been made to list alkene-forming dehydration reactions accompanying condensations or rearrangements.

17-2 Cleavage of Ethers to Alkenes

Hydro-alkoxy-elimination



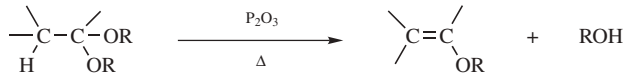
Alkenes can be formed by the treatment of ethers with very strong bases, such as alkylsodium or alkyllithium[179] compounds, sodium amide,[180] or LDA,[181] although there are side reactions with many of these reagents. The reaction is aided by electron-withdrawing groups in the β position, and, for example, $EtOCH_2CH(COOEt)_2$ can be converted to $CH_2{=}C(COOEt)_2$ without any base at all, but simply on heating.[182] *tert*-Butyl ethers are cleaved more easily than others. Several mechanisms are possible. In many cases, the mechanism is probably E1cB or on the E1cB side of the mechanistic spectrum,[183] since the base required is so strong, but it has been shown (by the use of $PhCD_2OEt$) that $PhCH_2OEt$ reacts by the five-membered E^i mechanism:[184] Propargylic benzyl ethers are converted to conjugated dienes by heating with a ruthenium catalyst.[185]



Ethers have also been converted to alkenes and alcohols by passing vapors over hot P_2O_5 or Al_2O_3 (this method is similar to **17-1**), but this is not a general reaction. Cyclic ethers, such as THF, react slowly with organolithium reagents with cleavage that produces a C=C unit.[186] Fragmentation of 2,5-dihydrofuran with ethylmagnesium chloride and a chiral zirconium catalyst leads to a chiral, homoallylic alcohol.[187] However, acetals can be converted to enol ethers (**31**) in this manner.

[179]Hodgson, D.M.; Stent, M.A.H.; Wilson, F.X. *Org. Lett.* ***2001***, *3*, 3401.
[180]For a review, see Maercker, A. *Angew. Chem. Int. Ed.* ***1987***, *26*, 972.
[181]Fleming, F.F.; Wang, Q.; Steward, O.W. *J. Org. Chem.* ***2001***, *66*, 2171.
[182]Feely, W.; Boekelheide, V. *Org Synth.* ***IV***, 298.
[183]For an investigation in the gas phase, see DePuy, C.H.; Bierbaum, V.M. *J. Am. Chem. Soc.* ***1981***, *103*, 5034.
[184]Letsinger, R.L.; Pollart, D.F. *J. Am. Chem. Soc.* ***1956***, *78*, 6079.
[185]Yeh, K.-L.; Liu, B.; Lo, C.-Y.; Huang, H.-L.; Liu, R.-S. *J. Am. Chem. Soc.* ***2002***, *124*, 6510.
[186]For the mechanism of *n*-butyllithium cleavage of 2-methyltetrahydrofuran, see Cohen, T.; Stokes, S. *Tetrahedron Lett.* ***1993***, *34*, 8023.
[187]Morken, J.P.; Didiuk, M.T.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***1993***, *115*, 6997.

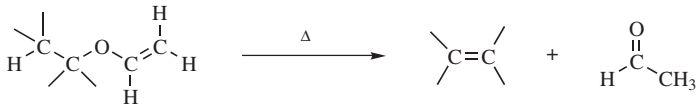
When ketals react with 2 equivalents of triisobutylaluminum, the product is a vinyl ether.[188]



31

This can also be done at room temperature by treatment with trimethylsilyl triflate and a tertiary amine[189] or with Me_3SiI in the presence of hexamethyldisilazane.[190]

Enol ethers can be pyrolyzed to alkenes and aldehydes in a manner similar to that of **17-4**



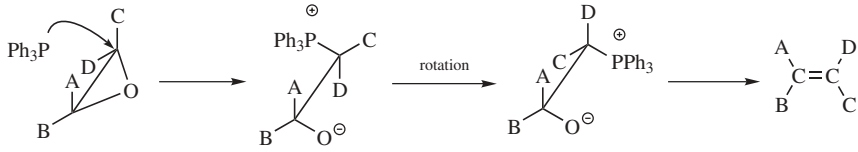
The rate of this reaction for R–O–CH=CH_2 increased in the order Et < *i*Pr < *t*-Bu.[191] The mechanism is similar to that of **17-4**.

OS **IV**, 298, 404; **V**, 25, 642, 859, 1145; **VI**, 491, 564, 584, 606, 683, 948; **VIII**, 444.

17-3 The Conversion of Epoxides and Episulfides to Alkenes

epi-Oxy-elimination

Epoxides can be converted to alkenes[192] by treatment with triphenylphosphine[193] or triethyl phosphite $P(OEt)_3$.[194] The first step of the mechanism is nucleophilic substitution (**10-35**), followed by a four-center elimination. Since inversion accompanies the substitution, the overall elimination is anti, that is, if two groups A and C are cis in the epoxide, they will be trans in the alkene:



Betaine

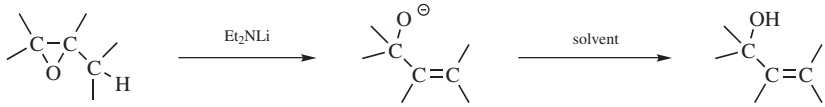
[188]Cabrera, G.; Fiaschi, R.; Napolitano, E. *Tetrahedron Lett.* ***2001***, *42*, 5867.
[189]Gassman, P.G.; Burns, S.J. *J. Org. Chem.* ***1988***, *53*, 5574.
[190]Miller, R.D.; McKean, D.R. *Tetrahedron Lett.* ***1982***, *23*, 323. For another method, see Marsi, M.; Gladysz, J.A. *Organometallics* ***1982***, *1*, 1467.
[191]McEwen, I.; Taylor, R. *J. Chem. Soc. Perkin Trans. 2* ***1982***, 1179. See also Taylor, R. *J. Chem. Soc. Perkin Trans. 2* ***1988***, 737.
[192]For reviews, see Wong, H.N.C.; Fok, C.C.M.; Wong, T. *Heterocycles* ***1987***, *26*, 1345; Sonnet, P.E. *Tetrahedron* ***1980***, *36*, 557, pp. 576.
[193]Wittig, G.; Haag, W. *Chem. Ber.* ***1955***, *88*, 1654.
[194]Scott, C.B. *J. Org. Chem.* ***1957***, *22*, 1118.

Alternatively, the epoxide can be treated with lithium diphenylphosphide, Ph_2PLi, and the product quaternized with methyl iodide.[195] Alkenes have also been obtained from epoxides by reaction with a large number of reagents,[196] among them Li in THF,[197] TsOH and NaI,[198] trimethylsilyl iodide,[199] PI_3,[200] F_3COOH–NaI,[201] SmI_2,[202] $Mo(CO)_6$, $TpReO_3$, where Tp is a pyrazolyl borate,[203] and the tungsten reagents mentioned in **17-18**. Some of these methods give syn elimination. Treatment of cyclooctane oxide with Ph_3P–$OPPh_3$ and NEt_3 gave cyclooctadiene.[204] Sodium amalgam with a cobalt–salen complex converted epoxides to alkenes.[205]

Epoxides can be converted to allylic alcohols[206] by treatment with several reagents, including *sec*-butyllithium,[207] *tert*-butyldimethylsilyl iodide,[208] and $i Pr_2N$-Li–*t*-BuOK (the *LIDAKOR reagent*).[209] Phenyllithium reacts with epoxides in the presence of lithium tetramethylpiperidide (LTMP) to give a trans alkene.[210] Sulfur ylids, such as $Me_2S{=}CH_2$, also convert epoxides to allylic alcohols.[211] Bromomethyl epoxides react with $InCl_3/NaBH_4$ to give an allylic alcohol.[212] α,β-Epoxy ketones are converted to conjugated ketones by treatment with NaI in acetone in the presence of Amberlyst 15,[213] or with 2.5 equivalents of SmI_2.[214] Cyclic epoxides are converted to conjugated dienes by heating with $(NMe_2)_2P(=O)Cl$ and H_2O.[215]

[195]Vedejs, E.; Fuchs, P.L. *J. Am. Chem. Soc*. ***1971***, *93*, 4070; ***1973***, *95*, 822.
[196]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 272–277.
[197]Gurudutt, K.N.; Ravindranath, B. *Tetrahedron Lett*. ***1980***, *21*, 1173.
[198]Baruah, R.N.; Sharma, R.P.; Baruah, J.N. *Chem. Ind. (London)* ***1983***, 524.
[199]Denis, J.N.; Magnane, R.; Van Eenoo, M.; Krief, A. *Nouv. J. Chim*. ***1979***, *3*, 705. For other silyl reagents, see Reetz, M.T.; Plachky, M. *Synthesis* ***1976***, 199; Dervan, P.B.; Shippey, M.A. *J. Am. Chem. Soc*. ***1976***, *98*, 1265; Caputo, R.; Mangoni, L.; Neri, O.; Palumbo, G. *Tetrahedron Lett*. ***1981***, *22*, 3551.
[200]Denis, J.N.; Magnaane, R.; Van Eenoo, M.; Krief, A. *Nouv. J. Chim*. ***1979***, *3*, 705.
[201]Sarma, D.N.; Sharma, R.P. *Chem. Ind. (London)* ***1984***, 712.
[202]Girard, P.; Namy, J.L.; Kagan, H.B. *J. Am. Chem. Soc*. ***1980***, *102*, 2693; Matsukawa, M.; Tabuchi, T.; Inanaga, J.; Yamaguchi, M. *Chem. Lett*. ***1987***, 2101.
[203]Gable, K.P.; Brown, E.C. *Synlett* ***2003***, 2243.
[204]Hendrickson, J.B.; Walker, M.A.; Varvak, A.; Hussoin, Md.S. *Synlett* ***1996***, 661.
[205]Isobe, H.; Branchaud, B.P. *Tetrahedron Lett*. ***1999***, *40*, 8747.
[206]For reviews, see Smith, J.G. *Synthesis* ***1984***, 629, pp. 637–642; Crandall, J.K.; Apparu, M. *Org. React*. ***1983***, *29*, 345. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 231–233. See also, Okovytyy, S.; Gorb, L.; Leszczynski, J. *Tetrahedron* ***2001***, *57*, 1509.
[207]Doris, E.; Dechoux, L.; Mioskowski, C. *Tetrahedron Lett*. ***1994***, *35*, 7943.
[208]Detty, M.R. *J. Org. Chem*. ***1980***, *45*, 924. For another silyl reagent, see Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc*. ***1979***, *101*, 2738.
[209]Mordini, A.; Ben Rayana, E.; Margot, C.; Schlosser, M. *Tetrahedron* ***1990***, *46*, 2401; Degl'Innocenti, A.; Mordini, A.; Pecchi, S.; Pinzani, D.; Reginato, G.; Ricci, A. *Synlett* ***1992***, 753, 803; Thurner, A.; Faigl, F.; Töke, L.; Mordini, A.; Valacchi, M.; Reginato, G.; Czira, G. *Tetrahedron* ***2001***, *57*, 8173.
[210]Hodgson, D.M.; Fleming, M.J.; Stanway, S.J. *J. Am. Chem. Soc*. ***2004***, *126*, 12250.
[211]Alcaraz, L.; Cridland, A.; Kinchin, E. *Org. Lett*. ***2001***, *3*, 4051.
[212]Ranu, B.C.; Banerjee, S.; Das, A. *Tetrahedron Lett*. ***2004***, *45*, 8579.
[213]Righi, G.; Bovicelli, P.; Sperandio, A. *Tetrahedron* ***2000***, *56*, 1733.
[214]Concellón, J.M.; Bardales, E. *J. Org. Chem*. ***2003***, *68*, 9492; Concellón, J.M.; Bardales, E. *Org. Lett*. ***2002***, *4*, 189. In a similar manner, epoxy amides are converted to conjugated amides, see Concellón, J.M.; Bardales, E. *Eur. J. Org. Chem*. ***2004***, 1523.
[215]Demir, A.S. *Tetrahedron* ***2001***, *57*, 227.

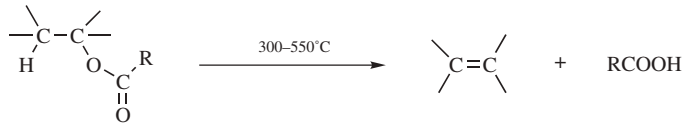
When an optically active reagent is used, optically active allylic alcohols can be produced from achiral epoxides.[216] Sparteine and *sec*-butyllithium generate a chiral base that leads to formation of chiral allylic alcohols.[217] Chiral diamines react with organolithium reagents to produce chiral bases that convert epoxides to allylic alcohols with good enantioselectivity.[218] Chiral diamines with a mixture of LDA and DBU (p. 1132) give similar results.[219]



Episulfides[220] can be converted to alkenes.[221] However, in this case the elimination is syn, so the mechanism cannot be the same as that for conversion of epoxides. The phosphite attacks sulfur rather than carbon. Among other reagents that convert episulfides to alkenes are Bu_3SnH,[222] certain rhodium complexes,[223] $LiAlH_4$[224] (this compound behaves quite differently with epoxides, see **19-35**), and meI.[225] The reaction of H_2S/PPh_3 and $MeReO_3$ converts episulfides to alkenes.[226] Episulfoxides can be converted to alkenes and sulfur monoxide simply by heating.[227]

17-4 Pyrolysis of Carboxylic Acids and Esters of Carboxylic Acids

Hydro-acyloxy-elimination



[216]Su, H.; Walder, L.; Zhang, Z.; Scheffold, R. *Helv. Chim. Acta* ***1988***, *71*, 1073, and references cited therein. Also see, Asami, M.; Suga, T.; Honda, K.; Inoue, S. *Tetrahedron Lett.* ***1997***, *38*, 6425.; Lill, S.O.N.; Pettersen, D.; Amedjkouh, M.; Ahlberg, P. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 3054; Brookes, P.C.; Milne, D.J.; Murphy, P.J.; Spolaore, B. *Tetrahedron* ***2002***, *58*, 4675.

[217]Alexakis, A.; Vrancken, E.; Mangeney, P. *J. Chem. Soc. Perkin Trans. 1* ***2000***, 3354.

[218]de Sousa, S.E.; O'Brien, P.; Steffens, H.C. *Tetrahedron Lett.* ***1999***, *40*, 8423; Equey, O.; Alexakis, A. *Tetrahedron Asymmetry* ***2004***, *15*, 1069.

[219]Bertilsson, S.K.; Södergren, M.J.; Andersson, P.G. *J. Org. Chem.* ***2002***, *67*, 1567; Bertilsson, S.K.; Andersson, P.G. *Tetrahedron* ***2002***, *58*, 4665.

[220]For a review of this reaction, see Sonnet, P.E. *Tetrahedron* ***1980***, *36*, 557, see p. 587. For a review of episulfides, see Goodman, L.; Reist, E.J., in Kharasch; Meyers *The Chemistry of Organic Sulfur Compounds*, Vol. 2; Pergamon: Elmsford, NY, ***1966***, pp. 93–113.

[221]Neureiter, N.P.; Bordwell, F.G. *J. Am. Chem. Soc.* ***1959***, *81*, 578; Davis, R.E. *J. Org. Chem.* ***1957***, *23*, 1767.

[222]Schauder, J.R.; Denis, J.N.; Krief, A. *Tetrahedron Lett.* ***1983***, *24*, 1657.

[223]Calet, S.; Alper, H. *Tetrahedron Lett.* ***1986***, *27*, 3573.

[224]Lightner, D.A.; Djerassi, C. *Chem. Ind. (London)* ***1962***, 1236; Latif, N.; Mishriky, N.; Zeid, I. *J. Prakt. Chem.* ***1970***, *312*, 421.

[225]Culvenor, C.J.; Davies, W.; Heath, N.S. *J. Chem. Soc.* ***1949***, 282; Helmkamp, G.K.; Pettitt, D.J. *J. Org. Chem.* ***1964***, *29*, 3258.

[226]Jacob, J.; Espenson, J.H. *Chem. Commun.* ***1999***, 1003.

[227]Hartzell, G.E.; Paige, J.N. *J. Am. Chem. Soc.* ***1966***, *88*, 2616, *J. Org. Chem.* ***1967***, *32*, 459; Aalbersberg, W.G.L.; Vollhardt, K.P.C. *J. Am. Chem. Soc.* ***1977***, *99*, 2792.

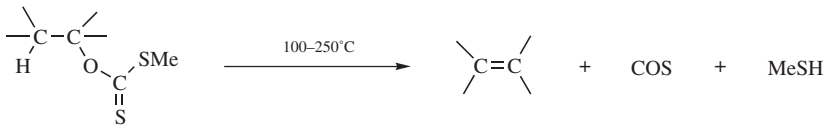
Direct elimination of a carboxylic acid to an alkene has been accomplished by heating in the presence of palladium catalysts.[228] Carboxylic esters in which the alkyl group has a β hydrogen can be pyrolyzed, most often in the gas phase, to give the corresponding acid and an alkene.[229] No solvent is required. Since rearrangement and other side reactions are few, the reaction is synthetically very useful and is often carried out as an indirect method of accomplishing **17-1**. The yields are excellent and the workup is easy. Many alkenes have been prepared in this manner. For higher alkenes (above $\sim C_{10}$) a better method is to pyrolyze the alcohol in the presence of acetic anhydride.[230]

The mechanism is E^i (see p. 1507). Lactones can be pyrolyzed to give unsaturated acids, provided that the six-membered transition state required for E^i reactions is available (it is not available for five- and six-membered lactones, but it is for larger rings[231]). Amides give a similar reaction, but require higher temperatures.

Allylic acetates give dienes when heated with certain palladium[232] or molybdenum[233] compounds.

OS **III**, 30; **IV**, 746; **V**, 235; **IX**, 293.

17-5 The Chugaev Reaction



Methyl xanthates are prepared by treatment of alcohols with NaOH and CS_2 to give RO–C(=S)–SNa, followed by treatment of this with methyl iodide.[234] Pyrolysis of the xanthate to give the alkene, COS, and the thiol is called the *Chugaev reaction*.[235] The reaction is thus, like **17-4**, an indirect method of accomplishing **17-2**. The temperatures required with xanthates are lower than with ordinary esters, which is advantageous because possible isomerization of the resulting alkene is minimized. The mechanism is E^i, similar to that of **17-4**. For a time there was doubt as to which sulfur atom closed the ring, but now there is much evidence, including

[228]Miller, J.A.; Nelson, J.A.; Byrne, M.P. *J. Org. Chem.* ***1993***, *58*, 18; Gooßen, L.J.; Rodríguez, N. *Chem. Commun.* ***2004***, 724.

[229]For a review, see DePuy, C.H.; King, R.W. *Chem. Rev.* ***1960***, *60*, 431, 432. For some procedures, see Jenneskens, L.W.; Hoefs, C.A.M.; Wiersum, U.E. *J. Org. Chem.* ***1989***, *54*, 5811, and references cited therein.

[230]Aubrey, D.W.; Barnatt, A.; Gerrard, W. *Chem. Ind. (London)* ***1965***, 681.

[231]See, for example, Bailey, W.J.; Bird, C.N. *J. Org. Chem.* ***1977***, *42*, 3895.

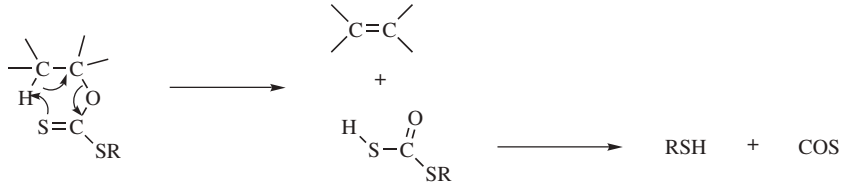
[232]For a review, see Heck, R.F. *Palladium Reagents in Organic Synthesis*; Academic Press, NY, ***1985***, pp. 172–178.

[233]Trost, B.M.; Lautens, M.; Peterson, B. *Tetrahedron Lett.* ***1983***, *24*, 4525.

[234]For a method of preparing xanthates from alcohols in one laboratory step, see Lee, A.W.M.; Chan, W.H.; Wong, H.C.; Wong, M.S. *Synth. Commun.* ***1989***, *19*, 547; Nagle, A.S.; Salvataore, R.N.; Cross, R.M.; Kapxhiu, E.A.; Sahab, S.; Yoon, C.H.; Jung, K.W. *Tetrahedron Lett.* ***2003***, *44*, 5695.

[235]For reviews, see DePuy, C.H.; King, R.W. *Chem. Rev.* ***1960***, *60*, 431, see p. 444; Nace, H.R. *Org. React.* ***1962***, *12*, 57.

the study of ^{34}S and ^{13}C isotope effects, to show that it is the C=S sulfur:[236] In a structural variation of this reaction, heating a propargylic xanthate with 2,4,6-trimethylpyridinium trifluoromethyl sulfonate leads to formation of an alkene.[237]



The mechanism is thus exactly analogous to that of **17-5**.

OS **VII**, 139.

17-6 Decomposition of Other Esters

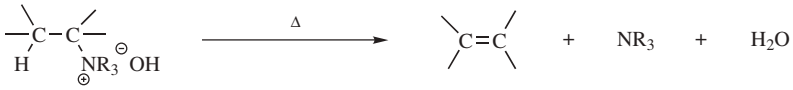
Hydro-tosyloxy-elimination

Several types of inorganic ester can be cleaved to alkenes by treatment with bases. Esters of sulfuric, sulfurous, and other acids undergo elimination in solution by E1 or E2 mechanisms, as do tosylates and other esters of sulfonic acids.[238] It has been shown that bis(tetra-*n*-butylammonium) oxalate, $(Bu_4N^+)_2\ (COO^-)_2$, is an excellent reagent for inducing tosylates to undergo elimination rather than substitution.[239] Aryl sulfonates have also been cleaved without a base. Esters of 2-pyridinesulfonic acid and 8-quinolinesulfonic acid gave alkenes in high yields simply on heating, without a solvent.[240] Phosphonate esters have been cleaved to alkenes by treatment with Lawesson's reagent.[241] Esters of $PhSO_2OH$ and TsOH behaved similarly when heated in a dipolar aprotic solvent, such as Me_2SO or HMPA.[242]

OS, **VI**, 837; **VII**, 117.

17-7 Cleavage of Quaternary Ammonium Hydroxides

Hydro-trialkylammonio-elimination



[236]Bader, R.F.W.; Bourns, A.N. *Can. J. Chem.* ***1961***, *39*, 348.

[237]Fauré-Tromeur, M.; Zard, S.Z. *Tetrahedron Lett.* ***1999***, *40*, 1305.

[238]For a list of reagents used for sulfonate cleavages, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 294–295.

[239]Corey, E.J.; Terashima, S. *Tetrahedron Lett.* ***1972***, 111.

[240]Corey, E.J.; Posner, G.G.; Atkinson, R.F.; Wingard, A.K.; Halloran, D.J.; Radzik, D.M.; Nash, J.J. *J. Org. Chem.* ***1989***, *54*, 389.

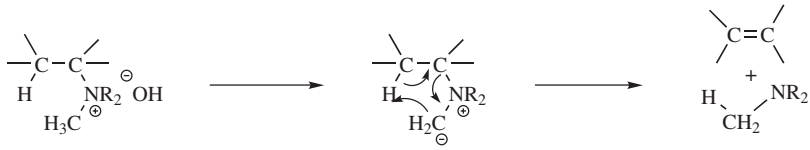
[241]Shimagaki, M.; Fujieda, Y.; Kimura, T.; Nakata, T. *Tetrahedron Lett.* ***1995***, *36*, 719.

[242]Nace, H.R. *J. Am. Chem. Soc.* ***1959***, *81*, 5428.

Cleavage of quaternary ammonium hydroxides is the final step of the process known as *Hofmann exhaustive methylation or Hofmann degradation*.[243] In the first step, a primary, secondary, or tertiary amine is treated with enough methyl iodide to convert it to the quaternary ammonium iodide (**10-31**). In the second step, the iodide is converted to the hydroxide by treatment with silver oxide. In the cleavage step, an aqueous or alcoholic solution of the hydroxide is distilled, often under reduced pressure. The decomposition generally takes place at a temperature between 100 and 200°C. Alternatively, the solution can be concentrated to a syrup by distillation or freeze-drying.[244] When the syrup is heated at low pressures, the cleavage reaction takes place at lower temperatures than are required for the reaction in the ordinary solution, probably because the base (HO^- or RO^-) is less solvated.[245] The reaction has never been an important synthetic tool, but in the nineteenth century and the first part of the twentieth century, it saw much use in the determination of the structure of unknown amines, especially alkaloids. In many of these compounds, the nitrogen is in a ring, or even at a ring junction, and in such cases the alkene still contains nitrogen. Repetitions of the process are required to remove the nitrogen completely, as in the conversion of 2-methylpiperidine to 1,5-hexadiene by two rounds of exhaustive methylation followed by pyrolysis.

A side reaction involving nucleophilic substitution to give an alcohol ($R_4N^+\ ^-OH \rightarrow ROH + R_3N$) generally accompanies the normal elimination reaction,[246] but seldom causes trouble. However, when none of the four groups on the nitrogen has a β hydrogen, substitution is the only reaction possible. On heating $Me_4N^+\ ^-OH$ in water, methanol is obtained, although without a solvent the product is not methanol, but dimethyl ether.[247]

The mechanism is usually E2. Hofmann's rule is generally obeyed by acyclic and Zaitsev's rule by cyclohexyl substrates (p. 1498). In certain cases, where the molecule is highly hindered, a five-membered E^i mechanism, similar to that in **17-8**, has been shown to operate. That is, the hydroxide in these cases does not attract the β hydrogen, but instead removes one of the methyl hydrogens:

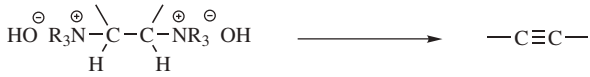


[243]For reviews, see Bentley, K.W., in Bentley, K.W.; Kirby, G.W *Elucidation of Organic Structures by Physical and Chemical Methods*, 2nd ed. (Vol. 4 of Weissberger *Techniques of Chemistry*), pt. 2, Wiley, NY, ***1973***, pp. 255–289; White, E.H.; Woodcock, D.J., in Patai, S. *The Chemistry of the Amino Group*, Wiley, NY, ***1968***, pp. 409–416; Cope, A.C.; Trumbull, E.R. *Org. React*. ***1960***, *11*, 317.
[244]Archer, D.A. *J. Chem. Soc. C* ***1971***, 1327.
[245]Saunders, Jr., W.H.; Cockerill, A.F. *Mechanisms of Elimination Reactions*, Wiley, NY, ***1973***, pp. 4–5.
[246]Baumgarten, R.J. *J. Chem. Educ*. ***1968***, *45*, 122.
[247]Musker, W.K. *J. Chem. Educ*. ***1968***, *45*, 200; Musker, W.K.; Stevens, R.R. *J. Am. Chem. Soc*. ***1968***, *90*, 3515; Tanaka, J.; Dunning, J.E.; Carter, J.C. *J. Org. Chem*. ***1966***, *31*, 3431.

The obvious way to distinguish between this mechanism and the ordinary E2 mechanism is by the use of deuterium labeling. For example, if the reaction is carried out on a quaternary hydroxide deuterated on the β carbon ($R_2CDCH_2NMe_3^+$ ^-OH), the fate of the deuterium indicates the mechanism. If the E2 mechanism is in operation, the trimethylamine produced would contain no deuterium (which would be found only in the water). But if the mechanism is E^i, the amine would contain deuterium. In the case of the highly hindered compound $(Me_3C)_2CDCH_2NMe_3^+$ ^-OH, the deuterium did appear in the amine, demonstrating an Ei mechanism for this case.[248] With simpler compounds, the mechanism is E2, since here the amine was deuterium-free.[249]

When the nitrogen bears more than one group possessing a β hydrogen, which group cleaves? The Hofmann rule says that *within* a group the hydrogen on the least alkylated carbon cleaves. This tendency is also carried over to the choice of which group cleaves: thus ethyl with three β hydrogens cleaves more readily than any longer *n*-alkyl group, all of which have two β hydrogens. "The β hydrogen is removed most readily if it is located on a methyl group, next from RCH_2, and least readily from R_2CH."[250] In fact, the Hofmann rule as first stated[251] in 1851 applied only to which group cleaved, not to the orientation within a group; the latter could not have been specified in 1851, since the structural theory of organic compounds was not formulated until 1857–1860. Of course, the Hofmann rule (applied to which group cleaves *or* to orientation within a group) is superseded by conjugation possibilities. Thus $PhCH_2CH_2NMe_2Et^+$ ^-OH gives mostly styrene instead of ethylene.

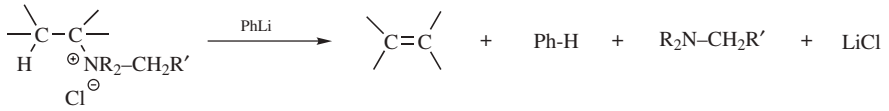
Triple bonds have been prepared by pyrolysis of 1,2-bis(ammonium) salts.[252]



OS **IV**, 980; **V**, 315, 608; **VI**, 552. Also see, OS **V**, 621, 883; **VI**, 75.

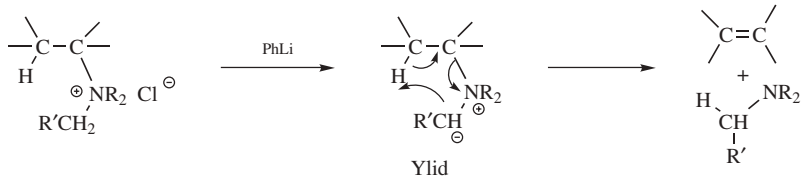
17-8 Cleavage of Quaternary Ammonium Salts With Strong Bases

Hydro-trialkylammonio-elimination



[248]Cope, A.C.; Mehta, A.S. *J. Am. Chem. Soc.* ***1963***, *85*, 1949. See also, Baldwin, M.A.; Banthorpe, D.V.; Loudon, A.G.; Waller, F.D. *J. Chem. Soc. B* ***1967***, 509.
[249]Cope, A.C.; LeBel, N.A.; Moore, P.T.; Moore, W.R. *J. Am. Chem. Soc.* ***1961***, *83*, 3861.
[250]Cope, A.C.; Trumbull, E.R. *Org. React.* ***1960***, *11*, 317, see p. 348.
[251]Hofmann, A.W. *Liebigs Ann. Chem.* ***1851***, *78*, 253.
[252]For a review, see Franke, W.; Ziegenbein, W.; Meister, H. *Angew. Chem.* ***1960***, *72*, 391, see p. 397–398.

When quaternary ammonium halides are treated with strong bases (e.g., PhLi, KNH_2 in liquid NH_3[253]), an elimination can occur that is similar in products, although not in mechanism, to **17-7**. This is an alternative to **17-7** and is done on the quaternary ammonium halide, so that it is not necessary to convert this to the hydroxide. The mechanism is E^i:



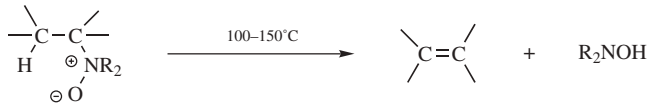
An α' hydrogen is obviously necessary in order for the ylid to be formed. This type of mechanism is called α',β elimination, since a β hydrogen is removed by the α' carbon. The mechanism has been confirmed by labeling experiments similar to those described at **17-7**,[254] and by isolation of the intermediate ylids.[255] An important synthetic difference between this and most instances of **17-7** is that syn-elimination is observed here and anti-elimination in **17-7**, so products of opposite configuration are formed when the alkene exhibits cis–trans isomerism.

An alternative procedure that avoids the use of a very strong base is heating the salt with KOH in polyethylene glycol monomethyl ether.[256]

Benzotriazole has been shown to be a good leaving group for elimination reactions. The reaction of an allylic benzotriazole (3-benzotriazoyl-4-trimethylsilyl-1-butene) with *n*-butyllithium, and then an alkyl halide leads to an alkylated 1,3-diene upon heating.[257]

17-9 Cleavage of Amine Oxides

Hydro-(Dialkyloxidoammonio)-elimination



Cleavage of amine oxides to produce an alkene and a hydroxylamine is called the *Cope reaction* or *Cope elimination* (not to be confused with the Cope *rearrangement*, **18-32**). It is an alternative to **17-7** and **17-8**.[258] The reaction is usually

[253]Bach, R.D.; Bair, K.W.; Andrzejewski, D. *J. Am. Chem. Soc.* ***1972***, *94*, 8608; *J. Chem. Soc., Chem. Commun.* ***1974***, 819.

[254]Weygand, F.; Daniel, H.; Simon, H. *Chem. Ber.* ***1958***, *91*, 1691; Bach, R.D.; Knight, J.W. *Tetrahedron Lett.* ***1979***, 3815.

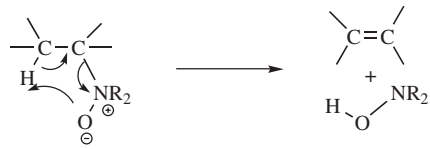
[255]Wittig, G.; Burger, T.F. *Liebigs Ann. Chem.* ***1960***, *632*, 85.

[256]Hünig, S.; Öller, M.; Wehner, G. *Liebigs Ann. Chem.* ***1979***, 1925.

[257]Katritzky, A.R.; Serdyuk, L.; Toader, D.; Wang, X. *J. Org. Chem.* ***1999***, *64*, 1888.

[258]For reviews, see Cope, A.C.; Trumbull, E.R. *Org. React.* ***1960***, *11*, 317, see p. 361; DePuy, C.H.; King, R.W. *Chem. Rev.* ***1960***, *60*, 431, see pp. 448–451.

performed with a mixture of amine and oxidizing agent (see **19-29**) without isolation of the amine oxide. Because of the mild conditions side reactions are few, and the alkenes do not usually rearrange. The reaction is thus very useful for the preparation of many alkenes. A limitation is that it does not open six-membered rings containing nitrogen, although it does open rings of 5 and 7–10 members.[259] Rates of the reaction increase with increasing size of α and β-substituents.[260] The reaction can be carried out at room temperature in dry Me_2SO or THF.[261] The elimination is a stereoselective syn process,[262] and the five-membered E^i mechanism operates:

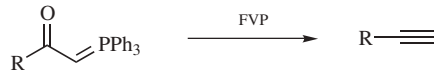


Almost all evidence indicates that the transition state must be planar. Deviations from planarity as in **17-4** (see p. 1507) are not found here, and indeed this is why six-membered heterocyclic nitrogen compounds do not react. Because of the stereoselectivity of this reaction and the lack of rearrangement of the products, it is useful for the formation of trans-cycloalkenes (eight-membered and higher). A polymer-bound Cope elimination reaction has been reported.[263]

OS **IV**, 612.

17-10 Pyrolysis of Keto-ylids

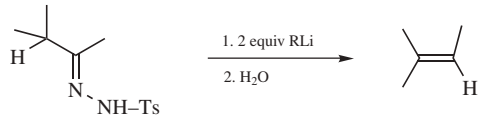
Hydro-(oxophosphoryl)-elimination



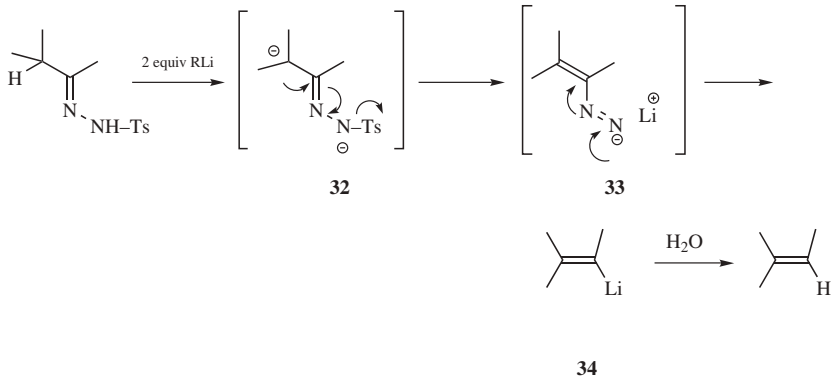
Phosphorus ylids are quite common (see **16-44**) and keto-phosphorus ylids [$RCOCH{=}PPh_3$] are also known. When these compounds are heating (flash vacuum pyrolysis, FVP) to $> 500°C$, alkynes are formed. Simple alkynes[264] can be formed as well as keto-alkynes[265] and en-ynes.[266] Rearrangement from ylids derived from tertiary amines an α-diazo ketones is also known.[267]

[259]Cope, A.C.; LeBel, N.A. *J. Am. Chem. Soc*. ***1960***, *82*, 4656; Cope, A.C.; Ciganek, E.; Howell, C.F.; Schweizer, E.E. *J. Am. Chem. Soc*. ***1960***, *82*, 4663.
[260]Závada, J.; Pánková, M.; Svoboda, M. *Collect. Czech. Chem. Commun*. ***1973***, *38*, 2102.
[261]Cram, D.J.; Sahyun, M.R.V.; Knox, G.R. *J. Am. Chem. Soc*. ***1962***, *84*, 1734.
[262]See, for example, Bach, R.D.; Andrzejewski, D.; Dusold, L.R. *J. Org. Chem*. ***1973***, *38*, 1742.
[263]Sammelson, R.E.; Kurth, M.J. *Tetrahedron Lett*. ***2001***, *42*, 3419.
[264]Aitken, R.A.; Atherton, J.I. *J. Chem. Soc. Perkin Trans. 1* ***1994***, 1281.
[265]Aitken, R.A.; Hérion, H.; Janosi, A.; Karodia, N.; Raut, S.V.; Seth, S.; Shannon, I.J.; Smith, F.C. *J. Chem. Soc. Perkin Trans. 1* ***1994***, 2467.
[266]Aitken, R.A.; Boeters, C; Morrison, J.J. *J. Chem. Soc. Perkin Trans. 1* ***1994***, 2473.
[267]DelZotto, A.; Baratta, W.; Miani, F.; Verardo, G.; Rigo, P. *Eur. J. Org. Chem*. ***2000***, 3731.

17-11 Decomposition of Toluene-*p*-sulfonylhydrazones



Treatment of the tosylhydrazone of an aldehyde or a ketone with a strong base leads to the formation of an alkene, the reaction being formally an elimination accompanied by a hydrogen shift.[268] The reaction (called the *Shapiro reaction*) has been applied to tosylhydrazones of many aldehydes and ketones. The most useful method synthetically involves treatment of the substrate with at least 2 equivalents of an organolithium compound[269] (usually MeLi) in ether, hexane, or tetramethylenediamine.[270] This procedure gives good yields of alkenes without side reactions and, where a choice is possible, predominantly gives the less highly substituted alkene. Tosylhydrazones of α,β-unsaturated ketones give conjugated dienes.[271] The mechanism[272] has been formulated as:



Evidence for this mechanism is (*1*) 2 equivalents of RLi are required; (*2*) the hydrogen in the product comes from the water and not from the adjacent carbon, as shown by deuterium labeling;[273] and (*3*) the intermediates **32–34** have been trapped.[274] This reaction, when performed in tetramethylenediamine, can be a synthetically useful method[275] of generating vinylic lithium compounds (**34**), which

[268]For reviews, see Adlington, R.M.; Barrett, A.G.M. *Acc. Chem. Res*. ***1983***, *16*, 55; Shapiro, R.H. *Org. React*. ***1976***, *23*, 405.

[269]Shapiro, R.H.; Heath, M.J. *J. Am. Chem. Soc*. ***1967***, *89*, 5734; Kaufman, G.; Cook, F.; Shechter, H.; Bayless, J.; Friedman, L. *J. Am. Chem. Soc*. ***1967***, *89*, 5736; Shapiro, R.H. *Tetrahedron Lett*. ***1968***, 345; Meinwald, J.; Uno, F. *J. Am. Chem. Soc*. ***1968***, *90*, 800.

[270]Stemke, J.E.; Bond, F.T. *Tetrahedron Lett*. ***1975***, 1815.

[271]See Dauben, W.G.; Rivers, G.T.; Zimmerman, W.T. *J. Am. Chem. Soc*. ***1977***, *99*, 3414.

[272]For a review of the mechanism, see Casanova, J.; Waegell, B. *Bull. Soc. Chim. Fr*. ***1975***, 922.

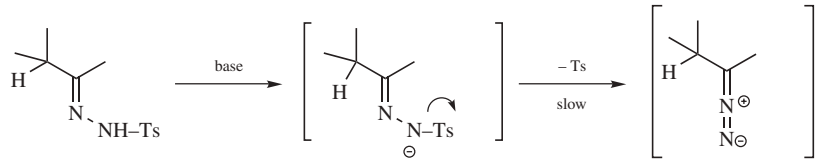
[273]Ref. 269; Shapiro, R.H.; Hornaman, E.C. *J. Org. Chem*. ***1974***, *39*, 2302.

[274]Lipton, M.F.; Shapiro, R.H. *J. Org. Chem*. ***1978***, *43*, 1409.

[275]See Traas, P.C.; Boelens, H.; Takken, H.J. *Tetrahedron Lett*. ***1976***, 2287; Stemke, J.E.; Chamberlin, A.R.; Bond, F.T. *Tetrahedron Lett*. ***1976***, 2947.

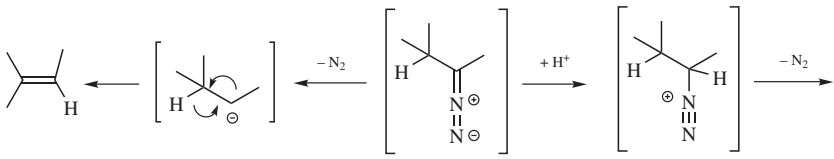
can be trapped by various electrophiles[276] such as D_2O (to give deuterated alkenes), CO_2 (to give α,β-unsaturated carboxylic acids, **16-30**), or DMF (to give α,β-unsaturated aldehydes, **16-82**). Treatment of *N*-aziridino hydrazones with LDA leads to alkenes with high cis selectivity.[277]

The reaction also takes place with other bases (e.g., LiH,[278] Na in ethylene glycol, NaH, $NaNH_2$) or with smaller amounts of RLi, but in these cases side reactions are common and the orientation of the double bond is in the other direction (to give the more highly substituted alkene). The reaction with Na in ethylene glycol is called the *Bamford–Stevens reaction*.[279] For these reactions two mechanisms are possible: a carbenoid and a carbocation mechanism.[280] The side reactions found are those expected of carbenes and carbocations. In general, the carbocation mechanism is chiefly found in protic solvents and the carbenoid mechanism in aprotic solvents. Both routes involve formation of a diazo compound (**35**) which in some cases can be isolated.

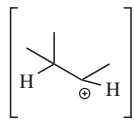


35

In fact, this reaction has been used as a synthetic method for the preparation of diazo compounds.[281] In the absence of protic solvents, **36** loses N_2, and hydrogen migrates, to give the alkene product. The migration of

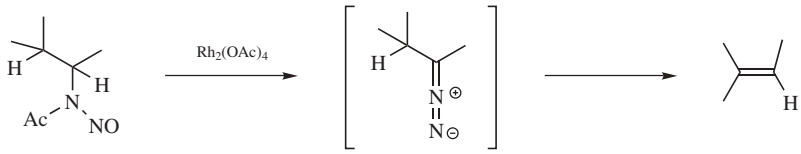


35 **36**



[276]For a review, see Chamberlin, A.R.; Bloom, S.H. *Org. React.* ***1990***, *39*, 1.
[277]Maruoka, K.; Oishi, M.; Yamamoto, H. *J. Am. Chem. Soc.* ***1996***, *118*, 2289.
[278]Biellmann, J.F.; Pète, J. *Bull. Soc. Chim. Fr.* ***1967***, 675.
[279]Bamford, W.R.; Stevens, R.R. *J. Chem. Soc.* ***1952***, 4735. For a tandem Bamford-Stevens–Claisen rearrangement, see May, J.A.; Stoltz, B.M. *J. Am. Chem. Soc.* ***2002***, *124*, 12426.
[280]Powell, J.W.; Whiting, M.C. *Tetrahedron* ***1959***, *7*, 305; ***1961***, *12* 168; DePuy, C.H.; Froemsdorf, D.H. *J. Am. Chem. Soc.* ***1960***, *82*, 634; Bayless, J.H.; Friedman, L.; Cook, F.B.; Shechter, H. *J. Am. Chem. Soc.* ***1968***, *90*, 531; Nickon, A.; Werstiuk, N.H. *J. Am. Chem. Soc.* ***1972***, *94*, 7081.
[281]For a review, see Regitz, M.; Maas, G. *Diazo Compounds*; Academic Press, NY, ***1986***, pp. 257–295. For an improved procedure, see Wulfman, D.S.; Yousefian, S.; White, J.M. *Synth. Commun.* ***1988***, *18*, 2349.

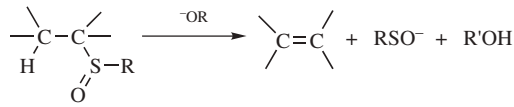
hydrogen may immediately follow, or be simultaneous with, the loss of N_2. In a protic solvent, **35** becomes protonated to give the diazonium ion **36**, which loses N_2 to give the corresponding carbocation, that may then undergo elimination or give other reactions characteristic of carbocations. A diazo compound is an intermediate in the formation of alkenes by treatment of *N*-nitrosoamides with a rhodium(II) catalyst.[282]



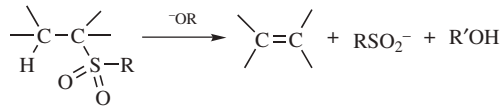
OS **VI**, 172; **VII**, 77; **IX**, 147. For the preparation of a diazo compound, see OS **VII**, 438.

17-12 Cleavage of Sulfoxides, Selenoxides, and Sulfones

Hydro-alkylsulfinyl-elimination



Hydro-alkylsulfinyl-elimination



Sulfonium compounds ($-C-^{+}SR_2$) undergo elimination similar to that of their ammonium counterparts (**17-7** and **17-8**) in scope and mechanism but this reaction is not of great synthetic importance. These syn-elimination reactions are related to the Cope elimination (**17-9**) and the Hofmann elimination (**17-7**).[283]

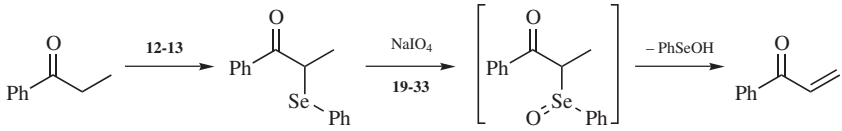
Sulfones and sulfoxides[284] with a β hydrogen, on the other hand, undergo elimination on treatment with an alkoxide or, for sulfones,[285] even with hydroxide.[286] Sulfones also eliminate in the presence of an organolithium reagent and a palladium catalyst.[287] Mechanistically, these reactions belong on the E1-E2-E1cB spectrum.[288] Although the leaving groups are uncharged, the orientation follows Hofmann's rule, not Zaitsev's. Sulfoxides (but not sulfones) also undergo elimination

[282]Godfrey, A.G.; Ganem, B. *J. Am. Chem. Soc.* ***1990***, *112*, 3717.
[283]For a discussion and leading references of this class of eliminations, see Smith, M.B. *Organic Synthesis*, 2nd ed., McGraw-Hill, NY, ***2001***, pp. 135–141.
[284]See Cubbage, J.W.; Guo, Y.; McCulla, R.D.; Jenks, W.S. *J. Org. Chem.* ***2001***, *66*, 8722.
[285]Certain sulfones undergo elimination with 5% HCl in THF: Yoshida, T.; Saito, S. *Chem. Lett.* ***1982***, 165.
[286]Hofmann, J.E.; Wallace, T.J.; Argabright, P.A.; Schriesheim, A. *Chem. Ind. (London)* ***1963***, 1234.
[287]Gai, Y.; Jin, L.; Julia, M.; Verpeaux, J.-N. *J. Chem. Soc., Chem. Commun.* ***1993***, 1625.
[288]Hofmann, J.E.; Wallace, T.L.; Schriesheim, A. *J. Am. Chem. Soc.* ***1964***, *86*, 1561.

on pyrolysis at ~80°C in a manner analogous to **17-9**. The mechanism is also analogous, being the five-membered E^i mechanism with syn elimination.[289]

Selenoxides[290] and sulfinate esters $R_2CH–CHR–SO–OMe$[291] also undergo elimination by the E^i mechanism, the selenoxide reaction taking place at room temperature. The reaction with selenoxides has been extended to the formation of triple bonds.[292]

Both the selenoxide[293] and sulfoxide[294] reactions have been used in a method for the conversion of ketones, aldehydes, and carboxylic esters to their α,β-unsaturated derivatives (illustrated for the selenoxide).



Because of the mildness of the procedure, this is probably the best means of accomplishing this conversion. Treatment of ketones with LDA and then PhClS=N*t*-Bu leads to the conjugated ketone.[295] Allylic sulfoxides undergo 1,4-elimination to give dienes.[296] Ketones also react with hypervalent iodine cmpound in DMSO to give conjugated ketone.[297] In a simialr manner, keotnes are converted to conjugated keotnes by heating with HIO_5/I_2O_5 in DMSO.[298]

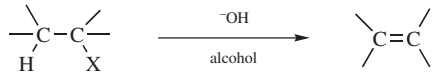
[289]Schmitz, C.; Harvey, J.N.; Viehe, H.G. *Bull. Soc. Chim. Belg*. ***1994***, *103*, 105; Yoshimura, T.; Tsukurimichi, E.; Iizuka, Y.; Mizuno, H.; Isaji, H.; Shimasaki, C. *Bull. Chem. Soc. Jpn*. ***1989***, *62*, 1891.
[290]For reviews, see Back, T.G., in Patai, S. *The Chemistry of Organic Selenium and Telurium Compounds*, Vol. 2, Wiley, NY, ***1987***, pp. 91–213, 95–109; Paulmier, C. *Selenium Reagents and Intermediates in Organic Synthesis*, Pergamon, Elmsford, NY, ***1986***, pp. 132–143; Reich, H.J. *Acc. Chem. Res*. ***1979***, *12*, 22, in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. C, Academic Press, NY, ***1978***, pp. 15–101; Sharpless, K.B.; Gordon, K.M.; Lauer, R.F.; Patrick, D.W.; Singer, S.P.; Young, M.W. *Chem. Scr*. ***1975***, *8A*; 9. See also, Liotta, D. *Organoselenium Chemistry*, Wiley, NY, ***1987***.
[291]Jones, D.N.; Higgins, W. *J. Chem. Soc. C* ***1970***, 81.
[292]Reich, H.J.; Willis, Jr., W.W. *J. Am. Chem. Soc*. ***1980***, *102*, 5967.
[293]Clive, D.L.J. *J. Chem. Soc., Chem. Commun*. ***1973***, 695; Reich, H.J.; Renga, J.M.; Reich, I.L. *J. Am. Chem. Soc*. ***1975***, *97*, 5434, and references cited therein; Sharpless, K.B.; Lauer, R.F.; Teranishi, A.Y. *J. Am. Chem. Soc*. ***1973***, *95*, 6137; Grieco, P.A.; Miyashita, M. *J. Org. Chem*. ***1974***, *39*, 120; Crich, D.; Barba, G.R. *Org. Lett*. ***2000***, *2*, 989. For lists of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 287–290. For a discussion of the effect of ortho substituents, see Sayama, S.; Onami, T. *Tetrahedron Lett*. ***2000***, *41*, 5557.
[294]Trost, B.M.; Salzmann, T.N.; Hiroi, K. *J. Am. Chem. Soc*. ***1976***, *98*, 4887. For a review of this and related methods, see Trost, B.M. *Acc. Chem. Res*. ***1978***, *11*, 453.
[295]Mukaiyama, T.; Matsuo, J.-i.; Kitgawa, H. *Chem. Lett*. ***2000***, 1250.
[296]de Groot, A.; Jansen, B.J.M.; Reuvers, J.T.A.; Tedjo, E.M. *Tetrahedron Lett*. ***1981***, *22*, 4137.
[297]Nicolaou, K.C.; Montagnon, T.; Baran, P.S.; Zhong, Y.-L. *J. Am. Chem. Soc*. ***2002***, *124*, 2245; Nicolaou, K.C.; Gray, D.L.F.; Montagnon, T.; Harrison, S.T. *Angew. Chem. Int. Ed*. ***2002***, *41*, 996.
[298]Nicolaou, K.C.; Montagnon, T.; Baran, P.S. *Angew. Chem. Int. Ed*. ***2002***, *41*, 1386.

A radical elimination reaction generates alkenes from sulfoxides. The reaction of a 2-bromophenyl alkylsulfoxide with Bu_3SnH and AIBN (see p. 935 for a discussion of these standard radical conditions) leads to an alkene.[299]

OS **VI**, 23, 737; **VIII**, 543; **IX**, 63.

17-13 Dehydrohalogenation of Alkyl Halides

Hydro-halo-elimination



The elimination of HX from an alkyl halide is a very general reaction and can be accomplished with chlorides, fluorides, bromides, and iodides.[300] Hot alcoholic KOH is the most frequently used base, although stronger bases[301] (^-OR, $^-NH_2$, etc.) or weaker ones (e.g., amines) are used where warranted.[302] The bicyclic amidines 1,5-diazabicyclo[3.4.0]nonene-5 (DBN)[303] and 1,8-diazabicyclo[5.4.0]undecene-7 (DBU)[304] are good reagents for difficult cases.[305] Dehydrohalogenation with the non-ionic base $(Me_2N)_3P{=}N\text{-}P(NMe_2)_2{=}NMe$ is even faster.[306] Phase-transfer catalysis has been used with hydroxide as base.[307] As previously mentioned (p. 1495), certain weak bases in dipolar aprotic solvents are effective reagents for dehydrohalogenation. Among those most often used for synthetic purposes are LiCl or LiBr–$LiCO_3$ in DMF.[308] Dehydrohalogenation has also been effected by heating of the alkyl halide in HMPA with no other reagent present.[309] As in

[299]Imboden, C.; Villar, F.; Renaud, P. *Org. Lett*. ***1999***, *1*, 873.

[300]For a review of eliminations involving the carbon–halogen bond, see Baciocchi, E., in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement D*, pt. 2, Wiley, NY, ***1983***, pp. 1173–1227.

[301]Triphenylmethylpotassium rapidly dehydrohalogenates secondary alkyl bromides and iodides, in >90% yields, at 0°C: Anton, D.R.; Crabtree, R.H. *Tetrahedron Lett*. ***1983***, *24*, 2449.

[302]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 256–258.

[303]Truscheit, E.; Eiter, K. *Liebigs Ann. Chem*. ***1962***, *658*, 65; Oediger, H.; Kabbe, H.; Möller, F.; Eiter, K. *Chem. Ber*. ***1966***, *99*, 2012; Vogel, E.; Klärner, F. *Angew. Chem. Int. Ed*. ***1968***, *7*, 374.

[304]Oediger, H.; Möller, F. *Angew. Chem. Int. Ed*. ***1967***, *6*, 76; Wolkoff, P. *J. Org. Chem*. ***1982***, *47*, 1944.

[305]For a review of these reagents, see Oediger, H.; Möller, F.; Eiter, K. *Synthesis* ***1972***, 591.

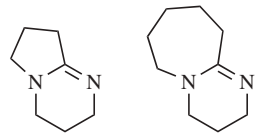
[306]Schwesinger, R.; Schlemper, H. *Angew. Chem. Int. Ed*. ***1987***, *26*, 1167.

[307]Kimura, Y.; Regen, S.L. *J. Org. Chem*. ***1983***, *48*, 195; Halpern, M.; Zahalka, H.A.; Sasson, Y.; Rabinovitz, M. *J. Org. Chem*. ***1985***, *50*, 5088. See also, Barry, J.; Bram, G.; Decodts, G.; Loupy, A.; Pigeon, P.; Sansoulet, J. *J. Org. Chem*. ***1984***, *49*, 1138.

[308]For a discussion, see Fieser, L.F.; Fieser, M. *Reagents for Organic Syntheses*, Vol. 1, Wiley, NY, ***1967***, pp. 606–609. For a review of alkali-metal fluorides in this reaction, see Yakobson, G.G.; Akhmetova, N.E. *Synthesis* ***1983***, 169, see pp. 170–173.

[309]Hanna, R. *Tetrahedron Lett*. ***1968***, 2105; Monson, R.S. *Chem. Commun*. ***1971***, 113; Hutchins, R.O.; Hutchins, M.G.; Milewski, C.A. *J. Org. Chem*. ***1972***, *37*, 4190; Hoye, T.R.; van Deidhuizen, J.J.; Vos, T.J.; Zhao, P. *Synth. Commun*. ***2001***, *31*, 1367.

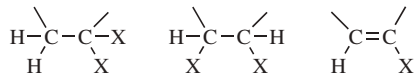
nucleophilic substitution (p. 496), the order of leaving group reactivity is I > Br > Cl > F.[310]



DBN DBU

Tertiary halides undergo elimination most easily. Eliminations of chlorides, bromides, and iodides follow Zaitsev's rule, except for a few cases where steric effects are important (for an example, see p. 1499). Eliminations of fluorides follow Hofmann's rule (p. 1500).

This reaction is by far the most important way of introducing a triple bond into a molecule.[311] Alkyne formation can be accomplished with substrates of the types:[312]



When the base is $NaNH_2$ 1-alkynes predominate (where possible), because this base is strong enough to form the salt of the alkyne, shifting any equilibrium between 1- and 2-alkynes. When the base is ^-OH or ^-OR, the equilibrium tends to be shifted to the internal alkyne, which is thermodynamically more stable. If another hydrogen is suitably located (e.g., $–CRH–CX_2–CH_2–$), allene formation can compete, although alkynes are usually more stable. 1,1,2-Trihalocyclopropanes are converted to alkynes by ring opening reactions.[313]

Dehydrohalogenation is generally carried out in solution, with a base, and the mechanism is usually E2, although the E1 mechanism has been demonstrated in some cases. However, elimination of HX can be accomplished by pyrolysis of the halide, in which case the mechanism is E^i (p. 1507) or, in some instances, the free-radical mechanism (p. 1510). Pyrolysis is normally performed without a catalyst at ~400°C. The pyrolysis reaction is not generally useful synthetically, because of its reversibility. Less work has been done on pyrolysis with a catalyst[314] (usually a metallic oxide or salt), but the mechanisms here are probably E1 or E2.

[310]Matsubara, S.; Matsuda, H.; Hamatani, T.; Schlosser, M. *Tetrahedron* ***1988***, *44*, 2855.

[311]For reviews, see Ben-Efraim, D.A. in Patai, S. *The Chemistry of the Carbon-Carbon Triple Bond*, pt. 2, Wiley, NY, ***1978***, p. 755; Köbrich, G.; Buck, P., in Viehe, H. G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 100–134; Franke, W.; Ziegenbein, W.; Meister, H. *Angew. Chem.* ***1960***, *72*, 391, see p. 391; Köbrich, G. *Angew. Chem. Int. Ed.* ***1965***, *4*, 49, see pp. 50–53.

[312]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 569–571.

[313]For a review, see Sydnes, L.K. *Eur. J. Org. Chem.* ***2000***, 3511.

[314]For a review, see Noller, H.; Andréu, P.; Hunger, M. *Angew. Chem. Int. Ed.* ***1971***, *10*, 172.

37

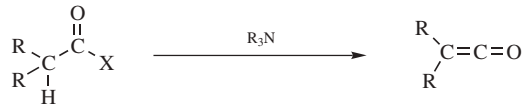
In the special case of the prochiral carboxylic acids **37**, dehydrohalogenation with an optically active lithium amide gave an optically active product with ee as high as 82%.[315]

Other regents lead to dehydrohalogenation. 1,1,1-Trichloro compounds are converted to vinyl chlorides with $CrCl_2$.[316]

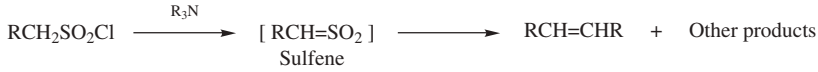
OS **I**, 191, 205, 209, 438; **II**, 10, 17, 515; **III**, 125, 209, 270, 350, 506, 623, 731, 785; **IV**, 128, 162, 398, 404, 555, 608, 616, 683, 711, 727, 748, 755, 763, 851, 969; **V**, 285, 467, 514; **VI**, 87, 210, 327, 361, 368, 427, 462, 505, 564, 862, 883, 893, 954, 991, 1037; **VII**, 126, 319, 453, 491; **VIII**, 161, 173, 212, 254; **IX**, 191, 656, 662. Also see, OS **VI**, 968.

17-14 Dehydrohalogenation of Acyl Halides and Sulfonyl Halides

Hydro-halo-elimination



Ketenes can be prepared by treatment of acyl halides with tertiary amines[317] or with NaH and a crown ether.[318] The scope is broad, and most acyl halides possessing an α hydrogen give the reaction, but if at least one R is hydrogen, only the ketene dimer, not the ketene, is isolated. However, if it is desired to use a reactive ketene in a reaction with a given compound, the ketene can be generated *in situ* in the presence of the given compound.[319]



Closely related is the reaction of tertiary amines with sulfonyl halides that contain an a hydrogen. In this case, the initial product is the highly reactive sulfene, which cannot be isolated but reacts further to give products, one of which may be the alkene that is the dimer of RCH.[320] Reactions of sulfenes *in situ* are also common (e.g., see **16-48**).

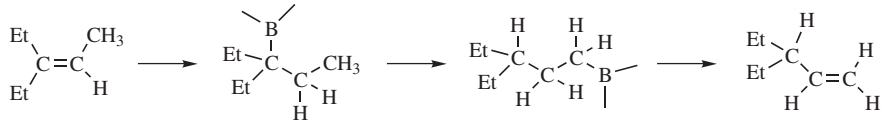
OS **IV**, 560; **V**, 294, 877; **VI**, 549, 1037; **VII**, 232; **VIII**, 82.

[315]Duhamel, L.; Ravard, A.; Plaquevent, J.C.; Plé, G.; Davoust, D. *Bull. Soc. Chim. Fr.* ***1990***, 787.
[316]Baati, R.; Barma, D.K.; Krishna, U.M.; Mioskowski, C.; Falck, J.R. *Tetrahedron Lett.* ***2002***, *43*, 959.
[317]For a monograph on the chemistry of ketenes, see Tidwell, T.T. *Ketenes*, Wiley, NY, ***1995***.
[318]Taggi, A.E.; Wack, H.; Hafez, A.M.; France, S.; Lectka, T. *Org. Lett.* ***2002***, *4*, 627.
[319]For a review of this procedure, see Luknitskii, F.I.; Vovsi, B.A. *Russ. Chem. Rev.* ***1969***, *38*, 487.
[320]For reviews of sulfenes, see King, J.F. *Acc. Chem. Res.* ***1975***, *8*, 10; Nagai, T.; Tokura, N. *Int. J. Sulfur Chem. Part B* ***1972***, 207; Truce, W.E.; Liu, L.K. *Mech. React. Sulfur Compd.* ***1969***, *4*, 145; Opitz, G. *Angew. Chem. Int. Ed.* ***1967***, *6*, 107; Wallace, T.J. *Q. Rev. Chem. Soc.* ***1966***, *20*, 67.

17-15 Elimination of Boranes

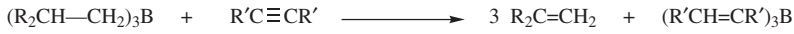
Hydro-boranetriyl-elimination

Trialkylboranes are formed from an alkene and BH_3 (**15-16**). When the resulting borane is treated with another alkene, an exchange reaction occurs.[321] This is an equilibrium process that can be shifted by using a large excess of alkene, by using an unusually reactive alkene, or by using an alkene with a higher boiling point than the displaced alkene and removing the latter by distillation. The reaction is useful for shifting a double bond in the direction opposite to that resulting from normal isomerization methods (**12-2**). This cannot be accomplished simply by treatment of a borane, such as **39**, with an alkene, because elimination in this reaction follows Zaitsev's rule: It is in the direction of the most stable alkene, and the product would be **38**, not **41**. However, if it is desired to convert **38** to **41**, this can be accomplished by converting **38** to **39**, isomerizing **39** to **40** (**18-11**) and then subjecting **40** to the exchange reaction with a higher boiling alkene (e.g., 1-decene), whereupon **41** is produced. In the usual isomerizations (**12-2**), **41** could be isomerized to **38**, but not the other way around. The reactions **39** → **40** and **40** → **41** proceed essentially without rearrangement. The mechanism is probably the reverse of borane addition (**15-16**).



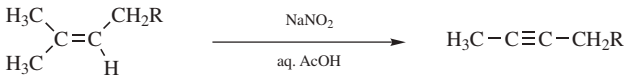
38 **39** **40** **41**

A similar reaction, but irreversible, has been demonstrated for alkynes.[322]



17-16 Conversion of Alkenes to Alkynes

Hydro-methyl-elimination



Alkenes of the form shown lose the elements of methane when treated with sodium nitrite in acetic acid and water, to form alkynes in moderate-to-high yields.[323] The R may contain additional unsaturation, as well as OH, OR, OAc,

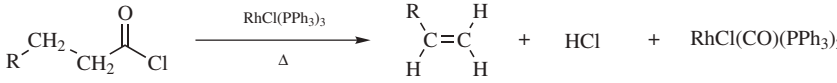
[321]Brown, H.C.; Bhatt, M.V.; Munekata, T.; Zweifel, G. *J. Am. Chem. Soc.* ***1967***, *89*, 567; Taniguchi, H. *Bull. Chem. Soc. Jpn.* ***1979***, *52*, 2942.
[322]Hubert, A.J. *J. Chem. Soc.* ***1965***, 6669.
[323]Abidi, S.L. *Tetrahedron Lett.* ***1986***, *27*, 267; *J. Org. Chem.* ***1986***, *51*, 2687.

C=O, and other groups, but the $Me_2C{=}CHCH_2$ portion of the substrate is necessary for the reaction to take place. The mechanism is complex, beginning with a nitration that takes place with allylic rearrangement [$Me_2C{=}CHCH_2R \rightarrow H_2C{=}CMeCH(NO_2)CH_2R$], and involving several additional intermediates.[324] The CH_3 lost from the substrate appears as CO_2, as demonstrated by the trapping of this gas.[324]

1,1-Dibromoalkenes are converted to alkynes when treated with *n*-butyllithium.[325] This transformation is a modification of the *Fritsch–Buttenberg–Wiechell rearrangement*.[326] Vinyl sulfoxides that contain a leaving group, such as chloride on the double bond, react with *tert*-butyllithium to give a lithio alkyne, and hydrolysis leads to the final product, an alkyne.

17-17 Decarbonylation of Acyl Halides

Hydro-chloroformyl-elimination

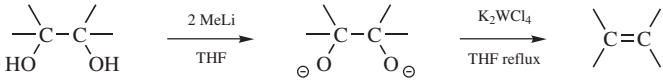


Acyl chlorides containing an a hydrogen are smoothly converted to alkenes, with loss of HCl and CO, on heating with chlorotris(triphenylphosphine)rhodium, with metallic platinum, or with certain other catalysts.[327] The mechanism probably involves conversion of RCH_2CH_2COCl to $RCH_2CH_2{-}RhCO(Ph_3P)_2Cl_2$ followed by a concerted syn elimination of Rh and H[328] (see also, **14-32** and **19-12**).

B. Reactions in Which Neither Leaving Atom Is Hydrogen

17-18 Deoxygenation of Vicinal Diols

Dihydroxy-elimination

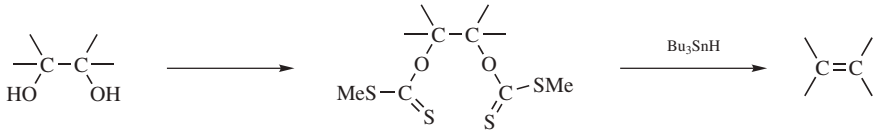


vic-Diols can be deoxygenated by treatment of the dilithium dialkoxide with the tungsten halide (K_2WCl_6), or with certain other tungsten reagents, in refluxing THF.[329] Tetrasubstituted diols react most rapidly. The elimination is largely, but

[324]Corey, E.J.; Seibel, W.L.; Kappos, J.C. *Tetrahedron Lett.* ***1987***, *28*, 4921.
[325]Chernick, E.T.; Eisler, S.; Tykwinski, R.R. *Tetrahedron Lett.* ***2001***, *42*, 8575.
[326]Fritsch, P. *Ann.* ***1894***, *279*, 319; Buttenberg, W.P. *Ann.*, ***1894***, *279*, 324; Wiechell, H. *Ann.* ***1894***, *279*, 337; Stang, P.J.; Fox, D.P.; Collins, C.J.; Watson, Jr., C.R. *J. Org. Chem.* ***1978***, *43*, 364. For a review, see Stang, P.J. *Chem. Rev.* ***1978***, *78*, 383.
[327]For a review, see Tsuji, J.; Ohno, K. *Synthesis* ***1969***, 157. For extensions to certain other acid derivatives, see Minami, I.; Nisar, M.; Yuhara, M.; Shimizu, I.; Tsuji, J. *Synthesis* ***1987***, 992.
[328]Lau, K.S.Y.; Becker, Y.; Huang, F.; Baenziger, N.; Stille, J.K. *J. Am. Chem. Soc.* ***1977***, *99*, 5664.
[329]Sharpless, K.B.; Flood, T.C. *J. Chem. Soc., Chem. Commun.* ***1972***, 370; Sharpless, K.B.; Umbreit, M.A.; Nieh, T.; Flood, T.C. *J. Am. Chem. Soc.* ***1972***, *94*, 6538.

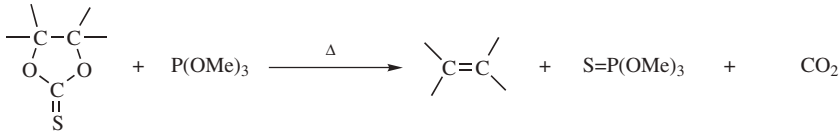
not entirely, syn. Several other methods have been reported,[330] in which the diol is deoxygenated directly, without conversion to the dialkoxide. These include treatment with titanium metal,[331] with TsOH–NaI,[332] and by heating with $CpReO_3$, where Cp is cyclopentadienyl.[333]

vic-Diols can also be deoxygenated indirectly, through sulfonate ester derivatives. For example, *vic*-dimesylates and *vic*-ditosylates have been converted to alkenes by treatment, respectively, with naphthalene-sodium[334] and with NaI in DMF.[335] In another procedure, the diols are converted to bisdithiocarbonates (bis xanthates), which undergo elimination (probably by a free-radical mechanism) when



treated with tri-*n*-butylstannane in toluene or benzene.[336] *vic*-Diols can also be deoxygenated through cyclic derivatives (**17-19**).

17-19 Cleavage of Cyclic Thionocarbonates

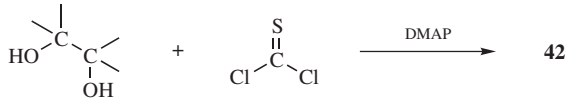


42

Cyclic thionocarbonates (**42**) can be cleaved to alkenes (the *Corey–Winter reaction*)[337] by heating with trimethyl phosphite[338] or other trivalent phosphorus compounds[339] or by treatment with bis(1,5-cyclooctadiene)nickel.[340] The

[330]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 297–299.
[331]McMurry, J.E. *Acc. Chem. Res*. ***1983***, *16*, 405, and references cited therein.
[332]Sarma, J.C.; Sharma, R.P. *Chem. Ind. (London)* ***1987***, 96.
[333]Cook, G.K.; Andrews, M.A. *J. Am. Chem. Soc*. ***1996***, *118*, 9448.
[334]Carnahan Jr., J.C.; Closson, W.D. *Tetrahedron Lett*. ***1972***, 3447.
[335]Dafaye, J. *Bull. Soc. Chim. Fr*. ***1968***, 2099.
[336]Barrett, A.G.M.; Barton, D.H.R.; Bielski, R. *J. Chem. Soc. Perkin Trans. 1* ***1979***, 2378.
[337]For reviews, see Block, E. *Org. React*. ***1984***, *30*, 457; Sonnet, P.E. *Tetrahedron* ***1980***, *36*, 557, 593–598; Mackie, R.K., in Cadogan, J.I.G. *Organophosphorus Reagents in Organic Synthesis*, Academic Press, NY, ***1979***, pp. 354–359.
[338]Corey, E.J.; Winter, R.A.E. *J. Am. Chem. Soc*. ***1963***, *85*, 2677.
[339]Corey, E.J. *Pure Appl. Chem*. ***1967***, *14*, 19, see pp. 32–33.
[340]Semmelhack, M.F.; Stauffer, R.D. *Tetrahedron Lett*. ***1973***, 2667. For another method, see Vedejs, E.; Wu, E.S.C. *J. Org. Chem*. ***1974***, *39*, 3641.

thionocarbonates can be prepared by treatment of 1,2-diols with thiophosgene and 4-dimethylaminopyridine (DMAP):[341]

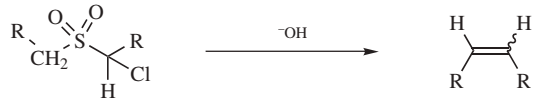


42

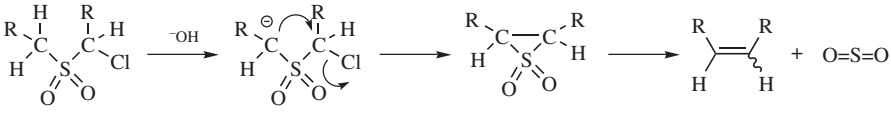
The elimination is of course syn, so the product is sterically controlled. Alkenes that are not sterically favored can be made this way in high yield, (e.g., *cis*-$PhCH_2CH{=}CHCH_2Ph$).[342] Certain other five-membered cyclic derivatives of 1,2-diols can also be converted to alkenes.[343]

17-20 The Ramberg–Bäcklund Reaction

Ramberg–Bäcklund halosulfone transformation



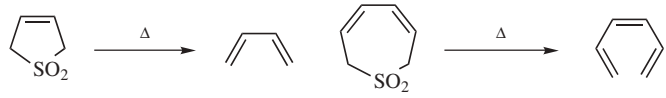
The reaction of an α-halo sulfone with a base to give an alkene is called the *Ramberg–Bäcklund reaction*.[344] The reaction is quite general for α-halo sulfones with an α' hydrogen, despite the unreactive nature of α-halo sulfones in normal S_N2 reactions (p. 486). Halogen reactivity is in the order I > Br ≫ Cl. Phase-transfer catalysis has been used.[345] In general, mixtures of cis and trans isomers are obtained, but usually the less stable cis isomer predominates. The mechanism involves formation of an episulfone, and then elimination of SO_2. There is much



[341]Corey, E.J.; Hopkins, P.B. *Tetrahedron Lett*. ***1982***, *23*, 1979.
[342]Corey, E.J.; Carey, F.A.; Winter, R.A.E. *J. Am. Chem. Soc*. ***1965***, *87*, 934.
[343]See Hines, J.N.; Peagram, M.J.; Whitham, G.H.; Wright, M. *Chem. Commun*. ***1968***, 1593; Josan, J.S.; Eastwood, F.W. *Aust. J. Chem*. ***1968***, *21*, 2013; Hiyama, T.; Nozaki, H. *Bull. Chem. Soc. Jpn*. ***1973***, *46*, 2248; Marshall, J.A.; Lewellyn, M.E. *J. Org. Chem*. ***1977***, *42*, 1311; Breuer, E.; Bannet, D.M. *Tetrahedron* ***1978***, *34*, 997; Hanessian, S.; Bargiotti, A.; LaRue, M. *Tetrahedron Lett*. ***1978***, 737; Hatanaka, K.; Tanimoto, S.; Oida, T.; Okano, M. *Tetrahedron Lett*. ***1981***, *22*, 5195; Ando, M.; Ohhara, H.; Takase, K. *Chem. Lett*. ***1986*** 879; King, J.L.; Posner, B.A.; Mak, K.T.; Yang, N.C. *Tetrahedron Lett*. ***1987***, *28*, 3919; Beels, C.M.D.; Coleman, M.J.; Taylor, R.J.K. *Synlett* ***1990***, 479.
[344]For reviews, see Paquette, L.A. *Org. React*. ***1977***, *25*, 1; *Mech. Mol. Migr*. ***1968***, *1*, 121; *Acc. Chem. Res*. ***1968***, *1*, 209; Meyers, C.Y.; Matthews, W.S.; Ho, L.L.; Kolb, V.M.; Parady, T.E., in Smith, G.V. *Catalysis in Organic Synthesis*, Academic Press, NY, ***1977***, pp. 197–278; Rappe, C., in Patai, S. *The Chemistry of the Carbon-Halogen Bond*, pt. 2, Wiley, NY, ***1973***, pp. 1105–1110; Bordwell, F.G. *Acc. Chem. Res*. ***1970***, *3*, 281, pp. 285–286; in Janssen, M.J. *Organosulfur Chemistry*, Wiley, NY, ***1967***, pp. 271–284.
[345]Hartman, G.D.; Hartman, R.D. *Synthesis* ***1982***, 504.

evidence for this mechanism,[346] including the isolation of the episulfone intermediate,[347] and the preparation of episulfones in other ways and the demonstration that they give alkenes under the reaction conditions faster than the corresponding α-halo sulfones.[348] Episulfones synthesized in other ways (e.g., **16-48**) are reasonably stable compounds, but eliminate SO_2 to give alkenes when heated or treated with base.

If the reaction is run on the unsaturated bromo sulfones $RCH_2CH{=}CHSO_2CH_2Br$ (prepared by reaction of $BrCH_2SO_2Br$ with $RCH_2CH{=}CH_2$ followed by treatment with Et_3N), the dienes $RCH{=}CHCH{=}CH_2$ are produced in moderate-to-good yields.[349] The compound mesyltriflone $CF_3SO_2CH_2SO_2CH_3$ can be used as a synthon for the tetraion $^{2-}C{=}C^{2-}$. Successive alkylation (**10-67**) converts it to $CF_3SO_2CR^1R^2SO_2CHR^3R^4$ (anywhere from one to four alkyl groups can be put in), which, when treated with base, gives $R^1R^2C{=}CR^3R^4$.[350] The nucleofuge here is the $CF_3SO_2^-$ ion.



43 **44**

2,5-Dihydrothiophene-1,1-dioxides (**43**) and 2,17-dihydrothiepin-1,1-dioxides (**44**) undergo analogous 1,4- and 1,6-eliminations, respectively (see also, **17-36**). These are concerted reactions and, as predicted by the orbital-symmetry rules (p. 1207), the former[351] is a suprafacial process and the latter[352] an antarafacial process. The rules also predict that elimination of SO_2 from episulfones cannot take place by a concerted mechanism (except antarafacially, which is unlikely for such a small ring), and the evidence shows that this reaction occurs by a nonconcerted pathway.[353] The eliminations of SO_2 from **43** and **44** are examples of *cheletropic reactions*,[354] which are defined as reactions in which two σ bonds that terminate

[346]See, for example, Paquette, L.A. *J. Am. Chem. Soc.* ***1964***, *86*, 4089; Neureiter, N.P. *J. Am. Chem. Soc.* ***1966***, *88*, 558; Bordwell, F.G.; Wolfinger, M.D. *J. Org. Chem.* ***1974***, *39*, 2521; Bordwell, F.G.; Doomes, E. *J. Org. Chem.* ***1974***, *39*, 2526, 2531.

[347]Sutherland, A.G.; Taylor, R.J.K. *Tetrahedron Lett.* ***1989***, *30*, 3267.

[348]Bordwell, F.G.; Williams Jr., J.M.; Hoyt, Jr., E.B.; Jarvis, B.B. *J. Am. Chem. Soc.* ***1968***, *90*, 429; Bordwell, F.G.; Williams, Jr., J.M. *J. Am. Chem. Soc.* ***1968***, *90*, 435.

[349]Block, E.; Aslam, M.; Eswarakrishnan, V.; Gebreyes, K.; Hutchinson, J.; Iyer, R.; Laffitte, J.; Wall, A. *J. Am. Chem. Soc.* ***1986***, *108*, 4568.

[350]Hendrickson, J.B.; Boudreaux, G.J.; Palumbo, P.S. *J. Am. Chem. Soc.* ***1986***, *108*, 2358.

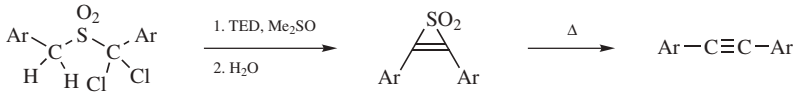
[351]Mock, W.L. *J. Am. Chem. Soc.* ***1966***, *88*, 2857; McGregor, S.D.; Lemal, D.M. *J. Am. Chem. Soc.* ***1966***, *88*, 2858.

[352]Mock, W.L. *J. Am. Chem. Soc.* ***1969***, *91*, 5682.

[353]Bordwell, F.G.; Williams, Jr., J.M.; Hoyt, Jr., E.B.; Jarvis, B.B. *J. Am. Chem. Soc.* ***1968***, *90*, 429; Bordwell, F.G.; Williams Jr., J.M. *J. Am. Chem. Soc.* ***1968***, *90*, 435. See also, Vilsmaier, E.; Tropitzsch, R.; Vostrowsky, O. *Tetrahedron Lett.* ***1974***, 3987.

[354]For a review, see Mock, W.L., in Marchand, A.P.; Lehr, R.E. *Pericyclic Reactions*, Vol. 2, Academic Press, NY, ***1977***, pp. 141–179.

at a single atom (in this case the sulfur atom) are made or broken in concert.[355]



45 **46** **47**

α,α-Dichlorobenzyl sulfones (**45**) react with an excess of the base triethylenediamine (TED) in DMSO at room temperature to give 2,3-diarylthiiren-1,1-dioxides (**46**), which can be isolated.[356] Thermal decomposition of **46** gives the alkynes **47**.[357]

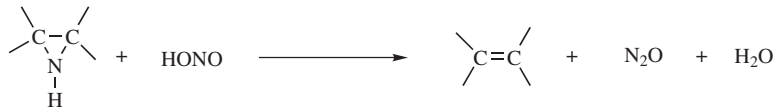
A Ramberg–Bäcklund-type reaction has been carried out on the α-halo *sulfides* ($ArCHClSCH_2Ar$), which react with *t*-BuOK and PPh_3 in refluxing THF to give the alkenes (ArCH=CHAr).[358] Cyclic sulfides lead to ring-contracted cyclic alkenes upon treatment with NCS in CCl_4 followed by oxidation with *m*-chloroperoxybenzoic acid.[359]

The Ramberg–Bäcklund reaction can be regarded as a type of extrusion reaction (see p. 1553).

OS **V**, 877; **VI**, 454, 555; **VIII**, 212.

17-21 The Conversion of Aziridines to Alkenes

epi-Imino-elimination



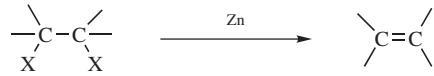
Aziridines not substituted on the nitrogen atom react with nitrous acid to produce alkenes.[360] An *N*-nitroso compound is an intermediate (**12-50**); other reagents that produce such intermediates also give alkenes. The reaction is stereospecific: cis aziridines give cis alkenes and trans aziridines give trans alkenes.[361] Aziridines carrying *N*-alkyl substituents can be converted to alkenes by treatment with ferrous iodide[362] or with *m*-chloroperoxybenzoic acid.[363] An *N*-oxide intermediate

[355]Woodward, R.B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Academic Press, NY, ***1970***, pp. 152–163.
[356]Philips, J.C.; Swisher, J.V.; Haidukewych, D.; Morales, O. *Chem. Commun*. ***1971***, 22.
[357]Carpino, L.A.; McAdams, L.V.; Rynbrandt, R.H.; Spiewak, J.W. *J. Am. Chem. Soc*. ***1971***, *93*, 476; Philips, J.C.; Morales, O. *J. Chem. Soc., Chem. Commun*. ***1977***, 713.
[358]Mitchell, R.H. *Tetrahedron Lett*. ***1973***, 4395. For a similar reaction without base treatment, see Pommelet, J.; Nyns, C.; Lahousse, F.; Merényi, R.; Viehe, H.G. *Angew. Chem. Int. Ed*. ***1981***, *20*, 585.
[359]MacGee, D.I.; Beck, E.J. *J. Org. Chem*. ***2000***, *65*, 8367.
[360]For reviews, see Sonnet, P.E. *Tetrahedron* ***1980***, *36*, 557, see p. 591; Dermer, O.C.; Ham, G.E. *Ethylenimine and other Aziridines*, Academic Press, NY, ***1969***, pp. 293–295.
[361]Clark, R.D.; Helmkamp, G.K. *J. Org. Chem*. ***1964***, *29*, 1316; Carlson, R.M.; Lee, S.Y. *Tetrahedron Lett*. ***1969***, 4001.
[362]Imamoto, T.; Yukawa, Y. *Chem. Lett*. ***1974***, 165.
[363]Heine, H.W.; Myers, J.D.; Peltzer III, E.T. *Angew. Chem. Int. Ed*. ***1970***, *9*, 374.

(**19-29**) is presumably involved in the latter case. *N*-Tosyl aziridines are converted to *N*-tosyl imines when treated with boron trifluoride.[364] 2-Tosylmethyl *N*-tosylaziridines react with Te^{2-} in the presence of Adogen 464 to give allylic *N*-tosyl amines.[365] 2-Halomethyl *N*-tosyl aziridines also react with indium metal in methanol to give *N*-tosyl allylic amines.[366]

17-22 Elimination of Vicinal Dihalides

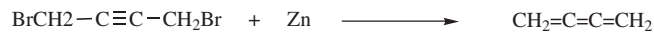
Dihalo-elimination



Dehalogenation has been accomplished with many reagents, the most common being zinc, magnesium, and iodide ion.[367] Heating in HMPA is often enough to convert a *vic*-dibromide to an alkene.[368] Among reagents used less frequently have been phenyllithium, phenylhydrazine, $CrCl_2$, Na_2S in DMF,[369] and $LiAlH_4$.[370] Electrochemical reduction has also been used.[371] Treatment with In[372] or Sm[373] metal in CH_3OH, $InCl_3/NaBH_4$,[374] a Grignard reagent and $Ni(dppe)Cl_2$, (dppe = 1, 2-diphenylphosphinoethane),[375] nickel compounds with Bu_3SnH,[376] or SmI_2[377] leads to the alkene. Although the reaction usually gives good yields, it is not very useful because the best way to prepare *vic*-dihalides is by the addition of halogen to a double bond (**15-39**). One useful feature of this reaction is that there is no doubt about the *position* of the new double bond, so that it can be used to give double bonds exactly where they are wanted. For example, allenes, which are not easily prepared by other methods, can be prepared from X–C–CX_2–C–X or X–C–CX=C– systems.[378] Cumulenes

[364]Sugihara, Y.; Iimura, S.; Nakayama, J. *Chem. Commun*. ***2002***, 134.
[365]Chao, B.; Dittmer, D.C. *Tetrahedron Lett*. ***2001***, *42*, 5789.
[366]Yadav, J.S.; Bandyapadhyay, A.; Reddy, B.V.S. *Synlett* ***2001***, 1608.
[367]For a review of this reaction, see Baciocchi, E., in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement D*, pt. 1, Wiley, NY, ***1983***, pp. 161–201. Also see, Bosser, G.; Paris, J. *J. Chem. Soc. Perkin Trans. 2* ***1992***, 2057.
[368]Khurana, J.M.; Bansal, G.; Chauhan, S. *Bull. Chem. Soc. Jpn*. ***2001***, *74*, 1089.
[369]Fukunaga, K.; Yamaguchi, H. *Synthesis* ***1981***, 879. See also, Nakayama, J.; Machida, H.; Hoshino, M. *Tetrahedron Lett*. ***1983***, *24* 3001; Landini, D.; Milesi, L.; Quadri, M.L.; Rolla, F. *J. Org. Chem*. ***1984***, *49*, 152.
[370]For a lists of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 259–263.
[371]See Shono, T. *Electroorganic Chemistry as a New Tool in Organic Synthesis*, Springer, NY, ***1984***, pp. 145–147; Fry, A.J. *Synthetic Organic Electrochemistry*, 2nd ed., Wiley, NY, ***1989***, pp. 151–154.
[372]Ranu, B.C.; Guchhait, S.K.; Sarkar, A. *Chem. Commun*. ***1998***, 2113.
[373]Yanada, R.; Negoro, N.; Yanada, K.; Fujita, T. *Tetrahedron Lett*. ***1996***, *37*, 9313.
[374]Ranu, B.C.; Das, A.; Hajra, A. *Synthesis* ***2003***, 1012.
[375]Malanga, C.; Aronica, L.A.; Lardicci, L. *Tetrahedron Lett*. ***1995***, *36*, 9189.
[376]Malanga, C.; Mannucci, S.; Lardicci, L. *Tetrahedron* ***1998***, *54*, 1021.
[377]Yanada, R.; Bessho, K.; Yanada, K. *Chem. Lett*, ***1994***, 1279.
[378]For reviews of allene formation, see Schuster, H.F.; Coppola, G.M. *Allenes in Organic Synthesis*, Wiley, NY, ***1984***, pp. 9–56; Landor, P.D., in Landor, S.R. *The Chemistry of the Allenes*, Vol. 1, Academic Press, NY, ***1982***; pp. 19–233; Taylor, D.R. *Chem. Rev*. ***1967***, *67*, 317.

have been obtained from 1,4-elimination:



Cumulenes have also been prepared by treating alkynyl epoxides with boron trifluoride.[379] 1,4-Elimination of BrC–C=C–CBr has been used to prepare conjugated dienes C=C–C=C.[380] Allenes are formed by heating propargylic alcohols with arylboronic acids (p. 815) and a palladium catalyst.[381] Allenes are also formed from propargylic amines using a CuI and a palladium catalyst.[382]

The reaction of a vicinal dibromide with triethylamine and DMF with microwave irradiation leads to vinyl bromide.[383] Alkenes are formed from vicinal bromides by heating with iron in methanol[384] or samarium in the presence of TMSCl and a trace of water.[385] α,β-Dibromo amides are converted to conjugated amides upon photolysis in methanol.[386]

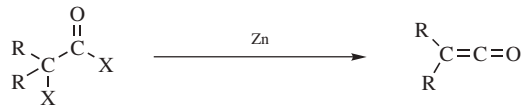
The reaction can be carried out for any combination of halogens, except where one is fluorine. Mechanisms are often complex and depend on the reagent and reaction conditions.[387] For different reagents, mechanisms involving carbocations, carbanions, and free-radical intermediates, as well as concerted mechanisms, have been proposed. When the reagent is zinc, anti stereospecificity has been observed in some cases,[388] but not in others.[389]

Note that geminal dibromo cyclopropanes (1,1-dibromocyclopropanes) are opened to conjugated dienes by heating to 500°C.[390]

OS **III**, 526, 531; **IV**, 195, 268; **V**, 22, 255, 393, 901; **VI**, 310, **VII**, 241. Also see, OS **IV**, 877, 914, 964.

17-23 Dehalogenation of α-Halo Acyl Halides

Dihalo-elimination



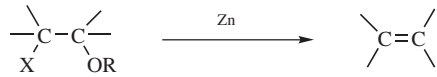
[379]Wang, X.; Ramos, B.; Rodriguez, A. *Tetrahedron Lett*. ***1994***, *35*, 6977.
[380]Engman, L.; Byström, S.E. *J. Org. Chem*. ***1985***, *50*, 3170.
[381]Yoshida, M.; Gotou, T.; Ihara, M. *Tetrahedron Lett*. ***2004***, *45*, 5573.
[382]Nakmura, H.; Kamakura, T.; Ishikura, M.; Biellmann, J.-F. *J. Am. Chem. Soc*. ***2004***, *126*, 5958.
[383]Kuang, C.; Senboku, H.; Tokuda, M. *Tetrahedron Lett*. ***2001***, *42*, 3893.
[384]Thakur, A.J.; Boruah, A.; Baruah, B.; Sandhu, J.S. *Synth. Commun*. ***2000***, *30*, 157.
[385]Xu, X.; Lu, P.; Zhang, Y. *Synth. Commun*. ***2000***, *30*, 1917.
[386]Aruna, S.; Kalyanakumar, R.; Ramakrishnan, V.T. *Synth. Commun*. ***2001***, *31*, 3125.
[387]For discussion, see Saunders, Jr., W.H.; Cockerill, A.F. *Mechanisms of Elimination Reactions*, Wiley, NY, ***1973***, pp. 332–368; Baciocchi, W., in Patai, S.; Rappoport, Z. *The Chemistry of Functional Grups, Supplement D*, pt. 2, Wiley, NY, ***1983***, p. 161.
[388]For example, see House, H.O.; Ro, R.S. *J. Am. Chem. Soc*. ***1958***, *80*, 182; Gordon, M.; Hay, J.V. *J. Org. Chem*. ***1968***, *33*, 427.
[389]For example, see Stevens, C.L.; Valicenti, J.A. *J. Am. Chem. Soc*. ***1965***, *87*, 838; Sicher, J.; Havel, M.; Svoboda, M. *Tetrahedron Lett*. ***1968***, 4269.
[390]Werstiuk, N.H.; Roy, C.D. *Tetrahedron Lett*. ***2001***, *42*, 3255.

Ketenes can be prepared by dehalogenation of α-halo acyl halides with zinc or with triphenylphosphine.[391] The reaction generally gives good results when the two R groups are aryl or alkyl, but not when either one is hydrogen.[392]

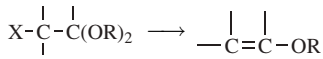
OS **IV**, 348; **VIII**, 377.

17-24 Elimination of a Halogen and a Hetero Group

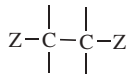
Alkoxy-halo-elimination



The elimination of OR and halogen from β-halo ethers is called the *Boord reaction*. It can be carried out with zinc, magnesium, sodium, or certain other reagents.[393] The yields are high and the reaction is of broad scope. β-Halo acetals readily yield vinylic ethers



and 2 equivalents of SmI_2 in HMPA is effective.[394] Besides β-halo ethers, the reaction can also be carried out on compounds of the formula



where X is halogen and Z is OCOR, OTs,[395] NR_2,[396] or SR.[397] When X = Cl and Z = OAc, heating in THF with an excess of SmI_2 followed by treatment with dilute aq. HCl gives an alkene.[398] When Z = I and the other Z is an oxygen of an oxazolone (a carbamate unit), heating with indium metal in methanol leads to an allylic amine.[399] The Z group may also be OH, but then X is limited to Br and I.[400] Like **17-22**, this method ensures that the new double bond will be in a specific position.

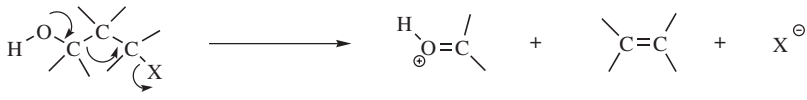
[391]Darling, S.D.; Kidwell, R.L. *J. Org. Chem.* ***1968***, *33*, 3974.
[392]For a procedure that gives 60–65% yields when one R = H, see McCarney, C.C.; Ward, R.S. *J. Chem. Soc. Perkin Trans. 1* ***1975***, 1600. See also, Masters, A.P.; Sorensen, T.S.; Ziegler, T. *J. Org. Chem.* ***1986***, *51*, 3558.
[393]See Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 263–267, for reagents that produce olefins from β-halo ethers and esters, and from halohydrins.
[394]Park, H.S.; Kim, S.H.; Park, M.Y.; Kim, Y.H. *Tetrahedron Lett.* ***2001***, *42*, 3729.
[395]Cristol, S.J.; Rademacher, L.E. *J. Am. Chem. Soc.* ***1959***, *81*, 1600; Reeve, W.; Brown, R.; Steckel, T.F. *J. Am. Chem. Soc.* ***1971***, *93*, 4607.
[396]Gurien, H. *J. Org. Chem.* ***1963***, *28*, 878.
[397]Amstutz, E.D. *J. Org. Chem.* ***1944***, *9*, 310.
[398]Concellón, J.M.; Bernad, P.L.; Bardales, E. *Org. Lett.* ***2001***, *3*, 937.
[399]Yadav, J.S.; Bandyopadhyay, A.; Reddy, B.V.S. *Tetrahedron Lett.* ***2001***, *42*, 6385.
[400]Concellón, J.M.; Pérez-Andrés, J.A.; Rodríguez-Solla, H. *Chem. Eur. J.* ***2001***, *7*, 3062.

The fact that magnesium causes elimination in these cases limits the preparation of Grignard reagents from these compounds. It has been shown that treatment of β-halo ethers and esters with zinc gives nonstereospecific elimination,[401] so the mechanism was not E2. An E1cB mechanism was postulated because of the poor leaving-group ability of OR and OCOR. Bromohydrins can be converted to alkenes (elimination of Br, OH) in high yields by treatment with $LiAlH_4$–$TiCl_3$.[402]

OS **III**, 698, **IV**, 748; **VI**, 675.

FRAGMENTATIONS

When carbon is the positive leaving group (the electrofuge) in an elimination, the reaction is called *fragmentation*.[403] These processes occur on substrates of the form W–C–C–X, where X is a normal nucleofuge (e.g., halogen, OH_2^+, OTs, NR_3^+) and W is a positive-carbon electrofuge. In most of the cases, W is HO–C– or R_2N–C–, so that the positive charge on the carbon atom is stabilized by the unshared pair of the oxygen or nitrogen, for example,

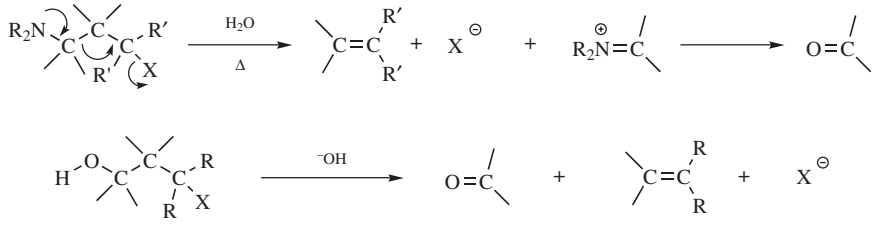


The mechanisms are mostly E1 or E2. We will discuss only a few fragmentations, since many are possible and not much work has been done on most of them. Reactions **17-25**–**17-28** and **17-30** may be considered fragmentations (see also **19-12** and **19-13**).

17-25 1,3-Fragmentation of γ-Amino, γ-Hydroxy Halides, and 1,3-Diols

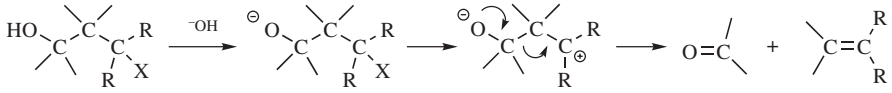
Dialkylaminoalkyl-halo-elimination, and so on

Hydroxyalkyl-hydroxy-elimination



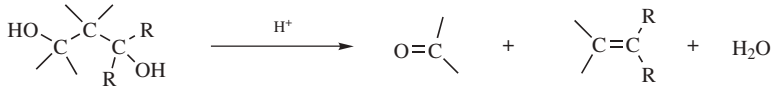
[401]House, H.O.; Ro, R.S. *J. Am. Chem. Soc*. ***1965***, *87*, 838.
[402]McMurry, J.E.; Hoz, T. *J. Org. Chem*. ***1975***, *40*, 3797.
[403]For reviews, see Becker, K.B.; Grob, C.A., in Patai, S. *The Chemistry of Functional Groups, Supplement A*, pt. 2, Wiley, NY, ***1977***, pp. 653–723; Grob, C.A. *Angew. Chem. Int. Ed*. ***1969***, *8*, 535; Grob, C.A.; Schiess, P.W. *Angew. Chem. Int. Ed*. ***1967***, *6*, 1.

γ-Dialkylamino halides undergo fragmentation when heated with water to give an alkene and an iminium salt, which under the reaction conditions is hydrolyzed to an aldehyde or ketone (**16-2**).[404] γ-Hydroxy halides and tosylates are fragmented with base. In this instance, the base does not play its usual role in elimination reactions, but instead serves to remove a proton from the OH group, which enables the carbon leaving group to come off more easily:



The mechanism of these reactions is often E1. However, in at least some cases, an E2 mechanism operates.[405] It has been shown that stereoisomers of cyclic γ-amino halides and tosylates in which the two leaving groups can assume an antiperiplanar conformation react by the E2 mechanism, while those isomers in which the groups cannot assume such a conformation either fragment by the E1 mechanism or do not undergo fragmentation at all, but in either case give rise to side products characteristic of carbocations.[406]

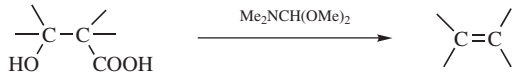
γ-Dialkylamino alcohols do not give fragmentation, since for ionization the OH group must be converted to OH_2^+ and this would convert NR_2 to NR_2H^+, which does not have the unshared pair necessary to form the double bond with the carbon.[407]



1,3-Diols in which at least one OH group is tertiary or is located on a carbon with aryl substituents can be cleaved by acid treatment.[408] The reaction is most useful synthetically when at least one of the OH groups is on a ring.[409]

17-26 Decarboxylation of β-Hydroxy Carboxylic Acids and of β-Lactones

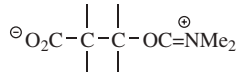
Carboxy-hydroxy-elimination



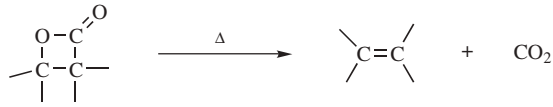
An OH and a COOH group can be eliminated from β-hydroxy carboxylic acids by refluxing with excess dimethylformamide dimethyl acetal.[410] Mono-, di-, tri-, and tetrasubstituted alkenes have been prepared by this method in good yields.[411]

[404]Grob, C.A.; Ostermayer, F.; Raudenbusch, W. *Helv. Chim. Acta* ***1962***, *45*, 1672.
[405]Fischer, W.; Grob, C.A. *Helv. Chim. Acta* ***1978***, *61*, 2336, and references cited therein.
[406]Geisel, M.; Grob, C.A.; Wohl, R.A. *Helv. Chim. Acta* ***1969***, *52*, 2206, and references cited therein.
[407]Grob, C.A.; Hoegerle, R.M.; Ohta, M. *Helv. Chim. Acta* ***1962***, *45*, 1823.
[408]Zimmerman, H.E.; English, Jr., J. *J. Am. Chem. Soc*. ***1954***, *76*, 2285, 2291, 2294.
[409]For a review of such cases, see Caine, D. *Org. Prep. Proced. Int*. ***1988***, *20*, 1.
[410]Hara, S.; Taguchi, H.; Yamamoto, H.; Nozaki, H. *Tetrahedron Lett*. ***1975***, 1545.
[411]For a 1,4 example of this reaction, see Rüttimann, A.; Wick, A.; Eschenmoser, A. *Helv. Chim. Acta* ***1975***, *58*, 1450.

There is evidence that the mechanism involves E1 or E2 elimination from the zwitterionic intermediate[412]



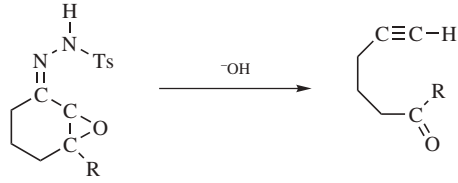
The reaction has also been accomplished[413] under extremely mild conditions (a few seconds at 0°C) with PPh_3 and diethyl azodicarboxylate EtOOC–N=N–COOEt.[414] In a related procedure, β-lactones undergo thermal decarboxylation to give alkenes in high yields. The reaction has been shown to be a stereospecific syn-elimination.[415] There is evidence that this reaction also involves a zwitterionic intermediate.[416]



There are no OS references, but see OS **VII**, 172, for a related reaction.

17-27 Fragmentation of α,β-Epoxy Hydrazones

Eschenmoser–Tanabe ring cleavage



Cyclic α,β-unsaturated ketones[417] can be cleaved by treatment with base of their epoxy tosylhydrazone derivatives to give acetylenic ketones.[418] The reaction can be applied to the formation of acetylenic aldehydes (R = H) by using the

[412]Mulzer, J.; Brüntrup, G. *Tetrahedron Lett*. ***1979***, 1909.

[413]For another method, see Tanzawa, T.; Schwartz, J. *Organometallics* ***1990***, *9*, 3026.

[414]Mulzer, J.; Brüntrup, G. *Angew. Chem. Int. Ed*. ***1977***, *16*, 255; Mulzer, J.; Lammer, O. *Angew. Chem. Int. Ed*. ***1983***, *22*, 628.

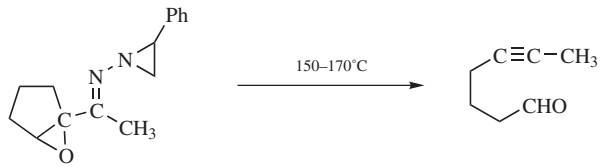
[415]Noyce, D.S.; Banitt, E.H. *J. Org. Chem*. ***1966***, *31*, 4043; Adam, W.; Baeza, J.; Liu, J. *J. Am. Chem. Soc*. ***1972***, *94*, 2000; Krapcho, A.P.; Jahngen, Jr., E.G.E. *J. Org. Chem*. ***1974***, *39*, 1322, 1650; Mageswaran, S.; Sultanbawa, M.U.S. *J. Chem. Soc. Perkin Trans. 1* ***1976***, 884; Adam, W.; Martinez, G.; Thompson, J.; Yany, F. *J. Org. Chem*. ***1981***, *46*, 3359.

[416]Mulzer, J.; Zippel, M.; Brüntrup, G. *Angew. Chem. Int. Ed*. ***1980***, *19*, 465; Mulzer, J.; Zippel, M. *Tetrahedron Lett*. ***1980***, *21*, 751. See also, Moyano, A.; Pericàs, M.A.; Valentí, E. *J. Org. Chem*. ***1989***, 573.

[417]For other methods of fragmentation of an α,β-epoxy ketone derivatives, see MacAlpine, G.A.; Warkentin, J. *Can. J. Chem*. ***1978***, *56*, 308, and references cited therein.

[418]Eschenmoser, A.; Felix, D.; Ohloff, G. *Helv. Chim. Acta* ***1967***, *50*, 708; Tanabe, M.; Crowe, D.F.; Dehn, R.L.; Detre, G. *Tetrahedron Lett*. ***1967***, 3739; Tanabe, M.; Crowe, D.F.; Dehn, R.L. *Tetrahedron Lett*. ***1967***, 3943.

corresponding, 2,4-dinitro-tosylhydrazone derivatives.[419] Hydrazones (e.g., **48**) prepared from epoxy ketones and ring-substituted *N*-aminoaziridines undergo similar fragmentation when heated.[420]

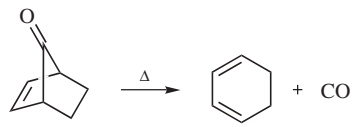


48

OS **VI**, 679.

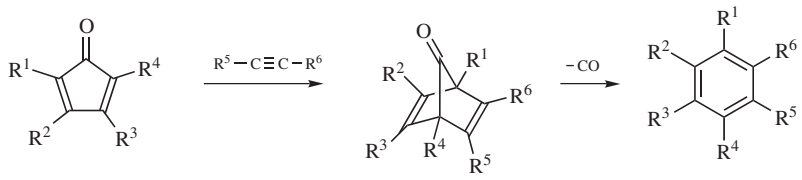
17-28 Elimination of CO and CO_2 from Bridged Bicyclic Compounds

seco-Carbonyl-1/4/elimination



49

On heating, bicyclo[2.2.1]hept-2,3-en-17-ones (**49**) usually lose CO to give cyclohexadienes,[421] in a type of reverse Diels–Alder reaction. Bicyclo[2.2.1]heptadienones (**50**) undergo the reaction so readily (because of the



50

stability of the benzene ring produced) that they cannot generally be isolated. The parent **50** has been obtained at 10–15°K in an Ar matrix, where its spectrum could be studied.[422] Both **49** and **50** can be prepared by Diels–Alder reactions between a cyclopentadienone and an alkyne or alkene, so that this reaction is a useful method for the preparation of specifically substituted benzene rings and cyclohexadienes.[423]

[419]Corey, E.J.; Sachdev, H.S. *J. Org. Chem.* ***1975***, *40*, 579.

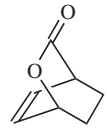
[420]Felix, D.; Müller, R.K.; Horn, U.; Joos, R.; Schreiber, J.; Eschenmoser, A. *Helv. Chim. Acta* ***1972***, *55*, 1276.

[421]For a review, see Stark, B.P.; Duke, A.J. *Extrusion Reactions*, Pergamon, Elmsford, NY, ***1967***, pp. 16–46.

[422]LeBlanc, B.F.; Sheridan, R.S. *J. Am. Chem. Soc*. ***1985***, *107*, 4554; Birney, D.M.; Wiberg, K.B.; Berson, J.A. *J. Am. Chem. Soc.* ***1988***, *110*, 6631.

[423]For a review with many examples; see Ogliaruso, M.A.; Romanelli, M.G.; Becker, E.I. *Chem. Rev.* ***1965***, *65*, 261, 300–348. For references to this and related reactions, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 207–213.

Unsaturated bicyclic lactones of the type **51** can also undergo the reaction, losing CO_2 (see also **17-35**).



51

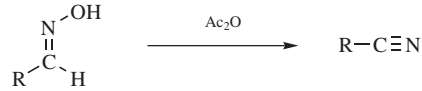
OS **III**, 807; **V**, 604, 1037.

Reversal of the Diels–Alder reaction may be considered a fragmentation (see **15-50**).

REACTIONS IN WHICH C≡N OR C=N BONDS ARE FORMED

17-29 Dehydration of Oximes and Similar Compounds

***C*-Hydro-*N*-hydroxy-elimination; *C*-Acyl-*N*-hydroxy-elimination**



Aldoximes can be dehydrated to nitriles[424] by many dehydrating agents, of which acetic anhydride is the most common. Among reagents that are effective under mild conditions[425] (room temperature) are Ph_3P–CCl_4,[426] SeO_2,[427] Me_2t-BuSiCl/imidazole,[428] ferric sulfate,[429] $SOCl_2$/benzotriazole,[430] $TiCl_3(OTf)$,[431] CS_2, and Amberlyst A26 (^-OH),[432] Montmorillonite KSF clay,[433] (*S,S*)-dimethyl dithiocarbonates,[434] and chloromethylene dimethylammonium chloride $Me_2N{=}CHCl^+$ Cl^-.[435] Heating an oxime with a ruthenium catalyst gives the nitrile.[436] Heating with the *Burgess reagent* [Et_3N^+ $^-SO_2N$–CO_2Me] in polyethylene glycol

[424]For reviews, see Friedrich, K., in Patai, S.; Rappoport, Z. *The Chemistry of the Carbon–Carbon Triple Bond*, pt. 2, Wiley, NY, ***1978***, pp. 1345–1390; Friedrich, K.; Wallenfels, K., in Rappoport, Z. *The Chemistry of the Cyano Group*, Wiley, NY, ***1970***, pp. 92–96. For a review of methods of synthesizing nitriles, see Fatiadi, K., in Friedrich, K. in Patai, S.; Rappoport, Z. *The Chemistry of the Carbon–Carbon Triple Bond*, pt. 2, Wiley, NY, ***1978***, pp. 1057–1303.

[425]For lists of some other reagents, with references, see Molina, P.; Alajarin, M.; Vilaplana, M.J. *Synthesis* ***1982***, 1016; Attanasi, O.; Palma, P.; Serra-Zanetti, F. *Synthesis* ***1983***, 741; Jurš ić, B. *Synth. Commun.* ***1989***, *19*, 689.

[426]Kim, J.N.; Chung, K.H.; Ryu, E.K. *Synth. Commun.* ***1990***, *20*, 2785.

[427]Shinozaki, H.; Imaizumi, M.; Tajima, M. *Chem. Lett.* ***1983***, 929.

[428]Ortiz-Marciales, M.; Piñero, L.; Ufret, L.; Algarín, W.; Morales, J. *Synth. Commun.* ***1998***, *28*, 2807.

[429]Desai, D.G.; Swami, S.S.; Mahale, G.D. *Synth. Commun.* ***2000***, *30*, 1623.

[430]Chaudhari, S.S.; Akamanchi, K.G. *Synth. Commun.* ***1999***, *29*, 1741.

[431]Iranpoor, N.; Zeynizadeh, B. *Synth. Commun.* ***1999***, *29*, 2747.

[432]Tamami, B.; Kiasat, A.R. *Synth. Commun.* ***2000***, *30*, 235.

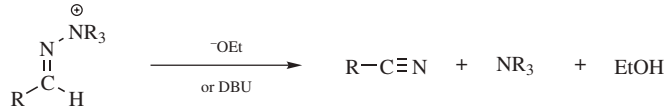
[433]Meshram, H.M. *Synthesis* ***1992***, 943.

[434]Khan, T.A.; Peruncheralathan, S.; Ila, H.; Junjappa, H. *Synlett* ***2004***, 2019.

[435]See Shono, T.; Matsumura, Y.; Tsubata, K.; Kamada, T.; Kishi, K. *J. Org. Chem.* ***1989***, *54*, 2249.

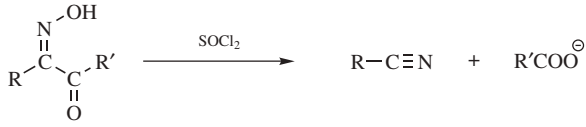
[436]Yang, S.H.; Chang, S. *Org. Lett.* ***2001***, *3*, 4209.

is effective for this transformation.[437] Microwave irradiation on EPZ-10[438] or sulfuric acid impregnated silica gel[439] gives the nitrile, as does microwave irradiation of an oxime with tetrachloropyridine on alumina.[440] Aldehydes can be converted to oximes *in situ* and microwave irradiation on alumina[441] or with ammonium acetate[442] gives the nitrile. Solvent-free reactions are known.[443] Electrochemical synthesis has also been used.[435] The reaction is most successful when the H and OH are anti. Various alkyl and acyl derivatives of aldoximes, for example, RCH=NOR, RCH=NOCOR, RCH=$NOSO_2Ar$, and so on, also give nitriles, as do chlorimines RCH=NCl (the latter with base treatment).[444] *N,N*-Dichloro derivatives of primary amines give nitriles on pyrolysis: $RCH_2NCl_2 \rightarrow RCN$.[445]



Quaternary hydrazonium salts (derived from aldehydes) give nitriles when treated with ^-OEt[446] or DBU (p. 1132):[447] as do dimethylhydrazones, RCH=$NNMe_2$, when treated with Et_2NLi and HMPA.[448] All these are methods of converting aldehyde derivatives to nitriles. For the conversion of aldehydes directly to nitriles, without isolation of intermediates (see **16-16**).

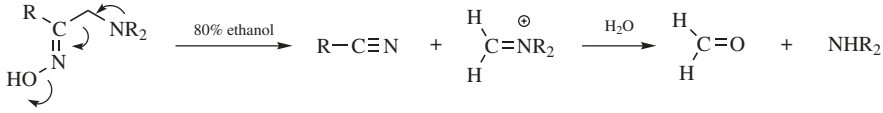
Hydroxylamines that have an α-proton are converted to nitrones when treated with a manganese salen complex.[449]



Certain ketoximes can be converted to nitriles by the action of proton or Lewis acids.[450] Among these are oximes of α-diketones (illustrated above), α-keto acids,

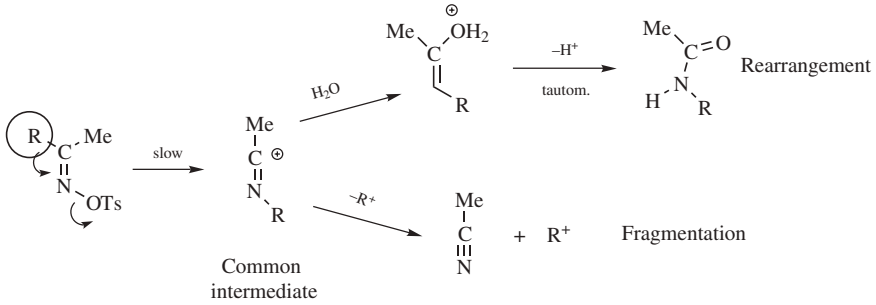
[437]Miller, C.P.; Kaufman, D.H. *Synlett* ***2000***, 1169.
[438]Bandgar, B.P.; Sadavarte, V.S.; Sabu, K.R. *Synth. Commun*. ***1999***, *29*, 3409.
[439]Kumar, H.M.S.; Mohanty, P.K.; Kumar, M.S.; Yadav, J.S. *Synth. Commun*. ***1997***, *27*, 1327; Sarvari, M.H. *Synthesis* ***2005***, 787.
[440]Lingaiah, N.; Narender, R. *Synth. Commun*. ***2002***, *32*, 2391.
[441]Bose, D.S.; Narsaiah, A.V. *Tetrahedron Lett*. ***1998***, *39*, 6533.
[442]Das, B.; Ramesh, C.; Madhusudhan, P. *Synlett* ***2000***, 1599.
[443]See Sharghi, H.; Sarvari, M.H. *Synthesis* ***2003***, 243.
[444]Hauser, C.R.; Le Maistre, J.W.; Rainsford, A.E. *J. Am. Chem. Soc*. ***1935***, *57*, 1056.
[445]Roberts, J.T.; Rittberg, B.R.; Kovacic, P. *J. Org. Chem*. ***1981***, *46*, 4111.
[446]Smith, R.F.; Walker, L.E. *J. Org. Chem*. ***1962***, *27*, 4372; Grandberg, I.I. *J. Gen. Chem. USSR*, ***1964***, *34*, 570; Grundon, M.F.; Scott, M.D. *J. Chem. Soc*. ***1964***, 5674; Ioffe, B.V.; Zelenina, N.L. *J. Org. Chem. USSR*, ***1968***, *4*, 1496.
[447]Moore, J.S.; Stupp, S.I. *J. Org. Chem*. ***1990***, *55*, 3374.
[448]Cuvigny, T.; Le Borgne, J.F.; Larchevêque, M.; Normant, H. *Synthesis* ***1976***, 237.
[449]Cicchi, S.; Cardona, F.; Brandi, A.; Corsi, M.; Goti, A. *Tetrahedron Lett*. ***1999***, *40*, 1989.
[450]For reviews, see Gawley, R.E. *Org. React*. ***1988***, *35*, 1; Conley, R.T.; Ghosh, S. *Mech. Mol. Migr.* ***1971***, *4*, 197, 197–251; McCarty, C.G., in Patai, S. *The Chemistry of the Carbon–Nitrogen Double Bond*, Wiley, NY, ***1970***, pp. 416–439; Casanova, J., in Rappoport, Z. *The Chemistry of the Cyano Group*, Wiley, NY, ***1970***, pp. 915–932.

α-dialkylamino ketones, α-hydroxy ketones, β-keto ethers, and similar compounds.[451] These are fragmentation reactions, analogous to **17-25**. For example, α-dialkylamino ketoximes also give amines and aldehydes or ketones besides nitriles:[452]



The reaction that normally occurs on treatment of a ketoxime with a Lewis or proton acid is the Beckmann rearrangement (**18-17**); fragmentations are considered side reactions, often called "abnormal" or "second-order" Beckmann rearrangements.[453] Obviously, the substrates mentioned are much more susceptible to fragmentation than are ordinary ketoximes, since in each case an unshared pair is available to assist in removal of the group cleaving from the carbon. However, fragmentation is a side reaction even with ordinary ketoximes[454] and, in cases where a particularly stable carbocation can be cleaved, may be the main reaction:[455]

There are indications that the mechanism at least in some cases first involves a rearrangement and then cleavage. The ratio of fragmentation to Beckmann rearrangement of a series of oxime tosylates, RC(=NOTs)Me, was not related to the solvolysis rate but *was* related to the stability of R^+ (as determined by the solvolysis rate of the corresponding RCl), which showed that fragmentation did not take place in the rate-determining step.[456] It may be postulated then that the first step in the fragmentation and in the rearrangement is the same and that this is the rate-determining step. The product is determined in the second step:



[451]For more complete lists with references, see Olah, G.A.; Vankar, Y.D.; Berrier, A.L. *Synthesis* ***1980***, 45; Conley, R.T.; Ghosh, S. *Mech. Mol. Migr.* ***1971***, *4*, 197.

[452]Fischer, H.P.; Grob, C.A.; Renk, E. *Helv. Chim. Acta* ***1962***, *45*, 2539; Fischer, H.P.; Grob, C.A. *Helv. Chim. Acta* ***1963***, *46*, 936.

[453]See the discussion in Ferris, A.F. *J. Org. Chem.* ***1960***, *25*, 12.

[454]See, for example, Hill, R.K.; Conley, R.T. *J. Am. Chem. Soc.* ***1960***, *82*, 645.

[455]Hassner, A.; Nash, E.G. *Tetrahedron Lett.* ***1965***, 525.

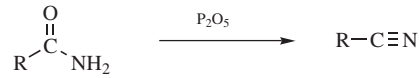
[456]Grob, C.A.; Fischer, H.P.; Raudenbusch, W.; Zergenyi, J. *Helv. Chim. Acta* ***1964***, *47*, 1003.

However, in other cases the simple E1 or E2 mechanisms operate.[457]

OS **V**, 266; **IX**, 281; OS **II**, 622; **III**, 690.

17-30 Dehydration of Unsubstituted Amides

***N,N*-Dihydro-*C*-oxo-bielimination**



Unsubstituted amides can be dehydrated to nitriles.[458] Phosphorous pentoxide is the most common dehydrating agent for this reaction, but many others, including $POCl_3$, PCl_5, CCl_4-Ph_3P,[459] HMPA,[460] LiCl with a zirconium catalyst,[461] $MeOOCNSO_2NEt_3$ (the Burgess reagent),[462] $Me_2N{=}CHCl^+\ Cl^-$,[463] $AlCl_3$/KI/H_2O,[464] Bu_2SnO with microwave irradiation,[465] PPh_3/NCS,[466] triflic anhydride,[467] oxalyl chloride/DMSO/–78°C[468] (Swern conditions, see **19-3**), and $SOCl_2$ have also been used.[469] Heating an amide with paraformaldehyde and formic acid gives the nitrile.[470] Treatment with benzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate converts amides to nitriles.[471] It is possible to convert an acid to the nitrile, without isolation of the amide, by heating its ammonium salt with the dehydrating agent,[472] or by other methods.[473] Acyl halides can also be directly converted to nitriles by heating with sulfamide $(NH_2)_2SO_2$.[474] The reaction may be formally looked on as a β-elimination from the enol form of the amide RC(OH)=NH, in which case it is like **17-29**, except that H and OH have changed

[457]Ahmad, A.; Spenser, I.D. *Can. J. Chem.* ***1961***, *39*, 1340; Ferris, A.F.; Johnson, G.S.; Gould, F.E. *J. Org. Chem.* ***1960***, *25*, 1813; Grob, C.A.; Sieber, A. *Helv. Chim. Acta* ***1967***, *50*, 2520; Green, M.; Pearson, S.C. *J. Chem. Soc. B* ***1969***, 593.

[458]For reviews, see Bieron J.F.; Dinan, F.J., in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 274–283; Friedrich, K.; Wallenfels, K., in Rappoport, Z. *The Chemistry of the Cyano Group*, Wiley, NY, ***1970***, pp. 96–103; Friedrich, K., in Patai, S.; Rapoport, Z. *The Chemistry of Functional Groups, Supplement C*, pt. 2, Wiley, NY, ***1978***, p. 1345.

[459]Yamato, E.; Sugasawa, S. *Tetrahedron Lett.* ***1970***, 4383; Appel, R.; Kleinstück, R.; Ziehn, K. *Chem. Ber.* ***1971***, *104*, 1030; Harrison, C.R.; Hodge, P.; Rogers, W.J. *Synthesis* ***1977***, 41.

[460]Monson, R.S.; Priest, D.N. *Can. J. Chem.* ***1971***, *49*, 2897.

[461]Ruck, R.T.; Bergman, R.G. *Angew. Chem. Int. Ed.* ***2004***, *43*, 5375.

[462]Claremon, D.A.; Phillips, B.T. *Tetrahedron Lett.* ***1988***, *29*, 2155.

[463]Barger, T.M.; Riley, C.M. *Synth. Commun.* ***1980***, *10*, 479.

[464]Boruah, M.; Konwar, D. *J. Org. Chem.* ***2002***, *67*, 7138.

[465]Bose, D.S.; Jayalakshmi, B. *J. Org. Chem.* ***1999***, *64*, 1713.

[466]Iranpoor, N.; Firouzabadi, H.; Aghapoor, G. *Synth. Commun.* ***2002***, *32*, 2535.

[467]Bose, D.S.; Jayalakshmi, B. *Synthesis* ***1999***, 64.

[468]Nakajima, N.; Ubukata, M. *Tetrahedron Lett.* ***1997***, *38*, 2099.

[469]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1983–1985.

[470]Heck, M.-P.; Wagner, A.; Mioskowski, C. *J. Org. Chem.* ***1996***, *61*, 6486.

[471]Bose, D.S.; Narsaiah, A.V. *Synthesis* ***2001***, 373.

[472]See, for example, Imamoto, T.; Takaoka, T.; Yokoyama, M. *Synthesis* ***1983***, 142.

[473]For a list of methods, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1949–1950.

[474]Hulkenberg, A.; Troost, J.J. *Tetrahedron Lett.* ***1982***, *23*, 1505.

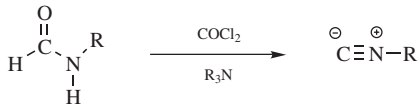
places. In some cases, for example, with $SOCl_2$, the mechanism probably *is* through the enol form, with the dehydrating agent forming an ester with the OH group, for example, RC(OSOCl)=NH, which undergoes elimination by the E1 or E2 mechanism.[475] *N,N*-Disubstituted ureas give cyanamides ($R_2N–CO–NH_2 \rightarrow R_2N–CN$) when dehydrated with $CHCl_3$–NaOH under phase-transfer conditions.[476] Treatment of an amide with aqueous NaOH and ultrasound leads to the nitrile.[477]

N-Alkyl-substituted amides can be converted to nitriles and alkyl chlorides by treatment with PCl_5. This is called the *von Braun reaction* (not to be confused with the other von Braun reaction, **10-54**).

OS **I**, 428; **II**, 379; **III**, 493, 535, 584, 646, 768; **IV**, 62, 144, 166, 172, 436, 486, 706; **VI**, 304, 465.

17-31 Conversion of *N*-Alkylformamides to Isonitriles (Isocyanides)

***CN*-Dihydro-*C*-oxo-bielimination**



Isocyanides (isonitriles) can be prepared by elimination of water from *N*-alkylformamides[478] with phosgene and a tertiary amine.[479] Other reagents, among them TsCl in quinoline, $POCl_3$ and a tertiary amine,[480] $Me_2N{=}CHCl^+\ Cl^-$,[481] triflic anhydride-$(i\text{Pr})_2\text{NEt}$,[482] PhOC(=S)Cl,[483] and $Ph_3P–CCl_4$-Et_3N[484] have also been employed. Formamides react with thionyl chloride (two sequential treatments) to give an intermediate that gives an isonitrile upon electrolysis in DMF with $LiClO_4$.[485]

A variation of this process uses carbodiimides,[486] which can be prepared by the dehydration of *N,N'*-disubstituted ureas with various dehydrating agents,[487] among

[475]Rickborn, B.; Jensen, F.R. *J. Org. Chem.* ***1962***, *27*, 4608.
[476]Schroth, W.; Kluge, H.; Frach, R.; Hodek, W.; Schädler, H.D. *J. Prakt. Chem.* ***1983***, *325*, 787.
[477]Sivakumar, M.; Senthilkumar, P.; Pandit, A.B. *Synth. Commun.* ***2001***, *31*, 2583.
[478]For a new synthesis see Creedon, S.M.; Crowley, H.K.; McCarthy, D.G. *J. Chem. Soc. Perkin Trans. 1* ***1998***, 1015.
[479]For reviews, see Hoffmann, P.; Gokel, G.W.; Marquarding, D.; Ugi, I., in Ugi, I. *Isonitrile Chemistry*, Academic Press, NY, ***1971***, pp. 10–17; Ugi, I.; Fetzer, U.; Eholzer, U.; Knupfer, H.; Offermann, K. *Angew. Chem. Int. Ed.* ***1965***, *4*, 472; *Newer Methods Prep. Org. Chem.* ***1968***, *4*, 37.
[480]See Obrecht, R.; Herrmann, R.; Ugi, I. *Synthesis* ***1985***, 400.
[481]Walborsky, H.M.; Niznik, G.E. *J. Org. Chem.* ***1972***, *37*, 187.
[482]Baldwin, J.E.; O'Neil, I.A. *Synlett* ***1991***, 603.
[483]Bose, D.S.; Goud, P.R. *Tetrahedron Lett.* ***1999***, *40*, 747.
[484]Appel, R.; Kleinstück, R.; Ziehn, K. *Angew. Chem. Int. Ed.* ***1971***, *10*, 132.
[485]Guirado, A.; Zapata, A.; Gómez, J.L.; Trebalón, L.; Gálvez, J. *Tetrahedron* ***1999***, *55*, 9631.
[486]For a review of the reactions in this section, see Bocharov, B.V. *Russ. Chem. Rev.* ***1965***, *34*, 212. For a review of carbodiimide chemistry; see Williams, A.; Ibrahim, I.T. *Chem. Rev.* ***1981***, *81*, 589.
[487]For some others not mentioned here, see Sakai, S.; Fujinami, T.; Otani, N.; Aizawa, T. *Chem. Lett.* ***1976***, 811; Shibanuma, T.; Shiono, M.; Mukaiyama, T. *Chem. Lett.* ***1977***, 575; Kim, S.; Yi, K.Y. *J. Org. Chem.* ***1986***, *51*, 2613, *Tetrahedron Lett.* ***1986***, *27*, 1925.

which are TsCl in pyridine, $POCl_3$, PCl_5, P_2O_5–pyridine, TsCl (with phase-transfer catalysis),[488] and Ph_3PBr_2–Et_3N.[489] Hydrogen sulfide can be removed from the corresponding thioureas by treatment with HgO, NaOCl, or diethyl azodicarboxylate–triphenylphosphine.[490]

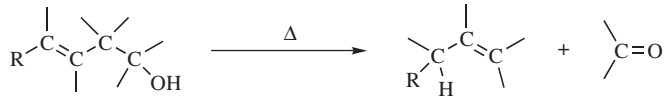
OS **V**, 300, 772; **VI**, 620, 751, 987. See also OS **VII**, 27. For the carbodiimide/thiourea dehydration, see OS **V**, 555; **VI**, 951.

REACTIONS IN WHICH C=O BONDS ARE FORMED

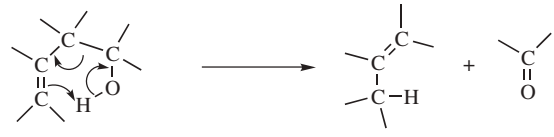
Many elimination reactions in which C=O bonds are formed were considered in Chapter 16, along with their more important reverse reactions (also see, **12-40** and **12-41**).

17-32 Pyrolysis of β-Hydroxy Alkenes

***O*-Hydro-*C*-allyl-elimination**

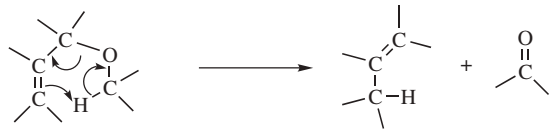


When pyrolyzed, β-hydroxy alkenes cleave to give alkenes and aldehydes or ketones.[491] Alkenes produced this way are quite pure, since there are no side reactions. The mechanism has been shown to be pericyclic, primarily by observations that the kinetics are first order[492] and that, for ROD, the deuterium appeared in the allylic position of the new alkene.[493] This mechanism is the reverse of that for the oxygen analog of the ene synthesis (**16-54**). β-Hydroxyacetylenes react similarly to give the corresponding allenes and carbonyl compounds.[494] The mechanism is the same despite the linear geometry of the triple bonds.



[488]Jászay, Z.M.; Petneházy, I.; Töke, L.; Szajáni, B. *Synthesis* ***1987***, 520.
[489]Bestmann, H.J.; Lienert, J.; Mott, L. *J.L. Liebigs Ann. Chem.* ***1968***, *718*, 24.
[490]Mitsunobu, O.; Kato, K.; Tomari, M. *Tetrahedron* ***1970***, *26*, 5731.
[491]Arnold, R.T.; Smolinsky, G. *J. Am. Chem. Soc*. ***1959***, *81*, 6643. For a review, see Marvell, E.N.; Whalley, W., in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 2, Wiley, NY, ***1971***, pp. 729–734.
[492]Voorhees, K.J.; Smith, G.G. *J. Org. Chem.* ***1971***, *36*, 1755.
[493]Arnold, R.T.; Smolinsky, G. *J. Org. Chem.* ***1960***, *25*, 128; Smith, G.G.; Taylor, R. *Chem. Ind. (London)* ***1961***, 949.
[494]Viola, A.; Proverb, R.J.; Yates, B.L.; Larrahondo, J. *J. Am. Chem. Soc*. ***1973***, *95*, 3609.

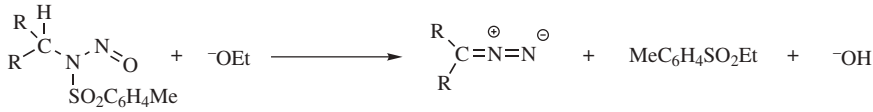
In a related reaction, pyrolysis of allylic ethers that contain at least one α hydrogen gives alkenes and aldehydes or ketones. The mechanism is also pericyclic[495]



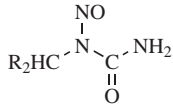
REACTIONS IN WHICH N=N BONDS ARE FORMED

17-33 Eliminations to Give Diazoalkanes

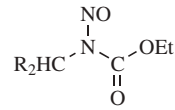
N-Nitrosoamine-diazoalkane transformation



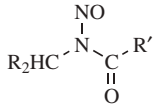
Various *N*-nitroso-*N*-alkyl compounds undergo elimination to give diazoalkanes.[496] One of the most convenient methods for the preparation of diazomethane involves base treatment of *N*-nitroso-*N*-methyl-*p*-toluenesulfonamide (illustrated above, with R = H).[497] However, other compounds commonly used are (base treatment is required in all cases):



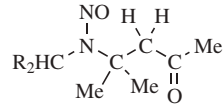
N-Nitroso-*N*-alkylureas



N-Nitroso-*N*-alkylcarbamates



N-Nitroso-*N*-alkyl amides



N-Nitroso-*N*-alkyl-4-amino-4-methyl-2-pentanone

All these compounds can be used to prepare diazomethane, although the sulfonamide, which is commercially available, is most satisfactory. *N*-Nitroso-*N*-methylcarbamate and *N*-nitroso-*N*-methylurea give good yields, but are highly irritating and carcinogenic.[498] For higher diazoalkanes the preferred substrates are nitrosoalkylcarbamates.

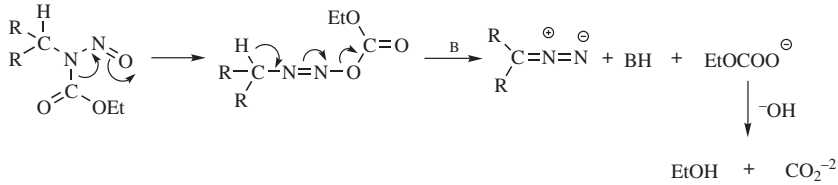
[495]Cookson, R.C.; Wallis, S.R. *J. Chem. Soc. B* ***1966***, 1245; Kwart, H.; Slutsky, J.; Sarner, S.F. *J. Am. Chem. Soc*. ***1973***, *95*, 5242; Egger, K.W.; Vitins, P. *Int. J. Chem. Kinet*. ***1974***, *6*, 429.

[496]For a review, see Regitz, M.; Maas, G. *Diazo Compounds*; Academic Press, NY, ***1986***, pp. 296–325. For a review of the preparation and reactions of diazomethane, see Black, T.H. *Aldrichimica Acta* ***1983***, *16*, 3. For discussions, see Cowell, G.W.; Ledwith, A. *Q. Rev. Chem. Soc*. ***1970***, *24*, 119, pp. 126–131; Smith, P.A.S. *Open-chain Nitrogen Compounds*; W. A. Benjamin, NY, ***1966***, especially pp. 257–258, 474–475, in Vol. 2.

[497]de Boer, T.J.; Backer, H.J. *Org. Synth*. ***IV***, 225, 250; Hudlicky, M. *J. Org. Chem*. ***1980***, *45*, 5377.

[498]Searle, C.E. *Chem. Br*. ***1970***, *6*, 5.

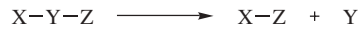
Most of these reactions probably begin with a 1,3 nitrogen-to-oxygen rearrangement, followed by the actual elimination (illustrated for the carbamate):



OS **II**, 165; **III**, 119, 244; **IV**, 225, 250; **V**, 351; **VI**, 981.

EXTRUSION REACTIONS

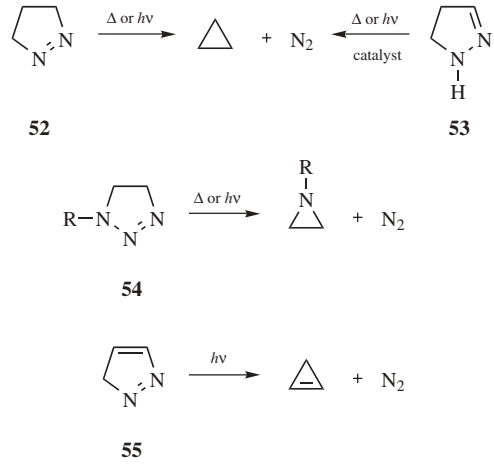
We consider an *extrusion reaction*[499] to be one in which an atom or group Y connected to two other atoms X and Z is lost from a molecule, leading to a product in which X is bonded directly to Z.



Reactions **14-32** and **17-20** also fit this definition. Reaction **17-28** does not fit the definition, but is often also classified as an extrusion reaction. An extrusibility scale has been developed, showing that the ease of extrusion of the common Y groups is in the order: –N=N– > –COO– > –SO_2– > –CO–.[500]

17-34 Extrusion of N_2 from Pyrazolines, Pyrazoles, and Triazolines

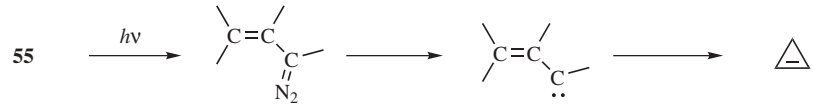
Azo-extrusion



[499]For a monograph, see Stark, B.P.; Duke, A.J. *Extrusion Reactions*, Pergamon, Elmsford, NY, ***1967***. For a review of extrusions that are photochemically induced, see Givens, R.S. *Org. Photochem.* ***1981***, *5*, 227.
[500]Paine, A.J.; Warkentin, J. *Can. J. Chem.* ***1981***, *59*, 491.

1-Pyrazolines (**52**) can be converted to cyclopropane and N_2 on photolysis[501] or pyrolysis.[502] The tautomeric 2-pyrazolines (**53**), which are more stable than **52** also give the reaction, but in this case an acidic or basic catalyst is required, the function of which is to convert **53** to **52**.[503] In the absence of such catalysts, **53** do not react.[504] In a similar manner, triazolines (**54**) are converted to aziridines.[505] Side reactions are frequent with both **52** and **54**, and some substrates do not give the reaction at all. However, the reaction has proved synthetically useful in many cases. In general, photolysis gives better yields and fewer side reactions than pyrolysis with both **52** and **54**. 3*H*-Pyrazoles[506] (**55**) are stable to heat, but in some cases can be converted to cyclopropenes on photolysis,[507] although in other cases other types of products are obtained.

There is much evidence that the mechanism[508] of the 1-pyrazoline reactions generally involves diradicals, although the mode of formation and detailed structure (e.g., singlet vs. triplet) of these radicals may vary with the substrate and reaction conditions. The reactions of the 3*H*-pyrazoles have been postulated to proceed through a diazo compound that loses N_2 to give a vinylic carbene.[509]

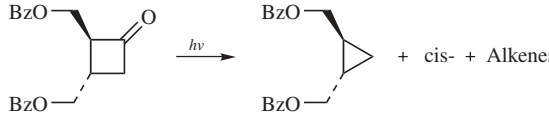


OS **V**, 96, 929. See also, OS **VIII**, 597.

[501]Van Auken, T.V.; Rinehart Jr., K.L. *J. Am. Chem. Soc*. ***1962***, *84*, 3736.
[502]For reviews of the reactions in this section, see Adam, W.; De Lucchi, O. *Angew. Chem. Int. Ed*. ***1980***, *19*, 762; Meier, H.; Zeller, K. *Angew. Chem. Int. Ed*. ***1977***, *16*, 835; Stark, B.P.; Duke, A.J. *Extrusion Reactions*, Pergamon, Elmsford, NY, ***1967***, pp. 116–151. For a review of the formation and fragmentation of cyclic azo compounds, see Mackenzie, K., in Patai, S. *The Chemistry of the Hydrazo, Azo, and Azoxy Groups*, pt. 1, Wiley, NY, ***1975***, pp. 329–442.
[503]For example, see Jones, W.M.; Sanderfer, P.O.; Baarda, D.G. *J. Org. Chem*. ***1967***, *32*, 1367.
[504]McGreer, D.E.; Wai, W.; Carmichael, G. *Can. J. Chem*. ***1960***, *38*, 2410; Kocsis K.; Ferrini, P.G.; Arigoni, D.; Jeger, O. *Helv. Chim. Acta* ***1960***, *43*, 2178.
[505]For a review, see Scheiner, P. *Sel. Org. Transform*. ***1970***, *1*, 327.
[506]For a review of 3*H*-pyrazoles, see Sammes, M.P.; Katritzky, A.R. *Adv. Heterocycl. Chem*. ***1983***, *34*, 2.
[507]Ege, G.*Tetrahedron Lett*. ***1963***, 1667; Closs, G.L.; Böll, W.A.; Heyn, H.; Dev, V. *J. Am. Chem. Soc*. ***1968***, *90*, 173; Franck-Neumann, M.; Buchecker, C. *Tetrahedron Lett*. ***1969***, 15; Pincock, J.A.; Morchat, R.; Arnold, D.R. *J. Am. Chem. Soc*. ***1973***, *95*, 7536.
[508]For a review of the mechanism; see Engel, P.S. *Chem. Rev*. ***1980***, *80*, 99. See also, Engel, P.S.; Nalepa, C.J. *Pure Appl. Chem*. ***1980***, *52*, 2621; Engel, P.S.; Gerth, D.B. *J. Am. Chem. Soc*. ***1983***, *105*, 6849; Reedich, D.E.; Sheridan, R.S. *J. Am. Chem. Soc*. ***1988***, *110*, 3697.
[509]Closs, G.L.; Böll, W.A.; Heyn, H.; Dev, V. *J. Am. Chem. Soc*. ***1968***, *90*, 173; Pincock, J.A.; Morchat, R.; Arnold, D.R. *J. Am. Chem. Soc*. ***1973***, *95*, 7536.

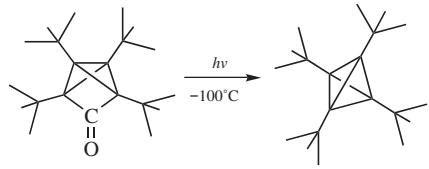
17-35 Extrusion of CO or CO_2

Carbonyl-extrusion



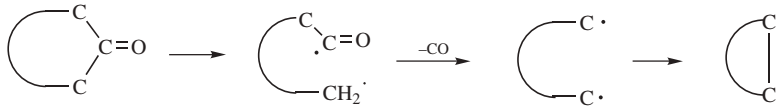
56 **57**

Although the reaction is not general, certain cyclic ketones can be photolyzed to give ring-contracted products.[510] In the example above, the cyclobutanone **56** was photolyzed to give **57**.[511] This reaction was used to synthesize tetra-*tert*-butyltetrahedrane, **58**.[512]

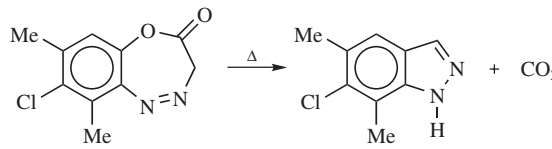


58

The mechanism probably involves a Norrish type I cleavage (p. 343), loss of CO from the resulting radical, and recombination of the radical fragments.



Certain lactones extrude CO_2 on heating or on irradiation, such as the pyrolysis of **59**.[513]



59

[510]For reviews of the reactions in this section, see Redmore, D.; Gutsche, C.D. *Adv. Alicyclic Chem.* ***1971***, *3*, 1, see pp. 91–107; Stark, B.P.; Duke, A.J. *Extrusion Reactions*, Pergamon, Elmsford, NY, ***1967***, pp. 47–71.

[511]Ramnauth, J.; Lee-Ruff, E. *Can. J. Chem.* ***1997***, *75*, 518. See also, Ramnauth, J.; Lee-Ruff, E. *Can. J. Chem.* ***2001***, *79*, 114.

[512]Maier, G.; Pfriem, S.; Schäfer, U.; Matusch, R. *Angew. Chem. Int. Ed.* ***1978***, *17*, 520.

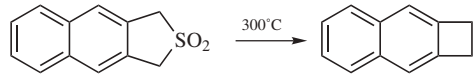
[513]Ried, W.; Wagner, K. *Liebigs Ann. Chem.* ***1965***, *681*, 45.

Decarboxylation of β-lactones (see **17-26**) may be regarded as a degenerate example of this reaction. Unsymmetrical diacyl peroxides RCO–OO–COR′ lose two molecules of CO_2 when photolyzed in the solid state to give the product RR′.[514] Electrolysis was also used, but yields were lower. This is an alternative to the Kolbe reaction (**11-34**) (see also **17-28** and **17-38**).

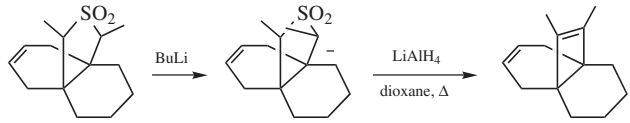
There are no OS references, but see OS **VI**, 418, for a related reaction.

17-36 Extrusion of SO_2

Sulfonyl-extrusion



In a reaction similar to **17-35**, certain sulfones, both cyclic and acyclic,[515] extrude SO_2 on heating or photolysis to give ring-contracted products.[516] An example is the preparation of naphtho(*b*)cyclobutene shown above.[517] In a different kind of reaction, five-membered cyclic sulfones can be converted to cyclobutenes by treatment with butyllithium followed by $LiAlH_4$,[518] for example,

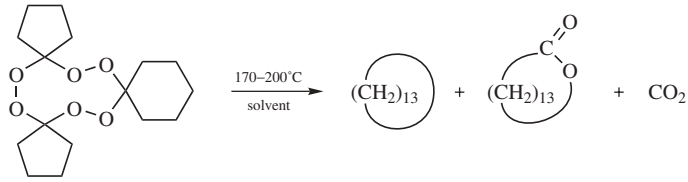


This method is most successful when both the α and α' position of the sulfone bear alkyl substituents (see also **17-20**). Treating four-membered ring sultams with $SnCl_2$ led to aziridine products via loss of SO_2.[519]

OS **VI**, 482.

[514]Lomölder, R.; Schäfer, H.J. *Angew. Chem. Int. Ed.* ***1987***, *26*, 1253.
[515]See, for example, Gould, I.R.; Tung, C.; Turro, N.J.; Givens, R.S.; Matuszewski, B. *J. Am. Chem. Soc.* ***1984***, *106*, 1789.
[516]For reviews of extrusions of SO_2, see Vögtle, F.; Rossa, L. *Angew. Chem. Int. Ed.* ***1979***, *18*, 515; Stark, B.P.; Duke, A.J. *Extrusion Reactions*, Pergamon, Elmsford, NY, ***1967***, pp. 72–90; Kice, J.L., in Kharasch, N.; Meyers, C.Y. *The Chemisry of Organic Sulfur Compounds*, Vol. 2, Pergamon, Elmsford, NY, ***1966***, pp. 115–136. For a review of extrusion reactions of S, Se, and Te compounds, see Guziec, Jr., F.S.; SanFilippo, L.J. *Tetrahedron* ***1988***, *44*, 6241.
[517]Cava, M.P.; Shirley, R.L. *J. Am. Chem. Soc.* ***1960***, *82*, 654.
[518]Photis, J.M.; Paquette, L.A. *J. Am. Chem. Soc.* ***1974***, *96*, 4715.
[519]Kataoka, T.; Iwama, T. *Tetrahedron Lett.* ***1995***, *36*, 5559.

17-37 The Story Synthesis



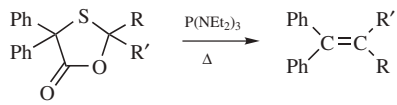
60

When cycloalkylidine peroxides (e.g., **60**) are heated in an inert solvent (e.g., decane), extrusion of CO_2 takes place; the products are the cycloalkane containing three carbon atoms less than the starting peroxide and the lactone containing two carbon atoms less[520] (the *Story synthesis*).[521] The two products are formed in comparable yields, usually ~15–25% each. Although the yields are low, the reaction is useful because there are not many other ways to prepare large rings. The reaction is versatile, having been used to prepare rings of every size from 8 to 33 members.

Both dimeric and trimeric cycloalkylidine peroxides can be synthesized[522] by treatment of the corresponding cyclic ketones with H_2O_2 in acid solution.[523] The trimeric peroxide is formed first and is subsequently converted to the dimeric compound.[524]

17-38 Alkene Synthesis by Twofold Extrusion

Carbon dioxide, thio-extrusion

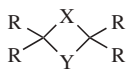


61

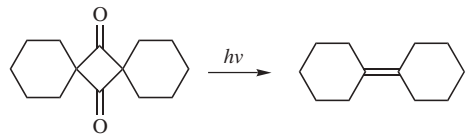
4,4-Diphenyloxathiolan-5-ones (**61**) give good yields of the corresponding alkenes when heated with tris(diethylamino)phosphine.[525] This reaction is an

[520]Sanderson, J.R.; Story, P.R.; Paul, K. *J. Org. Chem.* ***1975***, *40*, 691; Sanderson, J.R.; Paul, K.; Story, P.R. *Synthesis* ***1975***, 275.
[521]For a review, see Story, P.R.; Busch, P. *Adv. Org. Chem.* ***1972***, *8*, 67, see pp. 79–94.
[522]For synthesis of mixed trimeric peroxides (e.g., **60**), see Sanderson, J.R.; Zeiler, A.G. *Synthesis* ***1975***, 388; Paul, K.; Story, P.R.; Busch, P.; Sanderson, J.R. *J. Org. Chem.* ***1976***, *41*, 1283.
[523]Kharasch, M.S.; Sosnovsky, G. *J. Org. Chem.* ***1958***, *23*, 1322; Ledaal, T. *Acta Chem. Scand.*, ***1967***, *21*, 1656. For another method, see Sanderson, J.R.; Zeiler, A.G. *Synthesis* ***1975***, 125.
[524]Story, P.R.; Lee, B.; Bishop, C.E.; Denson, D.D.; Busch, P. *J. Org. Chem.* ***1970***, *35*, 3059. See also, Sanderson, J.R.; Wilterdink, R.J.; Zeiler, A.G. *Synthesis* ***1976***, 479.
[525]Barton, D.H.R.; Willis, B.J. *J. Chem. Soc. Perkin Trans. 1* ***1972***, 305.

example of a general type: alkene synthesis by twofold extrusion of X and Y from a molecule of the type **62**.[526] Other examples are photolysis of 1,4-diones[527] (e.g., **63**) and treatment of acetoxy sulfones [$RCH(OAc)CH_2SO_2Ph$] with Mg/EtOH and a catalytic amount of $HgCl_2$.[528] **61** can be prepared by the condensation of thiobenzilic acid $Ph_2C(SH)COOH$ with aldehydes or ketones.



62



63

OS **V**, 297.

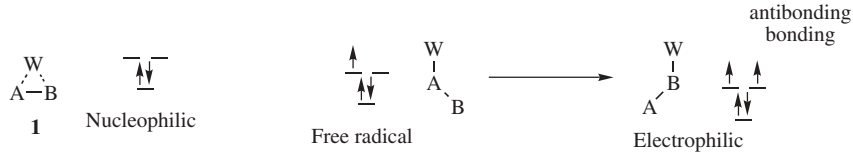
[526]For a review of those in which X or Y contains S, Se, or Te, see Guziec, Jr., F.S.; SanFilippo, L.J. *Tetrahedron* ***1988***, *44*, 6241.
[527]Turro, N.J.; Leermakers, P.A.; Wilson, H.R.; Neckers, D.C.; Byers, G.W.; Vesley, G.F. *J. Am. Chem. Soc*. ***1965***, *87*, 2613.
[528]Lee, G.H.; Lee, H.K.; Choi, E.B.; Kim, B.T.; Pak, C.S. *Tetrahedron Lett*. ***1995***, *36*, 5607.

CHAPTER 18

Rearrangements

In a rearrangement reaction a group moves from one atom to another in the same molecule.[1] Most are migrations from an atom to an adjacent one (called 1,2-shifts), but some are over longer distances. The migrating group (W)

may move with its electron pair (these can be called *nucleophilic* or *anionotropic* rearrangements; the migrating group can be regarded as a nucleophile), without its electron pair (*electrophilic* or *cationotropic* rearrangements; in the case of migrating hydrogen, *prototropic* rearrangements), or with just one electron (free-radical rearrangements). The atom A is called the *migration origin* and B is the *migration terminus*. However, there are some rearrangements that do not lend themselves to neat categorization in this manner. Among these are those with cyclic transition states (**18-27**–**18-36**).



As we will see, nucleophilic 1,2-shifts are much more common than electrophilic or free-radical 1,2-shifts. The reason for this can be seen by a consideration of the transition states (or in some cases intermediates) involved. We represent the transition state or intermediate for all three cases by **1**, in which the two-electron

[1]For books, see de Mayo, P. *Rearrangements in Ground and Excited States*, 3 vols., Academic Press, NY, ***1980***; Stevens, T.S.; Watts, W.E. *Selected Molecular Rearrangements*, Van Nostrand-Reinhold, Princeton, NJ, ***1973***. For a review of many of these rearrangements, see Collins, C.J.; Eastham, J.F., in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***, pp. 761–821. See also, the series *Mechanisms of Molecular Migrations.*

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Sixth Edition, by Michael B. Smith and Jerry March

A–W bond overlaps with the orbital on atom B, which contains zero, one, and two electrons, in the case of nucleophilic, free-radical, and electrophilic migration, respectively. The overlap of these orbitals gives rise to three new orbitals, which have an energy relationship similar to those on p. 72 (one bonding and two degenerate antibonding orbitals). In a nucleophilic migration, where only two electrons are involved, both can go into the bonding orbital and **1** is a low-energy transition state; but in a free-radical or electrophilic migration, there are, respectively, three or four electrons that must be accommodated, and antibonding orbitals must be occupied. It is not surprising therefore that, when 1,2-electrophilic or free-radical shifts are found, the migrating group W is usually aryl or some other group that can accommodate the extra one or two electrons and thus effectively remove them from the three-membered transition state or intermediate (see **41** on p. 1577).

In any rearrangement, we can in principle distinguish between two possible modes of reaction: In one of these, the group W becomes completely detached from A and may end up on the B atom of a different molecule (*intermolecular* rearrangement); in the other W goes from A to B in the *same* molecule (*intramolecular* rearrangement), in which case there must be some continuing tie holding W to the A–B system, preventing it from coming completely free. Strictly speaking, only the intramolecular type fits our definition of a rearrangement, but the general practice, which is followed here, is to include under the title ''rearrangement'' all net rearrangements whether they are inter- or intramolecular. It is usually not difficult to tell whether a given rearrangement is inter- or intramolecular. The most common method involves the use of *crossover* experiments. In this type of experiment, rearrangement is carried out on a mixture of W–A–B and V–A–C, where V is closely related to W (say, methyl vs. ethyl) and B to C. In an intramolecular process only A–B–W and A–C–V are recovered, but if the reaction is intermolecular, then not only will these two be found, but also A–B–V and A–C–W.

MECHANISMS

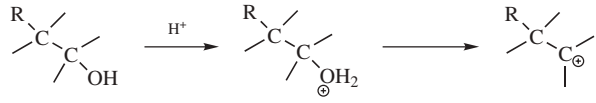
Nucleophilic Rearrangements[2]

Broadly speaking, such rearrangements consist of three steps, of which the actual migration is the second:

[2]For reviews, see Vogel, P. *Carbocation Chemistry*; Elsevier, NY, ***1985***, pp. 323–372; Shubin, V.G. *Top. Curr. Chem.* ***1984***, *116/117*, 267; Saunders, M.; Chandrasekhar, J.; Schleyer, P.v.R., in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 1, Academic Press, NY, ***1980***, pp. 1–53; Kirmse, W. *Top. Curr. Chem.* ***1979***, *80*, 89. For reviews of rearrangements in vinylic cations, see Shchegolev, A.A.; Kanishchev, M.I. *Russ. Chem. Rev.* ***1981***, *50*, 553; Lee, C.C. *Isot. Org. Chem.* ***1980***, *5*, 1.

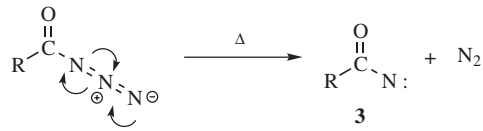
This process has been called the *Whitmore 1,2-shift*.[3] Since the migrating group carries the electron pair with it, the migration terminus B must be an atom with only six electrons in its outer shell (an open sextet). The first step therefore is creation of a system with an open sextet. Such a system can arise in various ways, but two of these are the most important:

1. *Formation of a Carbocation*. These can be formed in a number of ways (see p. 247), but one of the most common methods when a rearrangement is desired is the acid treatment of an alcohol to give **2** from an intermediate oxonium ion. These two steps are of course the same as the first two steps of the S_N1cA or the E1 reactions of alcohols.



2

2. *Formation of a Nitrene*. The decomposition of acyl azides is one of several ways in which acyl nitrenes **3** are formed (see p. 293). After the migration has taken place, the atom at the migration origin (A) must necessarily have an open sextet. In the third step, this atom acquires an octet. In the case of carbocations, the most common third steps are combinations with a nucleophile (rearrangement with substitution) and loss of H^+ (rearrangement with elimination).



3

Although we have presented this mechanism as taking place in three steps, and some reactions do take place in this way, in many cases two or all three steps are simultaneous. For example, in the nitrene example above, as the R migrates, an electron pair from the nitrogen moves into the C–N bond to give a stable isocyanate, **4**.

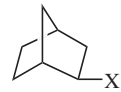
3 **4**

In this example, the second and third steps are simultaneous. It is also possible for the second and third steps to be simultaneous even when the "third" step involves more than just a simple motion of a pair of electrons. Similarly, there are many reactions in which the first two steps are simultaneous; that is, there is no actual formation of a species, such as **2** or **3**. In these instances, it may be said that

[3]It was first postulated by Whitmore, F.C. *J. Am. Chem. Soc.* ***1932***, *54*, 3274.

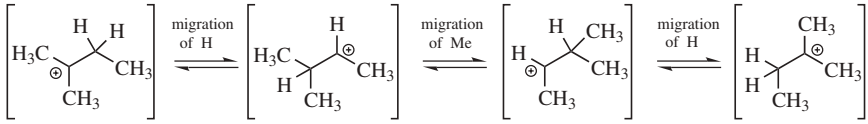
R assists in the removal of the leaving group, with migration of R and the removal of the leaving group taking place simultaneously. Many investigations have been carried out in attempts to determine, in various reactions, whether such intermediates as **2** or **3** actually form, or whether the steps are simultaneous (see, e.g., the discussions on pp. 1381, 1563), but the difference between the two possibilities is often subtle, and the question is not always easily answered.[4]

Evidence for this mechanism is that rearrangements of this sort occur under conditions where we have previously encountered carbocations: S_N1 conditions, Friedel–Crafts alkylation, and so on. Solvolysis of neopentyl bromide leads to rearrangement products, and the rate increases with increasing ionizing power of the solvent but is unaffected by concentration of base,[5] so that the first step is carbocation formation. The same compound under S_N2 conditions gave no rearrangement, but only ordinary substitution, though slowly. Thus with neopentyl bromide, formation of a carbocation leads only to rearrangement. Carbocations usually rearrange to more stable carbocations. Thus the direction of rearrangement is usually primary → secondary → tertiary. Neopentyl (Me_3CCH_2), neophyl ($PhCMe_2CH_2$), and norbornyl (e.g., **5**) type systems are especially prone to carbocation rearrangement reactions. It has been shown that the rate of migration increases with the degree of electron deficiency at the migration terminus.[6]



5

We have previously mentioned (p. 236) that stable tertiary carbocations can be obtained, in solution, at very low temperatures. The NMR studies have shown that when these solutions are warmed, rapid migrations of hydride and of alkyl groups take place, resulting in an equilibrium mixture of structures.[7] For example, the *tert*-pentyl cation (**5**)[8] equilibrates as follows:



6 **7** **7'** **6'**

[4]The IUPAC designations depend on the nature of the steps. For the rules, see Guthrie, R.D. *Pure Appl. Chem.* ***1989***, *61*, 23, 44–45.

[5]Dostrovsky, I.; Hughes, E.D. *J. Chem. Soc.* ***1946***, 166.

[6]Borodkin, G.I.; Shakirov, M.M.; Shubin, V.G.; Koptyug, V.A. *J. Org. Chem. USSR* ***1978***, *14*, 290, 924.

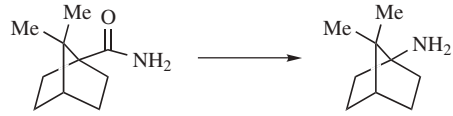
[7]For reviews, see Brouwer, D.M.; Hogeveen, H. *Prog. Phys. Org. Chem.* ***1972***, *9*, 179, see pp. 203–237; Olah, G.A.; Olah, J.A., in Olah, G.A.; Schleyer, P.V.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1970***, pp. 751–760, 766–778. For a discussion of the rates of these reactions, see Sorensen, T.S. *Acc. Chem. Res.* ***1976***, *9*, 257.

[8]Brouwer, D.M. *Recl. Trav. Chim. Pays-Bas* ***1968***, *87*, 210; Saunders, M.; Hagen, E.L. *J. Am. Chem. Soc.* ***1968***, *90*, 2436.

Carbocations that rearrange to give products of identical structure (e.g., **6** ⇄ **6'**,**7** ⇄ **7'**) are called *degenerate carbocations* and such rearrangements are *degenerate rearrangements*. Many examples are known.[9]

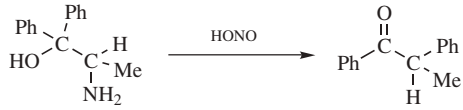
The Actual Nature of the Migration

Most nucleophilic 1,2-shifts are intramolecular. The W group does not become free, but always remains connected in some way to the substrate. Apart from the evidence from crossover experiments, the strongest evidence is that when the W group is chiral, the configuration is *retained* in the product. For example, (+)-PhCHMeCOOH was converted to (−)-PhCHMeNH$_2$ by the Curtius (**18-14**), Hofmann (**18-13**), Lossen (**18-15**), and Schmidt (**18-16**) reactions.[10] In these reactions, the extent of retention varied from 95.8 to 99.6%. Retention of configuration in the migrating group has been shown many times since.[11] Another experiment demonstrating retention was the



8 **9**

easy conversion of **8** to **9**.[11] Neither inversion nor racemization could take place at a bridgehead. There is much other evidence that retention of configuration usually occurs in W, and inversion never.[12] However, this is not the state of affairs at A and B. In many reactions, of course, the structure of W–A–B is such that the product has only one steric possibility at A or B or both, and in most of these cases nothing can be learned. But in cases where the steric nature of A or B can be investigated, the results are mixed. It has been shown that either inversion or racemization can occur at A or B. Thus the following conversion proceeded with inversion at B:[13]



(–) (+)

[9]For reviews, see Ahlberg, P.; Jonsäll, G.; Engdahl, C. *Adv. Phys. Org. Chem.* ***1983***, *19*, 223; Leone, R.E.; Barborak, J.C.; Schleyer, P.v.R., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 4, Wiley, NY, ***1970***, pp. 1837–1939; Leone, R.E.; Schleyer, P.v.R. *Angew. Chem. Int. Ed.* ***1970***, *9*, 860.

[10]Campbell, A.; Kenyon, J. *J. Chem. Soc.* ***1946***, 25, and references cited therein.

[11]For retention of migrating group configuration in the Wagner–Meerwein and pinacol rearrangements, see Beggs, J.J.; Meyers, M.B. *J. Chem. Soc. B* ***1970***, 930; Kirmse, W.; Gruber, W.; Knist, J. *Chem. Ber.* ***1973***, *106*, 1376; Shono, T.; Fujita, K.; Kumai, S. *Tetrahedron Lett.* ***1973***, 3123; Borodkin, G.I.; Panova, Y.B.; Shakirov, M.M.; Shubin, V.G. *J. Org. Chem. USSR* ***1983***, *19*, 103.

[12]See Cram, D.J., in Newman *Steric Effects in Organic Chemistry*, Wiley, NY, ***1956***; pp. 251–254; Wheland, G.W. *Advanced Organic Chemistry*, 3rd ed., Wiley, NY, ***1960***, pp. 597–604.

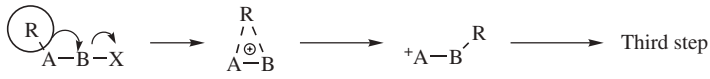
[13]Bernstein, H.I.; Whitmore, F.C. *J. Am. Chem. Soc.* ***1939***, *61*, 1324. For other examples, see Tsuchihashi, G.; Tomooka, K.; Suzuki, K. *Tetrahedron Lett.* ***1984***, *25*, 4253.

and inversion at A has been shown in other cases.[14] However, in many other cases, racemization occurs at A or B or both.[15] It is not always necessary for the product to have two steric possibilities in order to investigate the stereochemistry at A or B. Thus, in most Beckmann rearrangements (**18-17**), only the group trans (usually called *anti*) to the hydroxyl group migrates:

showing inversion at B.

This information tells us about the degree of concertedness of the three steps of the rearrangement. First consider the migration terminus B. If racemization is found at B, it is probable that the first step takes place before the second and that a positively charged carbon (or other sextet atom) is present at B:

With respect to B this is an S_N1-type process. If inversion occurs at B, it is likely that the first two steps are concerted, that a carbocation is *not* an intermediate, and that the process is S_N2-like:



10

In this case, participation by R assists in removal of X in the same way that neighboring groups do (p. 446). Indeed, R *is* a neighboring group here. The only difference is that, in the case of the neighboring-group mechanism of nucleophilic substitution, R never becomes detached from A, while in a rearrangement the bond between R and A is broken. In either case, the anchimeric assistance results in an increased rate of reaction. Of course, for such a process to take place, R must be in a favorable geometrical position (R and X antiperiplanar). Intermediate **10** may be a true intermediate or only a transition state, depending on what migrates. In certain cases of the S_N1-type process, it is possible for migration to take place with net retention of configuration at the migrating terminus because of conformational effects in the carbocation.[16]

We may summarize a few conclusions:

1. The S_N1-type process occurs mostly when B is a tertiary atom or has one aryl group and at least one other alkyl or aryl group. In other cases, the S_N2-type

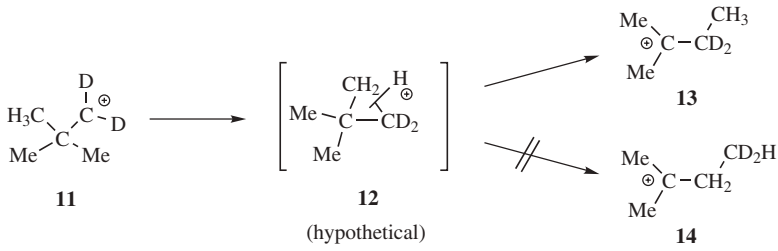
[14]See Meerwein, H.; van Emster, K. *Ber.* ***1920***, *53*, 1815; ***1922***, *55*, 2500; Meerwein, H.; Gérard, L. *Liebigs Ann. Chem.* ***1923***, *435*, 174.

[15]For example, see Winstein, S.; Morse, B.K. *J. Am. Chem. Soc.* ***1952***, *74*, 1133.

[16]Collins, C.J.; Benjamin, B.M. *J. Org. Chem.* ***1972***, *37*, 4358, and references cited therein.

process is more likely. Inversion of configuration (indicating an S_N2-type process) has been shown for a neopentyl substrate by the use of the chiral neopentyl-1-*d* alcohol.[17] On the other hand, there is other evidence that neopentyl systems undergo rearrangement by a carbocation (S_N1-type) mechanism.[18]

2. The question as to whether **10** is an intermediate or a transition state has been much debated. When R is aryl or vinyl, then **10** is probably an intermediate and the migrating group lends anchimeric assistance[19] (see p. 459 for resonance stabilization of this intermediate, when R is aryl). When R is alkyl, **10** is a protonated cyclopropane (edge- or corner-protonated; see p. 1026). There is much evidence that in simple migrations of a methyl group, the bulk of the products formed do not arise from protonated cyclopropane *intermediates*. Evidence for this statement has already been given (p. 467). Further evidence was obtained from experiments involving labeling.



Rearrangement of the neopentyl cation labeled with deuterium in the 1 position (**11**) gave only *tert*-pentyl products with the label in the 3 position (derived from **13**), though if **12** were an intermediate, the cyclopropane ring could just as well cleave the other way to give *tert*-pentyl derivatives labeled in the 4 position (derived from **14**).[20] Another experiment that led to the same conclusion was the generation, in several ways, of $Me_3C^{13}CH_2^+$. In this case, the only *tert*-pentyl products isolated were labeled in C-3, that is, $Me_2C^+–^{13}CH_2CH_3$ derivatives; no derivatives of $Me_2C^+–CH_2{}^{13}CH_3$ were found.[21]

Although the bulk of the products are not formed from protonated cyclopropane intermediates, there is considerable evidence that at least in 1-propyl

[17]Sanderson, W.A.; Mosher, H.S. *J. Am. Chem. Soc.* ***1966***, *88*, 4185; Mosher, H.S. *Tetrahedron* ***1974***, *30*, 1733. See also, Guthrie, R.D. *J. Am. Chem. Soc.* ***1967***, *89*, 6718.

[18]Nordlander, J.E.; Jindal, S.P.; Schleyer, P.v.R.; Fort Jr., R.C.; Harper, J.J.; Nicholas, R.D. *J. Am. Chem. Soc.* ***1966***, *88*, 4475; Shiner, Jr., V.J.; Imhoff, M.A. *J. Am. Chem. Soc.* ***1985***, *107*, 2121.

[19]For example, see Rachon, J.; Goedkin, V.; Walborsky, H.M. *J. Org. Chem.* ***1989***, *54*, 1006. For an opposing view, see Kirmse, W.; Feyen, P. *Chem. Ber.* ***1975***, *108*, 71; Kirmse, W.; Plath, P.; Schaffrodt, H. *Chem. Ber.* ***1975***, *108*, 79.

[20]Skell, P.S.; Starer, I.; Krapcho, A.P. *J. Am. Chem. Soc.* ***1960***, *82*, 5257.

[21]Karabatsos, G.J.; Orzech Jr., C.E.; Meyerson, S. *J. Am. Chem. Soc.* ***1964***, *86*, 1994.

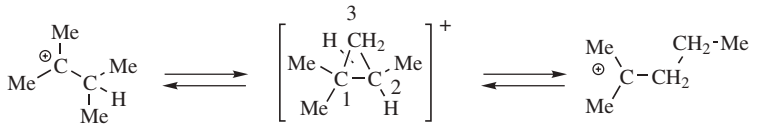
systems, a small part of the product can in fact arise from such intermediates.[22] Among this evidence is the isolation of 10–15% cyclopropanes (mentioned on p. 467). Additional evidence comes from propyl cations generated by diazotization of labeled amines ($CH_3CH_2CD_2^+$, $CH_3CD_2CH_2^+$, $CH_3CH_2{}^{14}CH_2^+$), where isotopic distribution in the products indicated that a small amount (∼5%) of the product had to be formed from protonated cyclopropane intermediates, for example,[23]

$$CH_3CH_2CD_2NH_2 \xrightarrow{HONO} -1\% \quad C_2H_4D\text{—}CHD\text{—}OH$$

$$CH_3CD_2CH_2NH_2 \xrightarrow{HONO} -1\% \quad C_2H_4D\text{—}CHD\text{—}OH$$

$$CH_3CH_{2}{}^{14}CH_2NH_2 \xrightarrow{HONO} -2\% \ {}^{14}CH_3CH_2CH_2OH + -2\% \ CH_3{}^{14}CH_2CH_2OH$$

Even more scrambling was found in trifluoroacetolysis of 1-propyl-1-^{14}C-mercuric perchlorate.[24] However, protonated cyclopropane intermediates accounted for <1% of the products from diazotization of labeled isobutylamine[25] and from formolysis of labeled 1-propyl tosylate.[26]



15 **16** **17**

It is likely that protonated cyclopropane transition states or intermediates are also responsible for certain non-1,2 rearrangements. For example, in super acid solution, the ions **15** and **17** are in equilibrium. It is not possible for these to interconvert solely by 1,2-alkyl or hydride shifts unless primary carbocations (which are highly unlikely) are intermediates. However, the reaction can be explained[27] by postulating that (in the forward reaction) it is the 1,2 bond

[22]For reviews, see Saunders, M.; Vogel, P.; Hagen, E.L.; Rosenfeld, J. *Acc. Chem. Res.* ***1973***, *6*, 53; Lee, C.C. *Prog. Phys. Org. Chem.* ***1970***, *7*, 129; Collins, C.J. *Chem. Rev.* ***1969***, *69*, 543. See also, Cooper, C.N.; Jenner, P.J.; Perry, N.B.; Russell-King, J.; Storesund, H.J.; Whiting, M.C. *J. Chem. Soc. Perkin Trans. 2* ***1982***, 605.

[23]Lee, C.C.; Kruger, J.E. *Tetrahedron* ***1967***, *23*, 2539; Lee, C.C.; Wan, K. *J. Am. Chem. Soc.* ***1969***, *91*, 6416; Karabatsos, G.J.; Orzech, Jr., C.E.; Fry, J.L.; Meyerson, S. *J. Am. Chem. Soc.* ***1970***, *92*, 606.

[24]Lee, C.C.; Cessna, A.J.; Ko, E.C.F.; Vassie, S. *J. Am. Chem. Soc.* ***1973***, *95*, 5688. See also, Lee, C.C.; Reichle, R. *J. Org. Chem.* ***1977***, *42*, 2058, and references cited therein.

[25]Karabatsos, G.J.; Hsi, N.; Meyerson, S. *J. Am. Chem. Soc.* ***1970***, *92*, 621. See also, Karabatsos, G.J.; Anand, M.; Rickter, D.O.; Meyerson, S. *J. Am. Chem. Soc.* ***1970***, *92*, 1254.

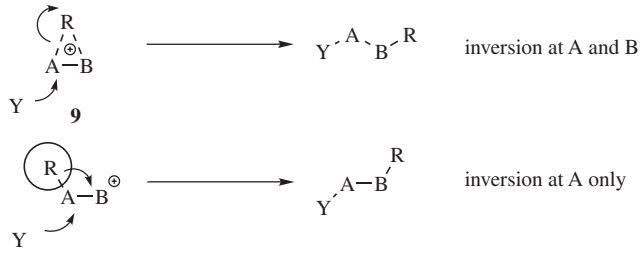
[26]Lee, C.C.; Kruger, J.E. *Can. J. Chem.* ***1966***, *44*, 2343; Shatkina, T.N.; Lovtsova, A.N.; Reutov, O.A. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1967***, 2616; Karabatsos, G.J.; Fry, J.L.; Meyerson, S. *J. Am. Chem. Soc.* ***1970***, *92*, 614. See also, Lee, C.C.; Zohdi, H.F. *Can. J. Chem.* ***1983***, *61*, 2092.

[27]Brouwer, D.M.; Oelderik, J.M. *Recl. Trav. Chim. Pays-Bas* ***1968***, *87*, 721; Saunders, M.; Jaffe, M.H.; Vogel, P. *J. Am. Chem. Soc.* ***1971***, *93*, 2558; Saunders, M.; Vogel, P. *J. Am. Chem. Soc.* ***1971***, *93*, 2559, 2561; Kirmse, W.; Loosen, K.; Prolingheuer, E. *Chem. Ber.* ***1980***, *113*, 129.

of the intermediate or transition state **16** that opens up rather than the 2,3 bond, which is the one that would open if the reaction were a normal 1,2-shift of a methyl group. In this case, opening of the 1,2 bond produces a tertiary cation, while opening of the 2,3 bond would give a secondary cation. (In the reaction **17** → **15**, it is of course the 1,3 bond that opens).

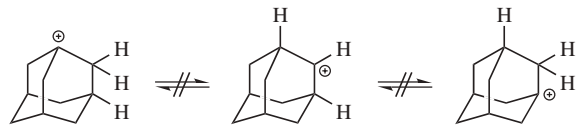
3. There has been much discussion of H as migrating group. There is no conclusive evidence that **10** in this case is or is not a true intermediate, although both positions have been argued (see p. 467).

The stereochemistry at the migration origin A is less often involved, since in most cases it does not end up as a tetrahedral atom; but when there is inversion here, there is an S_N2-type process at the beginning of the migration. This may or may not be accompanied by an S_N2 process at the migration terminus B:



In some cases, it has been found that, when H is the migrating species, the configuration at A may be *retained*.[28]

There is evidence that the configuration of the molecule may be important even where the leaving group is gone long before migration takes place. For example, the 1-adamantyl cation (**18**) does not equilibrate intramolecularly, even at temperatures up to 130°C,[29] though open-chain (e.g., **6** ⇄ **6'**) and cyclic tertiary



18 **18'**

carbocations undergo such equilibration at 0°C or below. On the basis of this and other evidence it has been concluded that for a 1,2-shift of hydrogen or methyl to proceed as smoothly as possible, the vacant *p* orbital of the carbon bearing the positive charge and the sp^3 orbital carrying the migrating group must be coplanar,[29] which is not possible for **18**.

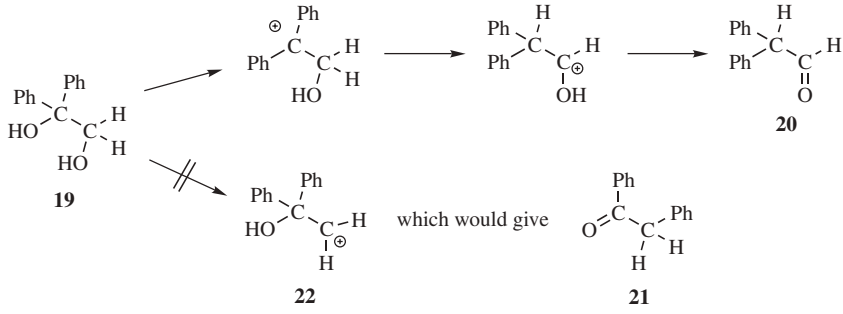
[28]Winstein, S.; Holness, N.J. *J. Am. Chem. Soc.* ***1955***, *77*, 5562; Cram, D.J.; Tadanier, J. *J. Am. Chem. Soc.* ***1959***, *81*, 2737; Bundel', Yu.G.; Pankratova, K.G.; Gordin, M.B.; Reutov, O.A. *Doklad. Chem.* ***1971***, *199*, 700; Kirmse, W.; Ratajczak, H.; Rauleder, G. *Chem. Ber.* ***1977***, *110*, 2290.

[29]Brouwer, D.M.; Hogeveen, H. *Recl. Trav. Chim. Pays-Bas* ***1970***, *89*, 211; Majerski, Z.; Schleyer, P.v.R.; Wolf, A.P. *J. Am. Chem. Soc.* ***1970***, *92*, 5731.

Migratory Aptitudes[30]

In many reactions, there is no question about which group migrates. For example, in the Hofmann, Curtius, and similar reactions there is only one possible migrating group in each molecule, and one can measure migratory aptitudes only by comparing the relative rearrangement rates of different compounds. In other instances, there are two or more potential migrating groups, but which migrates is settled by the geometry of the molecule. The Beckmann rearrangement (**18-17**) provides an example. As we have seen, only the group trans to the OH migrates. In compounds whose geometry is not restricted in this manner, there still may be eclipsing effects (see p. 1502), so that the choice of migrating group is largely determined by which group is in the right place in the most stable conformation of the molecule.[31] However, in some reactions, especially the Wagner–Meerwein (**18-1**) and the pinacol (**18-2**) rearrangements, the molecule may contain several groups that, geometrically at least, have approximately equal chances of migrating, and these reactions have often been used for the direct study of relative migratory aptitudes. In the pinacol rearrangement, there is the additional question of which OH group leaves and which does not, since a group can migrate only if the OH group on *the other* carbon is lost.

We deal with the second question first. To study this question, the best type of substrate to use is one of the form $\begin{matrix} R_2C & -CR'_2 \\ | & \quad | \\ OH & \quad OH \end{matrix}$, since the only thing that determines migratory aptitude is which OH group comes off. Once the OH group is gone, the migrating group is determined. As might be expected, the OH that leaves is the one whose loss gives rise to the more stable carbocation. Thus 1,1-diphenylethanediol (**19**) gives diphenylacetaldehyde (**20**), not phenylacetophenone (**21**). Obviously, it does not matter in this case whether phenyl has a greater



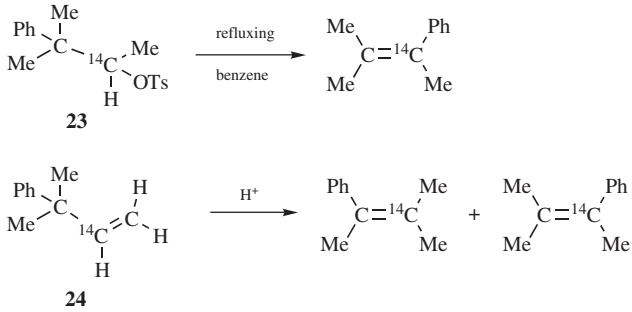
inherent migratory aptitude than hydrogen or not. Only the hydrogen can migrate because **22** is not formed. As we know, carbocation stability is enhanced by

[30]For discussions, see Koptyug, V.A.; Shubin, V.G. *J. Org. Chem. USSR* ***1980***, *16*, 1685; Wheland, G.W. *Advanced Organic Chemistry*, 3rd ed., Wiley, NY, ***1960***, pp. 573–597.

[31]For a discussion, see Cram, D.J., in Newman, M.S. *Steric Effects in Organic Chemistry*, Wiley, NY, ***1956***, pp. 270–276. For an interesting example, see Nickon, A.; Weglein, R.C. *J. Am. Chem. Soc.* ***1975***, *97*, 1271.

groups in the order aryl > alkyl > hydrogen, and this normally determines which side loses the OH group. However, exceptions are known, and which group is lost may depend on the reaction conditions (e.g., see the reaction of **53**, p. 1586).

In order to answer the question about inherent migratory aptitudes, the obvious type of substrate to use (in the pinacol rearrangement) is $R'RC(OH)-CRR'(OH)$, since the same carbocation is formed no matter which OH leaves, and it would seem that a direct comparison of the migratory tendencies of R and R′ is possible. On closer inspection, however, we can see that several factors are operating. Apart from the question of possible conformational effects, already mentioned, there is also the fact that whether the group R or R′ migrates is determined not only by the relative inherent migrating abilities of R and R′, but also by whether the group that does *not* migrate is better at stabilizing the positive charge that will now be found at the migration origin.[32] Thus, migration of R gives rise to the cation $R'C^+(OH)CR_2R'_2$, while migration of R' gives the cation $R^+C(OH)CRR'_2$, and these cations have different stabilities. It is possible that in a given case R might be found to migrate less than R′, not because it actually has a lower inherent migrating tendency, but because it is much better at stabilizing the positive charge. In addition to this factor,



migrating ability of a group is also related to its capacity to render anchimeric assistance to the departure of the nucleofuge. An example of this effect is the finding that in the decomposition of tosylate **23** only the phenyl group migrates, while in acid treatment of the corresponding alkene **24**, there is competitive migration of both methyl and phenyl (in these reactions ^{14}C labeling is necessary to determine which group has migrated).[33] Both **23** and **24** give the same carbocation; the differing results must be caused by the fact that in **23** the phenyl group can assist the leaving group, while no such process is possible for **24**. This example clearly illustrates the difference between migration to a relatively

[32]For example, see McCall, M.J.; Townsend, J.M.; Bonner, W.A. *J. Am. Chem. Soc.* ***1975***, *97*, 2743; Brownbridge, P.; Hodgson, P.K.G.; Shepherd, R.; Warren, S. *J. Chem. Soc. Perkin Trans. 1* ***1976***, 2024.
[33]Grimaud, J.; Laurent, A. *Bull. Soc. Chim. Fr.* ***1967***, 3599.

free terminus and one that proceeds with the migrating group lending anchimeric assistance.[34]

It is not surprising therefore that clear-cut answers as to relative migrating tendencies are not available. More often than not migratory aptitudes are in the order aryl > alkyl, but exceptions are known, and the position of hydrogen in this series is often unpredictable. In some cases, migration of hydrogen is preferred to aryl migration; in other cases, migration of alkyl is preferred to that of hydrogen. Mixtures are often found and the isomer that predominates often depends on conditions. For example, the comparison between methyl and ethyl has been made many times in various systems, and in some cases methyl migration and in others ethyl migration has been found to predominate.[35] However, it can be said that among aryl migrating groups, electron-donating substituents in the para and meta positions increase the migratory aptitudes, while the same substituents in the ortho positions decrease them. Electron-withdrawing groups decrease migrating ability in all positions. The following are a few of the relative migratory aptitudes determined for aryl groups by Bachmann and Ferguson:[36] *p*-anisyl, 500; *p*-tolyl, 15.7; *m*-tolyl, 1.95; phenyl, 1.00; *p*-chlorophenyl, 0.7; *o*-anisyl, 0.3. For the *o*-anisyl group, the poor migrating ability probably has a steric cause, while for the others there is a fair correlation with activation or deactivation of electrophilic aromatic substitution, which is what the process is with respect to the benzene ring. It has been reported that at least in certain systems acyl groups have a greater migratory aptitude than alkyl groups.[37]

Memory Effects[38]

Solvolysis of the endo bicyclic compound **25** (X = ONs, p. 497, or Br) gave mostly the bicyclic allylic alcohol, **28**, along with a smaller amount of the tricyclic alcohol **32**, while solvolysis of the exo isomers, **29**, gave mostly **32**, with smaller amounts of **28**.[39] Thus the two isomers gave entirely different ratios of products, although

[34]A number of studies of migratory aptitudes in the dienone-phenol rearrangement (**18-5**) are in accord with the above. For a discussion, see Fischer, A.; Henderson, G.N. *J. Chem. Soc., Chem. Commun.* ***1979***, 279, and references cited therein. See also, Palmer, J.D.; Waring, A.J. *J. Chem. Soc. Perkin Trans. 2* ***1979***, 1089; Marx, J.N.; Hahn, Y.P. *J. Org. Chem.* ***1988***, *53*, 2866.

[35]For examples, see Cram, D.J.; Knight, J.D. *J. Am. Chem. Soc.* ***1952***, *74*, 5839; Stiles, M.; Mayer, R.P. *J. Am. Chem. Soc.* ***1959***, *81*, 1497; Heidke, R.L.; Saunders, Jr., W.H. *J. Am. Chem. Soc.* ***1966***, *88*, 5816; Dubois, J.E.; Bauer, P. *J. Am. Chem. Soc.* ***1968***, *90*, 4510, 4511; Bundel', Yu. G.; Levina, I.Yu.; Reutov, O.A. *J. Org. Chem. USSR* ***1970***, *6*, 1; Pilkington, J.W.; Waring, A.J. *J. Chem. Soc. Perkin Trans. 2* ***1976***, 1349; Korchagina, D.V.; Derendyaev, B.G.; Shubin, V.G.; Koptyug, V.A. *J. Org. Chem. USSR* ***1976***, *12*, 378; Wistuba, E.; Rüchardt, C. *Tetrahedron Lett.* ***1981***, *22*, 4069; Jost, R.; Laali, K.; Sommer, J. *Nouv. J. Chim.* ***1983***, *7*, 79

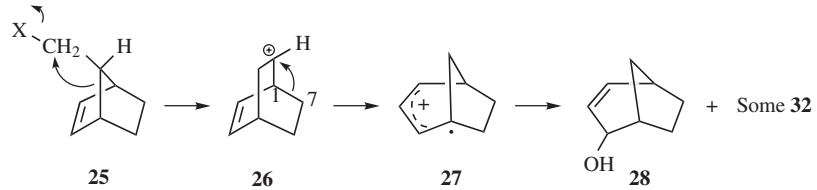
[36]Bachmann, W.E.; Ferguson, J.W. *J. Am. Chem. Soc.* ***1934***, *56*, 2081.

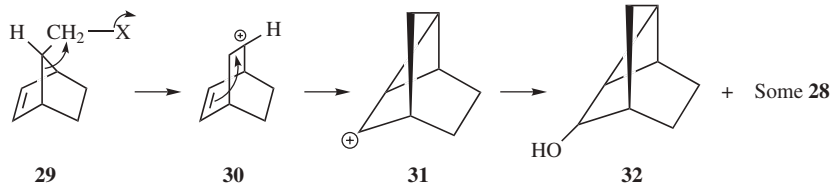
[37]Le Drian, C.; Vogel, P. *Helv. Chim. Acta* ***1987***, *70*, 1703; *Tetrahedron Lett.* ***1987***, *28*, 1523.

[38]For a review, see Berson, J.A. *Angew. Chem. Int. Ed.* ***1968***, *7*, 779.

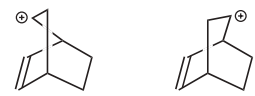
[39]Berson, J.A.; Poonian, M.S.; Libbey, W.J. *J. Am. Chem. Soc.* ***1969***, *91*, 5567; Berson, J.A.; Donald, D.S.; Libbey, W.J. *J. Am. Chem. Soc.* ***1969***, *91*, 5580; Berson, J.A.; Wege, D.; Clarke, G.M.; Bergman, R.G. *J. Am. Chem. Soc.* ***1969***, *91*, 5594, 5601.

the carbocation initially formed (**26** or **30**) seems to be the same for each. In the case of **26**, a second rearrangement (a shift of the 1,7 bond) follows, while with **30** what follows is an intramolecular addition of the positive carbon to the double bond.





It seems as if **26** and **30** ''remember'' how they were formed before they go on to give the second step. Such effects are called *memory effects* and other such cases are known.[40] The causes of these effects are not well understood, though there has been much discussion. One possible cause is differential solvation of the apparently identical ions **26** and **30**. Other possibilities are (*1*) that the ions have geometrical structures that are twisted in opposite senses (e.g., a twisted **30** might have its positive carbon closer to the double



Twisted **30** Twisted **26**

bond than a twisted **26**); (*2*) that ion pairing is responsible;[41] and (*3*) that nonclassical carbocations are involved.[42] One possibility that has been ruled out is that the steps **25** → **26** → **27** and **29** → **30** → **31** are concerted, so that **26** and **30** never exist at all. This possibility has been excluded by several kinds of evidence, including the fact that **25** gives not only **28**, but also some **32**; and **29** gives some **28**

[40]For examples of memory effects in other systems, see Berson, J.A.; Luibrand, R.T.; Kundu, N.G.; Morris, D.G. *J. Am. Chem. Soc.* ***1971***, *93*, 3075; Collins, C.J. *Acc. Chem. Res.* ***1971***, *4*, 315; Collins, J.A.; Glover, I.T.; Eckart, M.D.; Raaen, V.F.; Benjamin, B.M.; Benjaminov, B.S. *J. Am. Chem. Soc.* ***1972***, *94*, 899; Svensson, T. *Chem. Scr.,* ***1974***, *6*, 22.

[41]See Collins, C.J. *Chem. Soc. Rev.* ***1975***, *4*, 251.

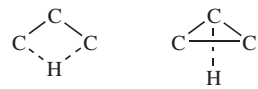
[42]See, for example, Seybold, G.; Vogel, P.; Saunders, M.; Wiberg, K.B. *J. Am. Chem. Soc.* ***1973***, *95*, 2045; Kirmse, W.; Günther, B. *J. Am. Chem. Soc.* ***1978***, *100*, 3619.

along with **32**. This means that some of the **26** and **30** ions interconvert, a phenomenon known as *leakage*.

Longer Nucleophilic Rearrangements

The question as to whether a group can migrate with its electron pair from A to C in W–A–B–C or over longer distances has been much debated. Although claims have been made that alkyl groups can migrate in this way, the evidence is that such migration is extremely rare, if it occurs at all. One experiment that demonstrated this was the generation of the 3,3-dimethyl-1-butyl cation $Me_3CCH_2CH_2^+$. If 1,3-methyl migrations are possible, this cation would appear to be a favorable substrate, since such a migration would convert a primary cation into the tertiary 2-methyl-2-pentyl cation $Me_2CCH_2CH_2CH_3$, while the only possible 1,2 migration (of hydride) would give only a secondary cation. However, no products arising from the 2-methyl-2-pentyl cation were found, the only rearranged products being those formed by the 1,2 hydride migration.[43] 1,3 Migration of bromine has been reported.[44]

However, most of the debate over the possibility of 1,3 migrations has concerned not methyl or bromine, but 1,3 hydride shifts.[45] There is no doubt that *apparent* 1,3 hydride shifts take place (many instances have been found), but the question is whether they are truly direct hydride shifts or whether they occur by another



A **B**

mechanism. There are at least two ways in which indirect 1,3-hydride shifts can take place: (*1*) by successive 1,2-shifts or (*2*) through the intervention of protonated cyclopropanes (see p. 1565). A direct 1,3-shift would have the transition state **A**, while the transition state for a 1,3-shift involving a protonated cyclopropane intermediate would resemble **B**. The evidence is that most reported 1,3 hydride shifts are actually the result of successive 1,2 migrations,[46] but that in some cases small amounts of products cannot be accounted for in this way. For example, the reaction of 2-methyl-1-butanol with KOH and bromoform gave a mixture of alkenes, nearly all of which could have arisen from simple

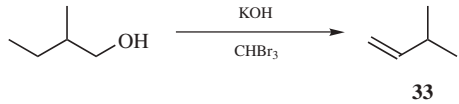
[43]Skell, P.S.; Reichenbacher, P.H. *J. Am. Chem. Soc.* ***1968***, *90*, 2309.

[44]Reineke, C.E.; McCarthy, Jr., J.R. *J. Am. Chem. Soc.* ***1970***, *92*, 6376; Smolina, T.A.; Gopius, E.D.; Gruzdneva, V.N.; Reutov, O.A. *Doklad. Chem.* ***1973***, *209*, 280.

[45]For a review, see Fry, J.L.; Karabatsos, G.J., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1970***, p. 527.

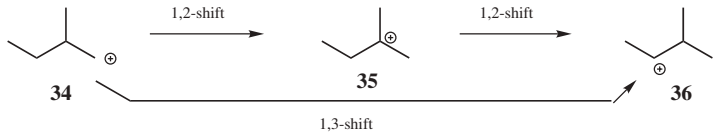
[46]For example, see Bundel', Yu.G.; Levina, I.Yu.; Krzhizhevskii, A.M.; Reutov, O.A. *Doklad. Chem.* ***1968***, *181*, 583; Fărcaşiu, D.; Kascheres, C.; Schwartz, L.H. *J. Am. Chem. Soc.* ***1972***, *94*, 180; Kirmse, W.; Knist, J.; Ratajczak, H. *Chem. Ber.* ***1976***, *109*, 2296.

elimination or 1,2-shifts of hydride or alkyl. However, 1.2% of the product was **33**:[47]

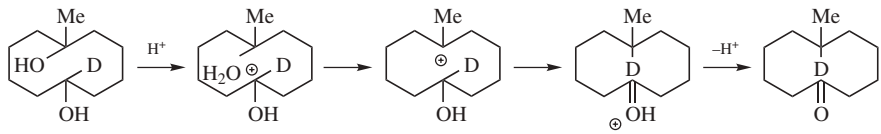


33

Hypothetically, **33** could have arisen from a 1,3-shift (direct or through a protonated cyclopropane) or from two successive 1,2-shifts:



However, the same reaction applied to 2-methyl-2-butanol gave no **33**, which demonstrated that **36** was not formed from **35**. The conclusion made was that **36** was formed directly from **34**. This experiment does not answer the question as to whether **36** was formed by a direct shift or through a protonated cyclopropane, but from other evidence[48] it appears that 1,3 hydride shifts that do not result from successive 1,2 migrations usually take place through protonated cyclopropane intermediates (which, as we saw on p. 1565, account for only a small percentage of the product in any case). However, there is evidence that direct 1,3 hydride shifts by way of **A** may take place in super acid solutions.[49] Although direct nucleophilic rearrangements over distances >1,2 are rare (or perhaps nonexistent) when the migrating atom or group must move along a chain, this is not so for a shift across a ring of 8–11 members. Many such transannular rearrangements are known.[50] Several examples are given on p. 223. This is the mechanism of one of these:[51]



[47]Skell, P.S.; Maxwell, R.J. *J. Am. Chem. Soc.* ***1962***, *84*, 3963. See also, Skell, P.S.; Starer, I. *J. Am. Chem. Soc.* ***1962***, *84*, 3962.

[48]For example, see Brouwer, D.M.; van Doorn, J.A. *Recl. Trav. Chim. Pays-Bas* ***1969***, *8*, 573; Dupuy, W.E.; Goldsmith, E.A.; Hudson, H.R. *J. Chem. Soc. Perkin Trans. 2* ***1973***, 74; Hudson, H.R.; Koplick, A.J.; Poulton, D.J. *Tetrahedron Lett.* ***1975***, 1449; Fry, J.L.; Karabatsos, G.J., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1970***, p. 527.

[49]Saunders, M.; Stofko Jr., J.J. *J. Am. Chem. Soc.* ***1973***, *95*, 252.

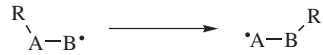
[50]For reviews, see Cope, A.C.; Martin, M.M.; McKervey, M.A. *Q. Rev. Chem. Soc.* ***1966***, *20*, 119. For many references, see Blomquist, A.T.; Buck, C.J. *J. Am. Chem. Soc.* ***1951***, *81*, 672.

[51]Prelog, V.; Küng, W. *Helv. Chim. Acta* ***1956***, *39*, 1394.

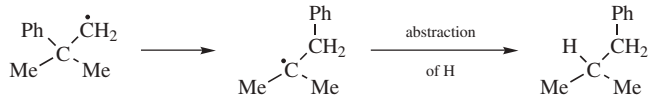
It is noteworthy that the *methyl* group does not migrate in this system. It is generally true that alkyl groups do not undergo transannular migration.[52] In most cases, it is hydride that undergoes this type of migration, though a small amount of phenyl migration has also been shown.[53]

Free-Radical Rearrangements[54]

1,2-Free-radical rearrangements are much less common than the nucleophilic type previously considered, for the reasons mentioned on p. 1559. Where they do occur, the general pattern is similar. There must first be generation of a free radical, and then the actual migration in which the migrating group moves with one electron:



Finally, the new free radical must stabilize itself by a further reaction. The order of radical stability leads us to predict that here too, as with carbocation rearrangements, any migrations should be in the order primary → secondary → tertiary, and that the logical place to look for them should be in neopentyl and neophyl systems. The most common way of generating free radicals for the purpose of detection of rearrangements is by decarbonylation of aldehydes (**14-32**). In this manner, it was found that neophyl radicals *do* undergo rearrangement. Thus, $PhCMe_2CH_2CHO$ treated with di-*tert*-butyl peroxide gave about equal amounts of the normal product $PhCMe_2CH_3$ and the product arising from migration of phenyl:[55]



[52]For an apparent exception, see Fărcaşiu, D.; Seppo, E.; Kizirian, M.; Ledlie, D.B.; Sevin, A. *J. Am. Chem. Soc.* ***1989***, *111*, 8466.

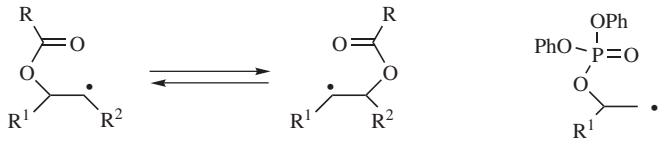
[53]Cope, A.C.; Burton, P.E.; Caspar, M.L. *J. Am. Chem. Soc.* ***1962***, *84*, 4855.

[54]For reviews, see Beckwith, A.L.J.; Ingold, K.U. in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 1, Academic Press, NY, ***1980***, pp. 161–310; Wilt, J.W., in Kochi, J.K. *Free Radicals*, Vol. 1, Wiley, NY, ***1973***, pp. 333–501; Stepukhovich, A.D.; Babayan, V.I. *Russ. Chem. Rev.* ***1972***, *41*, 750; Nonhebel, D.C.; Walton, J.C. *Free-Radical Chemistry*, Cambridge University Press, London, ***1974***, pp. 498–552; Huyser, E.S. *Free-Radical Chain Reactions*, Wiley, NY, ***1970***, pp. 235–255; Freidlina, R.Kh. *Adv. Free-Radical Chem.* ***1965***, *1*, 211–278; Pryor, W.A. *Free Radicals*, McGraw-Hill, NY, ***1966***, pp. 266–284.

[55]Winstein, S.; Seubold, Jr., F.H. *J. Am. Chem. Soc.* ***1947***, *69*, 2916; Seubold, Jr., F.H. *J. Am. Chem. Soc.* ***1953***, *75*, 2532. For the observation of this rearrangement by esr, see Hamilton, Jr., E.J.; Fischer, H. *Helv. Chim. Acta* ***1973***, *56*, 795.

Many other cases of free-radical migration of aryl groups have been found.[56] Intramolecular radical rearrangements are known.[57] The C-4 radicals of α- and β-thujone undergo two distinct rearrangement reactions, and it has been proposed that these could serve as simultaneous, but independent radical clocks.[58]

A 1,2-shift has been observed in radicals bearing an OCOR group at the β-carbon where the oxygen group migrates as shown in the interconversion of **37** and **38**. This has been proven by ^{18}O isotopic labeling experiments[59] and other mechanistic explorations.[60] A similar rearrangement was observed with phosphatoxy alkyl radicals, such as **39**.[61] A 1,2-shift of hydrogen atoms has been observed in aryl radicals.[62]



37 **38** **39**

A C → N 1,2-aryl rearrangement was observed when alkyl azides were treated with *n*-Bu_3SnH, proceeding via an C–N•–$SnBu_3$ species to give an imine.[63]

It is noteworthy that the extent of migration is much less than with corresponding carbocations: Thus in the example given, there was only ∼50% migration, whereas the carbocation would have given much more. Also noteworthy is that there was no migration of the methyl group. In general, it may be said that free-radical migration of alkyl groups does not occur at ordinary temperatures. Many attempts have been made to detect such migration on the traditional neopentyl and bornyl types of substrates. However, alkyl migration is not observed, even in substrates where the corresponding carbocations undergo facile rearrangement.[64] Another type of migration that is very common for carbocations, but not observed

[56]For example, see Curtin, D.Y.; Hurwitz, M.J. *J. Am. Chem. Soc.* ***1952***, *74*, 5381; Wilt, J.K.; Philip, H. *J. Org. Chem.* ***1959***, *24*, 441; ***1960***, *25*, 891; Pines, H.; Goetschel, C.T. *J. Am. Chem. Soc.* ***1964***, *87*, 4207; Goerner Jr., R.N.; Cote, P.N.; Vittimberga, B.M. *J. Org. Chem.* ***1977***, *42*, 19; Collins, C.J.; Roark, W.H.; Raaen, V.F.; Benjamin, B.M. *J. Am. Chem. Soc.* ***1979***, *101*, 1877; Walter, D.W.; McBride, J.M. *J. Am. Chem. Soc.* ***1981***, *103*, 7069, 7074. For a review, see Studer, A.; Bossart, M. *Tetrahedron* ***2001***, *57*, 9649.

[57]Prévost, N.; Shipman, M. *Org. Lett.* ***2001***, *3*, 2383.

[58]He, X.; Ortiz de Montellano, P.R. *J. Org. Chem.* ***2004***, *69*, 5684.

[59]Crich, D.; Filzen, G.F. *J. Org. Chem.* ***1995***, *60*, 4834.

[60]Beckwith, A.L.J.; Duggan, P.J. *J. Chem. Soc. Perkin Trans. 2* ***1992***, 1777; ***1993***, 1673.

[61]Crich, D.; Yao, Q. *Tetrahedron Lett.* ***1993***, *34*, 5677. See Ganapathy, S.; Cambron R.T.; Dockery, K.P.; Wu, Y.-W.; Harris, J.M.; Bentrude, W.G. *Tetrahedron Lett.* ***1993***, *34*, 5987 for a related triplet sensitized rearrangement of allylic phosphites and phosphonates.

[62]Brooks, M.A.; Scott, L.T. *J. Am. Chem. Soc.* ***1999***, *121*, 5444.

[63]Kim, S.; Do, J.Y. *J. Chem. Soc., Chem. Commun.* ***1995***, 1607.

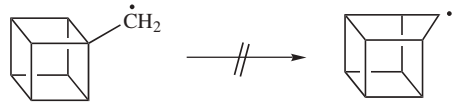
[64]For a summary of unsuccessful attempts, see Slaugh, L.H.; Magoon, E.F.; Guinn, V.P. *J. Org. Chem.* ***1963***, *28*, 2643.

for free radicals, is 1,2 migration of hydrogen. We confine ourselves to a few examples of the lack of migration of alkyl groups and hydrogen:

1. 3,3-Dimethylpentanal ($EtCMe_2CH_2CHO$) gave no rearranged products on decarbonylation.[65]
2. Addition of RSH to norbornene gave only *exo*-norbornyl sulfides, though **40** is an intermediate, and the corresponding carbocation cannot be formed without rearrangement.[66]

40

3. The cubylcarbinyl radical did not rearrange to the 1-homocubyl radical, though doing so would result in a considerable decrease in strain.[67]



Cubylcarbinyl radical — 1-Homocubyl radical

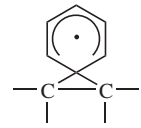
4. It was shown[68] that no rearrangement of isobutyl radical to *tert*-butyl radical (which would involve the formation of a more stable radical by a hydrogen shift) took place during the chlorination of isobutane.

However, 1,2 migration of alkyl groups has been shown to occur in certain *diradicals*.[69] For example, the following rearrangement has been established by tritium labeling.[70]

In this case, the fact that migration of the methyl group leads directly to a compound in which all electrons are paired undoubtedly contributes to the driving force of the reaction.

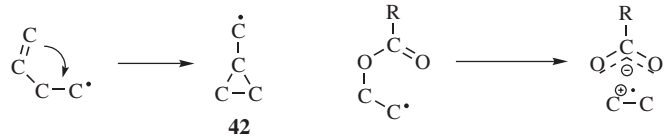
[65]Seubold, Jr., F.H. *J. Am. Chem. Soc.* ***1954***, *76*, 3732.
[66]Cristol, S.J.; Brindell, G.D. *J. Am. Chem. Soc.* ***1954***, *76*, 5699.
[67]Eaton, P.E.; Yip, Y. *J. Am. Chem. Soc.* ***1991***, *113*, 7692.
[68]Brown, H.C.; Russel, G.A. *J. Am. Chem. Soc.* ***1952***, *74*, 3995. See also, Desai, V.R.; Nechvatal, A.; Tedder, J.M. *J. Chem. Soc. B* ***1970***, 386.
[69]For a review, see Freidlina, R.Kh.; Terent'ev, A.B. *Russ. Chem. Rev.* ***1974***, *43*, 129.
[70]McKnight, C.; Rowland, F.S. *J. Am. Chem. Soc.* ***1966***, *88*, 3179. For other examples, see Greene, F.D.; Adam, W.; Knudsen Jr., G.A. *J. Org. Chem.* ***1966***, *31*, 2087; Gajewski, J.J.; Burka, L.T. *J. Am. Chem. Soc.* ***1972***, *94*, 8857, 8860, 8865; Adam, W.; Aponte, G.S. *J. Am. Chem. Soc.* ***1971***, *93*, 4300.

The fact that aryl groups migrate, but alkyl groups and hydrogen generally do not, leads to the proposition that **41**, in which the odd electron is not found in the three-membered ring, may be an intermediate. There has been much controversy on this point, but the bulk of the evidence indicates that **41** is a transition state, not an intermediate.[71] Among the evidence is the failure to observe **41** either by ESR[72] or CIDNP.[73] Both of these techniques can detect free radicals with extremely short lifetimes (pp. 266–268).[74]



41

Besides aryl, vinylic[75] and acetoxy groups[76] also migrate. Vinylic groups migrate by way of a cyclopropylcarbinyl radical intermediate (**42**),[77] while the migration of acetoxy groups may involve the charge-separated structure shown.[78] Thermal isomerization of 1-(3-butenyl)cyclopropane at 415°C leads to bicyclo[2.2.1]heptane.[79] Migration has been observed for chloro (and to a much lesser extent



42

bromo) groups. For example, in the reaction of $Cl_3CCH{=}CH_2$ with bromine under the influence of peroxides, the products were 47% $Cl_3CCHBrCH_2Br$

[71]For molecular-orbital calcualtions indicating that **41** is an intermediate, see Yamabe, S. *Chem. Lett.* ***1989***, 1523.

[72]Edge, D.J.; Kochi, J.K. *J. Am. Chem. Soc.* ***1972***, *94*, 7695.

[73]Shevlin, P.B.; Hansen, H.J. *J. Org. Chem.* ***1977***, *42*, 3011; Olah, G.A.; Krishnamurthy, V.V.; Singh, B.P.; Iyer, P.S. *J. Org. Chem.* ***1983***, *48*, 955. **37** has been detected as an intemediate in a different reaction: Effio, A.; Griller, D.; Ingold, K.U.; Scaiano, J.C.; Sheng, S.J. *J. Am. Chem. Soc.* ***1980***, *102*, 6063; Leardini, R.; Nanni, D.; Pedulli, G.F.; Tundo, A.; Zanardi, G.; Foresti, E.; Palmieri, P. *J. Am. Chem. Soc.* ***1989***, *111*, 7723.

[74]For other evidence, see Martin, M.M. *J. Am. Chem. Soc.* ***1962***, *84*, 1986; Rüchardt, C.; Hecht, R. *Chem. Ber.* ***1965***, *98*, 2460, 2471; Rüchardt, C.; Trautwein, H. *Chem. Ber.* ***1965***, *98*, 2478.

[75]For example, see Slaugh, L.H. *J. Am. Chem. Soc.* ***1965***, *87*, 1522; Newcomb, M.; Glenn, A.G.; Williams, W.G. *J. Org. Chem.* ***1989***, *54*, 2675.

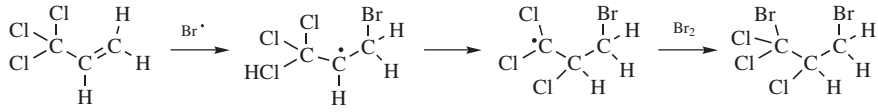
[76]Surzur, J.; Teissier, P. *Bull. Soc. Chim. Fr.* ***1970***, 3060; Tanner, D.D.; Law, F.C.P. *J. Am. Chem. Soc.* ***1969***, *91*, 7535; Julia, S.; Lorne, R. *C. R. Acad. Sci. Ser. C* ***1971***, *273*, 174; Lewis, S.N.; Miller, J.J.; Winstein, S. *J. Org. Chem.* ***1972***, *37*, 1478.

[77]For evidence for this species, see Montgomery, L.K.; Matt, J.W.; Webster, J.R. *J. Am. Chem. Soc.* ***1967***, *89*, 923; Montgomery, L.K.; Matt, J.W. *J. Am. Chem. Soc.* ***1967***, *89*, 934, 6556; Giese, B.; Heinrich, N.; Horler, H.; Koch, W.; Schwarz, H. *Chem. Ber.* ***1986***, *119*, 3528.

[78]Beckwith, A.L.J.; Thomas, C.B. *J. Chem. Soc. Perkin Trans. 2* ***1973***, 861; Barclay, L.R.C.; Lusztyk, J.; Ingold, K.U. *J. Am. Chem. Soc.* ***1984***, *106*, 1793.

[79]Baldwin, J.E.; Burrell, R.C.; Shukla, R. *Org. Lett.* ***2002***, *4*, 3305.

(the normal addition product) and 53% $BrCCl_2CHClCH_2Br$, which arose by rearrangement:



In this particular case, the driving force for the rearrangement is the particular stability of dichloroalkyl free radicals. Nesmeyanov, Freidlina, and co-workers have extensively studied reactions of this sort.[80] It has been shown that the 1,2 migration of Cl readily occurs if the migration origin is tertiary and the migration terminus primary.[81] Migration of Cl and Br could take place by a transition state in which the odd electron is accommodated in a vacant *d* orbital of the halogen.

Migratory aptitudes have been measured for the phenyl and vinyl groups, and for three other groups, using the system $RCMe_2CH_2\bullet \rightarrow Me_2\dot{C}\,CH_2R$. These were found to be in the order $R = H_2C{=}CH_2 > Me_3CC{=}O > Ph > Me_3C{\equiv}C > CN$.[82]

In summary then, 1,2 free-radical migrations are much less prevalent than the analogous carbocation processes, and are important only for aryl, vinylic, acetoxy, and halogen migrating groups. The direction of migration is normally toward the more stable radical, but ''wrong-way'' rearrangements are also known.[83]

Despite the fact that hydrogen atoms do not migrate 1,2, longer free-radical migrations of hydrogen are known.[84] The most common are 1,5-shifts, but 1,6 and longer shifts have also been found. The possibility of 1,3 hydrogen shifts has been much investigated, but it is not certain if any actually occur. If they do they are rare, presumably because the most favorable geometry for C•••H•••C in the transition state is linear and this geometry cannot be achieved in a 1,3-shift. 1,4-Shifts are definitely known, but are still not very common. These long shifts are best regarded as internal abstractions of hydrogen (for reactions involving them, see **14-6** and **18-40**):

Transannular shifts of hydrogen atoms have also been observed.[85]

[80]For reviews, see Freidlina, R.Kh.; Terent'ev, A.B. *Russ. Chem. Rev.* ***1979***, *48*, 828; Freidlina, R.Kh. *Adv. Free-Radical Chem.* ***1965***, *1*, 211, 231–249.

[81]See, for example, Skell, P.S.; Pavlis, R.R.; Lewis, D.C.; Shea, K.J. *J. Am. Chem. Soc.* ***1973***, *95*, 6735; Chen, K.S.; Tang, D.Y.H.; Montgomery, L.K.; Kochi, J.K. *J. Am. Chem. Soc.* ***1974***, *96*, 2201.

[82]Lindsay, D.A.; Lusztyk, J.L.; Ingold, K.U. *J. Am. Chem. Soc.* ***1984***, *106*, 7087.

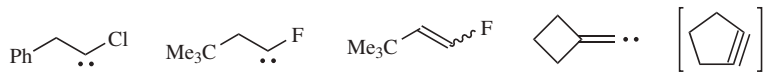
[83]Slaugh, L.H.; Raley, J.H. *J. Am. Chem. Soc.* ***1960***, *82*, 1259; Bonner, W.A.; Mango, F.D. *J. Org. Chem.* ***1964***, *29*, 29; Dannenberg, J.J.; Dill, K. *Tetrahedron Lett.* ***1972***, 1571.

[84]For a discussion, see Freidlina, R.Kh.; Terent'ev, A.B. *Acc. Chem. Res.* ***1977***, *10*, 9.

[85]Heusler, K.; Kalvoda, J. *Tetrahedron Lett.* ***1963***, 1001; Cope, A.C.; Bly, R.S.; Martin, M.M.; Petterson, R.C. *J. Am. Chem. Soc.* ***1965***, *87*, 3111; Fisch, M.; Ourisson, G. *Chem. Commun.* ***1965***, 407; Traynham, J.G.; Couvillon, T.M. *J. Am. Chem. Soc.* ***1967***, *89*, 3205.

Carbene Rearrangements[86]

Carbenes can rearrange to alkenes in many cases.[87] A 1,2-hydrogen shift leads to an alkene, and this is often competitive with insertion reactions.[88] Benzylchlorocarbene (**43**) rearranges via a 1,2 hydrogen shift to give the alkene.[89] Similarly, carbene **44** rearranges to alkene **45**, and replacement of H on the α-carbon with D showed a deuterium isotope effect of ~5.[90] Vinylidene carbene ($H_2C{=}C{:}$) rearranges to acetylene.[91] Rearrangement of alkylidene carbene **46** has been calculated to give the highly unstable cyclopentyne (**47**), which cannot be isolated, but can give a [2 + 2]-cycloaddition product when generated in the presence of a simple alkene.[92] The spiro carbenes undergo rearrangement reactions.[93]



43 **44** **45** **46** **47**

Electrophilic Rearrangements[94]

Rearrangements in which a group migrates without its electrons are much rarer than the two kinds previously considered, but the general principles are the same. A carbanion (or other negative ion) is created first, and the actual rearrangement step involves migration of a group without its electrons:

The product of the rearrangement may be stable or may react further, depending on its nature (see also, pp. 1585). An *ab initio* study predicts that a [1,2]-alkyl shift in alkyne anions should be facile.[95]

[86]For a review of thermally induced cyclopropane–carbene rearrangements, see Baird, M.S. *Chem. Rev.* ***2003***, *103*, 1271.
[87]de Meijere, A.; Kozhushkov, S.I.; Faber, D.; Bagutskii, V.; Boese, R.; Haumann, T.; Walsh, R. *Eur. J. Org. Chem.* ***2001***, 3607.
[88]Nickon, A.; Stern, A.G.; Ilao, M.C. *Tetrahedron Lett.* ***1993***, *34*, 1391.
[89]Merrer, D.C.; Moss, R.A.; Liu, M.T.H.; Banks, J.-T.; Ingold, K.U. *J. Org. Chem.* ***1998***, *63*, 3010.
[90]Moss, R.A.; Ho, C.-J.; Liu, W.; Sierakowski, C. *Tetrahedron Lett.* ***1992***, *33*, 4287.
[91]Hayes, R.L.; Fattal, E.; Govind, N.; Carter, E.A. *J. Am. Chem. Soc.* ***2001***, *123*, 641.
[92]Gilbert, J.C.; Kirschner, S. *Tetrahedron Lett.* ***1993***, *34*, 599, 603.
[93]Moss, R.A.; Zheng, F.; Krough-Jespersen, K. *Org. Lett.* ***2001***, *3*, 1439.
[94]For reviews, see Hunter, D.H.; Stothers, J.B.; Warnhoff, E.W. in de Mayo, P. *Rearrangments in Ground and Excited States*, Vol. 1, Academic Press, NY, ***1980***, pp. 391–470; Grovenstein, Jr., E. *Angew. Chem. Int. Ed.* ***1978***, *17*, 313; *Adv. Organomet. Chem.* ***1977***, *16*, 167; Jensen, F.R.; Rickborn, B. *Electrophilic Substitution of Organomercurials*, McGraw-Hill, NY, ***1968***, pp. 21–30; Cram, D.J. *Fundamentals of Carbanion Chemistry*, Academic Press, NY, ***1965***, pp. 223–243.
[95]Borosky, G.L. *J. Org. Chem.* ***1998***, *63*, 3337.

REACTIONS

The reactions in this chapter are classified into three main groups and 1,2-shifts are considered first. Within this group, reactions are classified according to (*1*) the identity of the substrate atoms A and B and (*2*) the nature of the migrating group W. In the second group are the cyclic rearrangements. The third group consists of rearrangements that cannot be fitted into either of the first two categories.

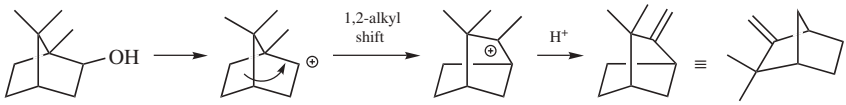
Reactions in which the migration terminus is on an aromatic ring have been treated under aromatic substitution. These are **11-27**–**11-32**, **11-36**, **13-30**–**13-32**, and, partially, **11-33**, **11-38**, and **11-39**. Double-bond shifts have also been treated in other chapters, though they may be considered rearrangements (p. $$$, p. $$$, and **12-2**). Other reactions that may be regarded as rearrangements are the Pummerer (**19-83**) and Willgerodt (**19-84**) reactions.

1,2-REARRANGEMENTS

A. Carbon-to-Carbon Migrations of R, H, and Ar

18-1 Wagner–Meerwein and Related Reactions

1/Hydro,1/hydroxy-(2/ → 1/alkyl)-*migro*-elimination, and so on



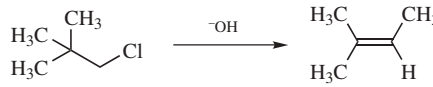
isoborneol **48** **49** camphene

Wagner–Meerwein rearrangements were first discovered in the bicyclic terpenes, and most of the early development of this reaction was with these compounds.[96] An example is the conversion of isoborneol to camphene. It fundamentally involves a 1,2 alkyl shift of an intermediate carbocation, such as **48** → **49**. When alcohols are treated with acids, simple substitution (e.g., **10-48**) or elimination (**17-1**) usually accounts for most or all of the products. But in many cases, especially where two or three alkyl or aryl groups are on the β carbon, some or all of the product is rearranged. These rearrangements have been called *Wagner–Meerwein rearrangements*, although this term is nowadays reserved for relatively specific transformations, such as isoborneol to camphene and related reactions. As pointed out previously, the carbocation that is a direct product of the rearrangement must stabilize itself, and most often it does this by the loss

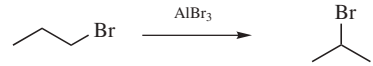
[96]For a review of rearrangements in bicyclic systems, see Hogeveen, H.; van Kruchten, E.M.G.A. *Top. Curr. Chem.* ***1979***, *80*, 89. For reviews concerning caranes and pinanes see, respectively, Arbuzov, B.A.; Isaeva, Z.G. *Russ. Chem. Rev.* ***1976***, *45*, 673; Banthorpe, D.V.; Whittaker, D. *Q. Rev. Chem. Soc.* ***1966***, *20*, 373.

of a hydrogen β to it, so the rearrangement product is usually an alkene.[97] If there is a choice of protons, Zaitsev's rule (p. 1482) governs the direction, as we might expect. Sometimes a different positive group is lost instead of a proton. Less often, the new carbocation stabilizes itself by combining with a nucleophile instead of losing a proton. The nucleophile may be the water that is the original leaving group, so that the product is a rearranged alcohol, or it may be some other species present (solvent, added nucleophile, etc.). Rearrangement is usually predominant in neopentyl and neophyl types of substrates, and with these types normal nucleophilic substitution is difficult (normal elimination is of course impossible). Under S_N2 conditions, substitution is extremely slow;[98] and under S_N1 conditions, carbocations are formed that rapidly rearrange. However, free-radical substitution, unaccompanied by rearrangement, can be carried out on neopentyl systems, though, as we have seen (p. 1574), neophyl systems undergo rearrangement as well as substitution.

Example *a*

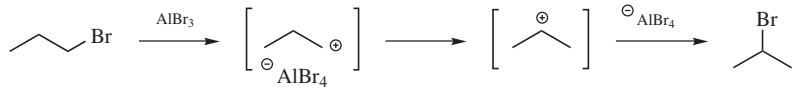


Example *b*



Examples of Wagner–Meerwein-type rearrangements are found in simpler systems, such as neopentyl chloride (example *a*) and even 1-bromopropane (example *b*). These two examples illustrate the following points:

1. Hydride ion can migrate. In example *b*, it was hydride that shifted, not bromine:



2. The leaving group does not have to be H_2O, but can be any departing species whose loss creates a carbocation, including N_2 from aliphatic diazonium ions[99] (see the section on leaving groups in nucleophilic substitution, p. 438). Also, rearrangement may follow when the carbocation is created by addition of a proton or other positive species to a double bond. Even alkanes give

[97]For a review of such rearrangements, see Kaupp, G. *Top. Curr. Chem.* ***1988***, *146*, 57.

[98]See, however, Lewis, R.G.; Gustafson, D.H.; Erman, W.F. *Tetrahedron Lett.* ***1967***, 401; Paquette, L.A.; Philips, J.C. *Tetrahedron Lett.* ***1967***, 4645; Anderson, P.H.; Stephenson, B.; Mosher, H.S. *J. Am. Chem. Soc.* ***1974***, *96*, 3171.

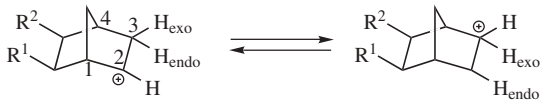
[99]For reviews of rearrangements arising from diazotization of aliphatic amines, see, in Patai, S. *The Chemistry of the Amino Group*, Wiley, NY, ***1968***, the articles by White, E.H.; Woodcock, D.J. pp. 407–497 (473–483) and by Banthorpe, D.V. pp. 585–667 (586–612).

rearrangements when heated with Lewis acids, provided some species is initially present to form a carbocation from the alkane.

3. Example *b* illustrates that the last step can be substitution instead of elimination.

4. Example *a* illustrates that the new double bond is formed in accord with Zaitsev's rule.

2-Norbornyl cations (see **48**), besides displaying the 1,2-shifts of a CH_2 group previously illustrated for the isoborneol → camphene conversion, are also prone to rapid hydride shifts from the 3 to the 2 position (known as 3,2-shifts). These 3,2-shifts usually take place from the exo side;[100] that is, the 3-exo hydrogen migrates to the 2-exo position.[101] This stereoselectivity is analogous to the behavior we have previously seen for norbornyl



systems, namely, that nucleophiles attack norbornyl cations from the exo side (p. 461) and that addition to norbornenes is also usually from the exo direction (p. 1023).

For rearrangements of alkyl carbocations, the direction of rearrangement is usually toward the most stable carbocation (or radical), which is tertiary > secondary > primary, but rearrangements in the other direction have also been found,[102] and often the product is a mixture corresponding to an equilibrium mixture of the possible carbocations. In the Wagner–Meerwein rearrangement, the rearrangement has been observed for a secondary to a secondary carbocation rearrangement, leading to some controversy. Winstein[103] described norbornyl cations in terms of the resonance structures represented by the nonclassical ion **50**.[104] This view was questioned, primarily by Brown,[105] who suggested that the facile rearrangements could be explained by a series of fast 1,3-Wagner–Meerwein shifts.[106]

[100]For example, see Kleinfelter, D.C.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1961***, *83*, 2329; Collins, C.J.; Cheema, Z.K.; Werth, R.G.; Benjamin, B.M. *J. Am. Chem. Soc.* ***1964***, *86*, 4913; Berson, J.A.; Hammons, J.H.; McRowe, A.W.; Bergman, R.G.; Remanick, A.; Houston, D. *J. Am. Chem. Soc.* ***1967***, *89*, 2590.

[101]For examples of 3,2-endo shifts, see Bushell, A.W.; Wilder, Jr., P. *J. Am. Chem. Soc.* ***1967***, *89*, 5721; Wilder, Jr., P.; Hsieh, W. *J. Org. Chem.* ***1971***, *36*, 2552.

[102]See, for example, Cooper, C.N.; Jenner, P.J.; Perry, N.B.; Russell-King, J.; Storesund, H.J.; Whiting, M.C. *J. Chem. Soc. Perkin Trans. 2* ***1982***, 605.

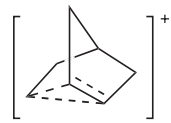
[103]Winstein, S. *Quart. Rev. Chem. Soc.* ***1969***, *23*, 141; Winstein, S.; Trifan, D.S. *J. Am. Chem. Soc.* ***1949***, *71*, 2953; Winstein, S.; Trifan, D.S. *J. Am. Chem. Soc.* ***1952***, *74*, 1154.

[104]Berson, J.A., in de Mayo, P. *Molecular Rearrangements*, Vol. 1, Academic Press, NY, ***1980***, p. 111; Sargent, G.D. *Quart. Rev. Chem. Soc.* ***1966***, *20*, 301; Olah, G.A. *Acc. Chem. Res.* ***1976***, *9*, 41; Scheppelle, S.E. *Chem. Rev.* ***1972***, *72*, 511.

[105]Brown, H.C. *The Non–Classical Ion Problem*, Plenum, New York, ***1977***; Brown, H.C. *Tetrahedron* ***1976***, *32*, 179; Brown, H.C.; Kawakami, J.H. *J. Am. Chem. Soc.* ***1970***, *92*, 1990. See also, Story, R.R.; Clark, B.C., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 3, Wiley, New York, ***1972***, p. 1007.

[106]Brown, H.C.; Ravindranathan, M. *J. Am. Chem. Soc.* ***1978***, *100*, 1865.

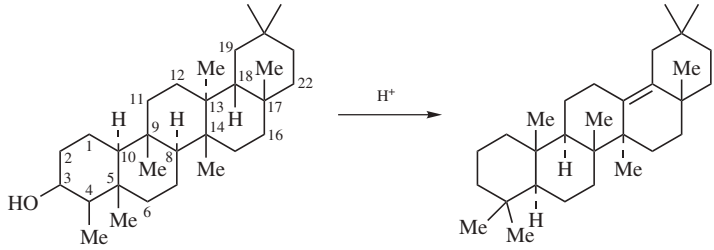
There is considerable evidence, however, that the norbornyl cation rearranges with σ-participation,[107] and there is strong NMR evidence for the nonclassical ion in super acids at low temperatures.[108]



50

As alluded to above, the term "Wagner–Meerwein rearrangement" is not precise. Some use it to refer to all the rearrangements in this section and in **18-2**. Others use it only when an alcohol is converted to a rearranged alkene. Terpene chemists call the migration of a methyl group the *Nametkin rearrangement*. The term *retropinacol rearrangement* is often applied to some or all of these. Fortunately, this disparity in nomenclature does not seem to cause much confusion.

Sometimes several of these rearrangements occur in one molecule, either simultaneously or in rapid succession. A spectacular example is found in the triterpene series. Friedelin is a triterpenoid ketone found in cork. Reduction gives 3β-friedelanol (**51**). When this compound is treated with acid, 13(18)-oleanene (**52**) is formed.[109] In this case, *seven* 1,2-shifts take place. On removal of H_2O from position 3 to leave a positive



51 **52**

charge, the following shifts occur: hydride from 4 to 3; methyl from 5 to 4; hydride from 10 to 5; methyl from 9 to 10; hydride from 8 to 9; methyl from 14 to 8; and methyl from 13 to 14. This leaves a positive charge at position 13, which is stabilized by loss of the proton at the 18 position to give **52**. All these shifts are stereospecific, the group always migrating on the side of the ring system on which it is located; that is, a group above the "plane" of the ring system (indicated by a solid line in **51**) moves above the plane, and a group below the plane (dashed line) moves

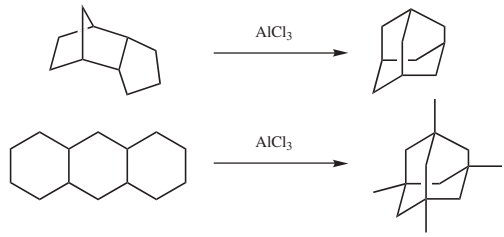
[107]Coates, R.M.; Fretz, E.R. *J. Am. Chem. Soc.* ***1977***, *99*, 297; Brown, H.C.; Ravindranathan, M. *J. Am. Chem. Soc.* ***1977***, *99*, 299.

[108]Olah, G.A. *Carbocations and Electrophilic Reactions*, Verlag Chemie/Wiley, New York, ***1974***, pp. 80–89; Olah, G.A.; White, A.M.; DeMember, J.R.; Commeyras, A.; Lui, C.Y. *J. Am. Chem. Soc.* ***1970***, *92*, 4627.

[109]Corey, E.J.; Ursprung, J.J. *J. Am. Chem. Soc.* ***1956***, *78*, 5041.

below it. It is probable that the seven shifts are not all concerted, although some of them may be, for intermediate products can be isolated.[110] As an illustration of point 2 (p. 1581), it may be mentioned that friedelene, derived from dehydration of **51**, also gives **52** on treatment with acid.[111]

It was mentioned above that even alkanes undergo Wagner–Meerwein rearrangements if treated with Lewis acids and a small amount of initiator. Catalytic asymmetric Wagner–Meerwein shifts have been observed.[112] An interesting application of this reaction is the conversion of tricyclic molecules to adamantane and its derivatives.[113] It has been found that *all* tricyclic alkanes containing 10 carbons are converted to adamantane by treatment with a Lewis acid, such as $AlCl_3$. If the substrate contains >10 carbons, alkyl-substituted adamantanes are produced. The IUPAC name for these reactions is *Schleyer adamantization*. Two examples are



If 14 or more carbons are present, the product may be diamantane or a substituted diamantane.[114] These reactions are successful because of the high thermodynamic stability of adamantane, diamantane, and similar diamond-like molecules. The most stable of a set of C_nH_m isomers (called the *stabilomer*) will be the end product if the reaction reaches equilibrium.[115] Best yields are obtained by the use of "sludge" catalysts[116] (i.e., a mixture of AlX_3 and *tert*-butyl bromide or *sec*-butyl bromide).[117] Though it is certain that these adamantane-forming reactions take place by nucleophilic 1,2-shifts, the exact pathways are not easy to unravel

[110]For a discussion, see Whitlock Jr., H.W.; Olson, A.H. *J. Am. Chem. Soc.* ***1970***, *92*, 5383.

[111]Dutler, H.; Jeger, O.; Ruzicka, L. *Helv. Chim. Acta* ***1955***, *38*, 1268; Brownlie, G.; Spring, F.S.; Stevenson, R.; Strachan, W.S. *J. Chem. Soc.* ***1956***, 2419; Coates, R.M. *Tetrahedron Lett.* ***1967***, 4143.

[112]Trost, B.M.; Yasukata, T. *J. Am. Chem. Soc.* ***2001***, *123*, 7162.

[113]For reviews, see McKervey, M.A.; Rooney, J.J., in Olah, G.A. *Cage Hydrocarbons*, Wiley, NY, ***1990***, pp. 39–64; McKervey, M.A. *Tetrahedron* ***1980***, *36*, 971; *Chem. Soc. Rev.* ***1974***, *3*, 479; Greenberg, A.; Liebman, J.F. *Strained Organic Molecules*, Academic Press, NY, ***1978***, pp. 178–202; Bingham, R.C.; Schleyer, P.v.R. *Fortschr. Chem. Forsch.* ***1971***, *18*, 1, 3–23.

[114]See Gund, T.M.; Osawa, E.; Williams, Jr., V.Z.; Schleyer, P.v.R. *J. Org. Chem.* ***1974***, *39*, 2979.

[115]For a method for the prediction of stabilomers, see Godleski, S.A.; Schleyer, P.v.R.; Ōsawa, E.; Wipke, W.T. *Prog. Phys. Org. Chem.* ***1981***, *13*, 63.

[116]Schneider, A.; Warren, R.W.; Janoski, E.J. *J. Org. Chem.* ***1966***, *31*, 1617; Williams, Jr., V.Z.; Schleyer, P.v.R.; Gleicher, G.J.; Rodewald, L.B. *J. Am. Chem. Soc.* ***1966***, *88*, 3862; Robinson, M.J.T.; Tarratt, H.J.F. *Tetrahedron Lett.* ***1968***, 5.

[117]For other methods, see Johnston, D.E.; McKervey, M.A.; Rooney, J.J. *J. Am. Chem. Soc.* ***1971***, *93*, 2798; Olah, G.A.; Wu, A.; Farooq, O.; Prakash, G.K.S. *J. Org. Chem.* ***1989***, *54*, 1450.

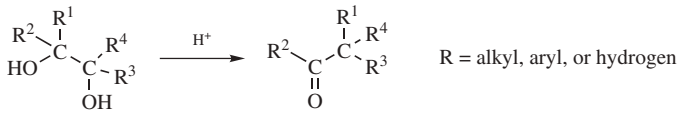
because of their complexity.[118] Treatment of adamantane-2-^{14}C with $AlCl_3$ results in total carbon scrambling on a statistical basis.[119]

As already indicated, the mechanism of the Wagner–Meerwein rearrangement is usually nucleophilic. Free-radical rearrangements are also known (see the mechanism section of this chapter), though virtually only with aryl migration. However, carbanion mechanisms (electrophilic) have also been found.[94] Thus Ph_3CCH_2Cl treated with sodium gave Ph_2CHCH_2Ph along with unrearranged products.[120] This is called the *Grovenstein–Zimmerman rearrangement*. The intermediate is Ph_3CCH_2-, and the phenyl moves without its electron pair. Only aryl and vinylic,[121] and not alkyl, groups migrate by the electrophilic mechanism (p. $$$) and transition states or intermediates analogous to **41** and **42** are likely.[122]

OS **V**, 16, 194; **VI**, 378, 845.

18-2 The Pinacol Rearrangement

1/*O*-Hydro,3/hydroxy-(2/ → 3/alkyl)-*migro*-elimination



When *vic*-diols (glycols) are treated with acids,[123] they can be rearranged to give aldehydes or ketones, although elimination without rearrangement can also be accomplished. This reaction is called the *pinacol rearrangement*; the reaction gets its name from a prototype compound pinacol ($Me_2COHCOHMe_2$), which is rearranged to pinacolone (Me_3CCOCH_3).[124] In this type of reaction, reduction can compete with rearrangement.[125] The reaction has been accomplished many times, with alkyl, aryl, hydrogen, and even ethoxycarbonyl (COOEt)[126] as migrating

[118]See, for example, Engler, E.M.; Fărcaşiu, M.; Sevin, A.; Cense, J.M.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1973***, *95*, 5769; Klester, A.M.; Ganter, C. *Helv. Chim. Acta* ***1983***, *66*, 1200; ***1985***, *68*, 734.

[119]Majerski, Z.; Liggero, S.H.; Schleyer, P.v.R.; Wolf, A.P. *Chem. Commun.* ***1970***, 1596.

[120]Grovenstein, Jr., E. *J. Am. Chem. Soc.* ***1957***, *79*, 4985; Grovenstein, Jr., E.; Williams Jr., L.P. *J. Am. Chem. Soc.* ***1961***, *83*, 412; Zimmerman, H.E.; Zweig, A. *J. Am. Chem. Soc.* ***1961***, *83*, 1196. See also, Crimmins, T.F.; Murphy, W.S.; Hauser, C.R. *J. Org. Chem.* ***1966***, *31*, 4273; Grovenstein, Jr., E.; Cheng, Y. *J. Am. Chem. Soc.* ***1972***, *94*, 4971.

[121]See Grovenstein, Jr., E.; Black, K.W.; Goel, S.C.; Hughes, R.L.; Northrop, J.H.; Streeter, D.L.; VanDerveer, D. *J. Org. Chem.* ***1989***, *54*, 1671, and references cited therein.

[122]Bertrand, J.A.; Grovenstein, Jr., E.; Lu, P.; VanDerveer, D. *J. Am. Chem. Soc.* ***1976***, *98*, 7835.

[123]For a reaction initiated by iminium salts, see Lopez, L.; Mele, G.; Mazzeo, C. *J. Chem. Soc. Perkin Trans. 1* ***1994***, 779. For reactions initiated by radical cations, see de Sanabia, J.A.; Carrión, A.E. *Tetrahedron Lett.* ***1993***, *34*, 7837. $SbCl_5$ has been used: see Harada, T.; Mukaiyama, T. *Chem. Lett.* ***1992***, 81.

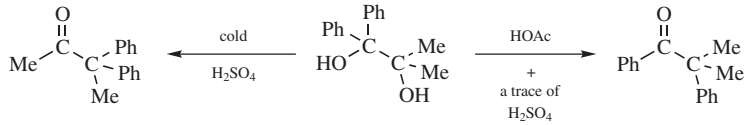
[124]For reviews, see Bartók, M.; Molnár, A., in Patai, S. *The Chemistry of Functional Groups, Supplement E*, Wiley, NY, ***1980***, pp. 722–732; Collins, C.J.; Eastham, J.F., in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***, pp. 762–771.

[125]Grant, A.A.; Allukian, M.; Fry, A.J. *Tetrahedron Lett.* ***2002***, *43*, 4391.

[126]Kagan, J.; Agdeppa Jr., D.A.; Mayers, D.A.; Singh, S.P.; Walters, M.J.; Wintermute, R.D. *J. Org. Chem.* ***1976***, *41*, 2355. COOH has been found to migrate in a Wagner–Meerwein reaction: Berner, D.; Cox, D.P.; Dahn, H. *J. Am. Chem. Soc.* ***1982***, *104*, 2631.

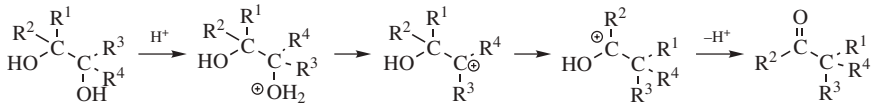
groups. In most cases, each carbon has at least one alkyl or aryl group, and the reaction is most often carried out with tri- and tetrasubstituted glycols. As mentioned earlier, glycols in which the four R groups are not identical can give rise to more than one product, depending on which group migrates (see p. 1568 for a discussion of migratory aptitudes). A noncatalytic reaction is possible in supercritical water.[127]

Stereodifferentiation is possible in this reaction.[128] When TMSOTf was used to initiate the reaction, it was shown to be highly regioselective.[129] Mixtures are often produced, and which group preferentially migrates may depend on the reaction conditions, as well as on the nature of the substrate. Thus the



54 **53** **55**

action of cold, concentrated sulfuric acid on **53** produces mainly the ketone **54** (methyl migration), while treatment of **53** with acetic acid containing a trace of sulfuric acid gives mostly **55** (phenyl migration).[130] If at least one R is hydrogen, aldehydes can be produced as well as ketones. Generally, aldehyde formation is favored by the use of mild conditions (lower temperatures, weaker acids), because under more drastic conditions the aldehydes may be converted to ketones (**18-4**). The reaction has been carried out in the solid state, by treating solid substrates with HCl gas or with an organic solid acid.[131]



56

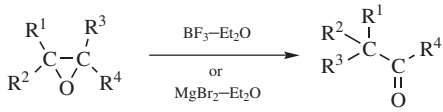
The mechanism involves a simple 1,2-shift. The ion **56** (where all four R groups are Me) has been trapped by the addition of tetrahydrothiophene.[132] It may seem odd that a migration takes place when the positive charge is already at a tertiary position, but carbocations stabilized by an oxygen atom are even more stable than tertiary alkyl cations (p. 242). There is also the driving force supplied by the fact that the new carbocation can immediately stabilize itself by losing a proton.

It is obvious that other compounds in which a positive charge can be placed on a carbon α to one bearing an OH group can also give this rearrangement. This is true for β-amino alcohols, which rearrange on treatment with nitrous acid (this is called

[127]Ikushima, Y.; Hatakeda, K.; Sato, O.; Yokoyama, T.; Arai, M. *J. Am. Chem. Soc.* ***2000***, *122*, 1908.
[128]Paquette, L.A.; Lanter, J.C.; Johnston, J.N. *J. Org. Chem.* ***1997***, *62*, 1702.
[129]Kudo, K.; Saigo, K.; Hashimoto, Y.; Saito, K.; Hasegawa, M. *Chem. Lett.* ***1992***, 1449.
[130]Ramart-Lucas, P.; Salmon-Legagneur, F. *C. R. Acad. Sci.* ***1928***, *188*, 1301.
[131]Toda, F.; Shigemasa, T. *J. Chem. Soc. Perkin Trans. 1* ***1989***, 209.
[132]Bosshard, H.; Baumann, M.E.; Schetty, G. *Helv. Chim. Acta* ***1970***, *53*, 1271.

the *semipinacol* rearrangement), iodohydrins, for which the reagent is mercuric oxide or silver nitrate, β-hydroxyalkyl selenides, $R^1R^2C(OH)C(SeR^5)R^3R^4$,[133] and allylic alcohols,[134] which can rearrange on treatment with a strong acid that protonates the double bond.

A similar rearrangement is given by epoxides,[135]



R = alkyl, aryl, or hydrogen

when treated with acidic[136] reagents, such as BF_3–etherate or $MgBr_2$–etherate, 5 *M* $LiClO_4$ in ether,[137] $InCl_3$,[138] $Al(OC_6F_3)_3$,[139] $Bi(OTf)_3$,[140] $VO(OEt)Cl_2$,[141] or sometimes by heat alone.[142] Epoxides are converted to aldehydes or ketones on treatment with certain metallic catalysts[143] including treatment with iron complexes in refluxing dioxane,[144] $IrCl_3$,[145] or with $BiOClO_4$ in dichloromethane.[146] A related rearrangement called the *Meinwald rearrangement* was induced by the enzyme pig liver esterase.[147] It has been shown that epoxides are intermediates in the pinacol rearrangements of certain glycols.[148] Among the evidence for the mechanism given is that $Me_2COHCOHMe_2$, $Me_2COHCNH_2Me_2$, and $Me_2COHCClMe_2$ gave the reaction at different rates (as expected), but yielded the *same mixture* of two products pinacol and pinacolone indicating a common intermediate.[149]

[133]For a review, see Krief, A.; Laboureur, J.L.; Dumont, W.; Labar, D. *Bull. Soc. Chim. Fr.* ***1990***, 681.

[134]See Wang, B.M.; Song, Z.L.; Fan, C.A.; Tu, Y.Q.; Chen, W.M. *Synlett* ***2003***, 1497; Hurley, P.B.; Dake, G.R. *Synlett* ***2003***, 2131.

[135]For a discussion of the mechanism, see Hodgson, D.M.; Robinson, L.A.; Jones, M.L. *Tetrahedron Lett.* ***1999***, *40*, 8637.

[136]Epoxides can also be rearranged with basic catalysts, though the products are usually different. For a review, see Yandovskii, V.N.; Ershov, B.A. *Russ. Chem. Rev.* ***1972***, *41*, 403, 410.

[137]Sudha, R.; Narashimhan, K.M.; Saraswathy, V.G.; Sankararaman, S. *J. Org. Chem.* ***1996***, *61*, 1877; Sankararaman, S.; Nesakumar, J.E. *J. Chem. Soc., Perkin Trans. 1* ***1999***, 3173.

[138]Ranu, B.C.; Jana, U. *J. Org. Chem.* ***1998***, *63*, 8212.

[139]Kita, Y.; Furukawa, A.; Futamura, J.; Ueda, K.; Sawama, Y.; Hamamoto, H.; Fujioka, H. *J. Org. Chem.* ***2001***, *66*, 8779.

[140]Bhatia, K.A.; Eash, K.J.; Leonard, N.M.; Oswald, M.C.; Mohan, R.S. *Tetrahedron Lett.* ***2001***, *42*, 8129.

[141]Martínez, F.; del Campo., C.; Llama, E.F. *J. Chem. Soc., Perkin Trans. 1* ***2000***, 1749.

[142]For a list of reagents that accomplish this transformation, with references, see Larock, R.C. *Comprehensive Organic Transformations*; 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1277–1280.

[143]For example, see Alper, H.; Des Roches, D.; Durst, T.; Legault, R. *J. Org. Chem.* ***1976***, *41*, 3611; Milstein, D.; Buchman, O.; Blum, J. *J. Org. Chem.* ***1977***, *42*, 2299; Prandi, J.; Namy, J.L.; Menoret, G.; Kagan, H.B. *J. Organomet. Chem.* ***1985***, *285*, 449; Miyashita, A.; Shimada, T.; Sugawara, A.; Nohira, H. *Chem. Lett.* ***1986***, 1323; Maruoka, K.; Nagahara, S.; Ooi, T.; Yamamoto, H. *Tetrahedron Lett.* ***1989***, *30*, 5607.

[144]Suda, K.; Baba, K.; Nakajima, S.-I.; Takanami, T. *Tetrahedron Lett.* ***1999***, *40*, 7243.

[145]Karamé, I.; Tommasino, M.L.; LeMaire, M. *Tetrahedron Lett.* ***2003***, *44*, 7687.

[146]Anderson, A.M.; Blazek, J.M.; Garg, P.; Payne, B.J.; Mohan, R.S. *Tetrahedron Lett.* ***2000***, *41*, 1527.

[147]Niwayama, S.; Noguchi, H.; Ohno, M.; Kobayashi, S. *Tetrahedron Lett.* ***1993***, *34*, 665.

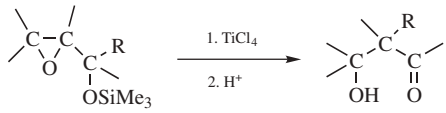
[148]See, for example, Matsumoto, K. *Tetrahedron* ***1968***, *24*, 6851; Pocker, Y.; Ronald, B.P. *J. Am. Chem. Soc.* ***1970***, *92*, 3385; *J. Org. Chem.* ***1970***, *35*, 3362; Tamura, K.; Moriyoshi, T. *Bull. Chem. Soc. Jpn.* ***1974***, *47*, 2942.

[149]Pocker, Y. *Chem. Ind.* (*London*), ***1959***, 332. See also, Herlihy, K.P. *Aust. J. Chem.* ***1981***, *34*, 107.

A good way to prepare β-diketones consists of heating α,β-epoxy ketones at 80–140°C in toluene with small amounts of $(Ph_3P)_4Pd$ and 1,2-bis(diphenylphosphino)ethane.[150] Epoxides are converted to 1,2-diketones with Bi, DMSO, O_2, and a catalytic amounts of $Cu(OTf)_2$ at 100°C.[151] α,β–Epoxy ketones are also converted to 1,2-diketones with a ruthenium catalyst[152] or an iron catalyst.[153] Epoxides with an α-hydroxyalkyl substituent give a pinacol rearrangement product in the presence of a $ZnBr_2$[154] or $Tb(OTf)_3$[155] catalyst to give a γ-hydroxy ketone.

Oxaziridines are converted to ring-expanded lactams under photochemical conditions.[156] *N*-Tosyl aziridines with an α-hydroxyalkyl substituent give a pinacol rearrangement product in the presence of Lewis acids, such as SmI_2, in this case a keto-*N*-tosyl amide.[157]

β-Hydroxy ketones can be prepared by treating the silyl ethers (**57**) of α,β-epoxy alcohols with $TiCl_4$.[158]

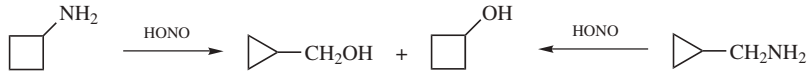


57

OS **I**, 462; **II**, 73, 408; **III**, 312; **IV**, 375, 957; **V**, 326, 647; **VI**, 39, 320; **VII**, 129. See also, OS **VII**, 456.

18-3 Expansion and Contraction of Rings

Demyanov ring contraction; Demyanov ring expansion



When a positive charge is formed on an alicyclic carbon, migration of an alkyl group can take place to give ring contraction, producing a ring that is one carbon smaller than the original, as in the interconversion of the cyclobutyl cation and the

[150]Suzuki, M.; Watanabe, A.; Noyori, R. *J. Am. Chem. Soc.* ***1980***, *102*, 2095.
[151]Antoniotti, S.; Duñach, E. *Chem. Commun.* ***2001***, 2566.
[152]Chang, C.-L.; Kumar, M.P.; Liu, R.-S. *J. Org. Chem.* ***2004***, *69*, 2793.
[153]Suda, K.; Baba, K.; Nakajima, S.; Takanami, T. *Chem. Commun.* ***2002***, 2570.
[154]Tu, Y.Q.; Fan, C.A.; Ren, S.K.; Chan, A.S.C. *J. Chem. Soc., Perkin Trans. 1* ***2000***, 3791.
[155]Bickley, J.F.; Hauer, B.; Pena, P.C.A.; Roberts, S.M.; Skidmore, J. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 1253.
[156]Bourguet, E.; Baneres, J.-L.; Girard, J.-P.; Parello, J.; Vidal, J.-P.; Lusinchi, X.; Declerzq, J.-P. *Org. Lett.* ***2001***, *3*, 3067.
[157]Wang, B.M.; Song, Z.L.; Fan, C.A.; Tu, Y.Q.; Shi, Y. *Org. Lett.* ***2002***, *4*, 363.
[158]Maruoka, K.; Hasegawa, M.; Yamamoto, H.; Suzuki, K.; Shimazaki, M.; Tsuchihashi, G. *J. Am. Chem. Soc.* ***1986***, *108*, 3827. For a different rearrangement of **53**, see Maruoka, K.; Ooi, T.; Yamamoto, H. *J. Am. Chem. Soc.* ***1989***, *111*, 6431.

cyclopropylcarbinyl cation.

Note that this change involves conversion of a secondary to a primary carbocation. In a similar manner, when a positive charge is placed on a carbon a to an alicyclic ring, ring expansion can take place.[159] The new carbocation, and the old one, can then give products by combination with a nucleophile (e.g., the alcohols shown above), or by elimination, so that this reaction is a special case of **18-1**. Often, both rearranged and unrearranged products are formed, so that, for example, cyclobutylamine and cyclopropylmethylamine give similar mixtures of the two alcohols shown above on treatment with nitrous acid (a small amount of 3-buten-1-ol is also produced). When the carbocation is formed by diazotization of an amine, the reaction is called the *Demyanov rearrangement*,[160] but of course similar products are formed when the carbocation is generated in other ways. The expansion reaction has been performed on rings of C_3–C_8,[161] but yields are best with the smaller rings, where relief of small-angle strain provides a driving force for the reaction. The contraction reaction has been applied to four-membered rings and to rings of C_6–C_8, but contraction of a cyclopentyl cation to a cyclobutylmethyl system is generally not feasible because of the additional strain involved. Strain is apparently much less of a factor in the cyclobutyl–cyclopropylmethyl interconversion (for a discussion of this interconversion, see p. 450). The influence of substituents on this rearrangement has been examined.[162]

Ring expansions of certain hydroxyamines, such as **58**

58

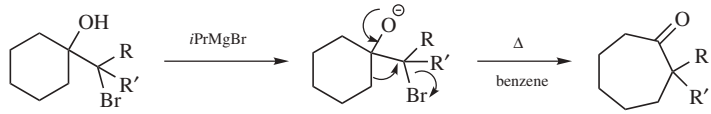
[159]For monographs on ring expansions, see Hesse, M. *Ring Enlargement in Organic Chemistry*, VCH, NY, ***1991***; Gutsche, C.D.; Redmore, D. *Carbocyclic Ring Expansion Reactions*, Academic Press, NY, ***1968***. For a review of ring contractions, see Redmore, D.; Gutsche, C.D. *Adv. Alicyclic Chem.* ***1971***, *3*, 1. For reviews of ring expansions in certain systems, see Baldwin, J.E.; Adlington, R.M.; Robertson, J. *Tetrahedron* ***1989***, *45*, 909; Stach, H.; Hesse, M. *Tetrahedron* ***1988***, *44*, 1573; Dolbier Jr., W.R. *Mech. Mol. Migr.* ***1971***, *3*, 1. For reviews of expansions and contractions of three- and four membered rings, see Salaün, J., in Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, pt. 2, Wiley, NY, ***1987***, pp. 809–878; Conia, J.M.; Robson, M.J. *Angew. Chem. Int. Ed.* ***1975***, *14*, 473. For a list of ring expansions and contractions, with references, see Larock, R.C. *Comprehensive Organic Transformation*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1283–1302.

[160]For a review, see Smith, P.A.S.; Baer, D.R. *Org. React.* ***1960***, *11*, 157. See also, Chow, L.; McClure, M.; White, J. *Org. Biomol. Chem.* ***2004***, *2*, 648.

[161]For a review concerning three-membered rings, see Wong, H.N.C.; Hon, M.; Tse, C.; Yip, Y.; Tanko, J.; Hudlicky, T. *Chem. Rev.* ***1989***, *89*, 165, see pp. 182–186. For a review concerning three- and four-membered rings, see Breslow, R., in Mayo, P. *Molecular Rearrangements*, Vol. 1, Wiley, NY, ***1963***, pp. 233–294.

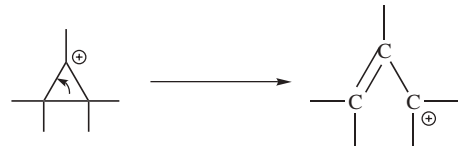
[162]Wiberg, K.B.; Shobe, D.; Nelson, G.C. *J. Am. Chem. Soc.* ***1993***, *115*, 10645.

are analogous to the semipinacol rearrangement (**18-2**). This reaction is called the *Tiffeneau–Demyanov ring expansion*. These have been performed on rings of C_4–C_8 and the yields are better than for the simple Demyanov ring expansion. A similar reaction has been used to expand rings of from five to eight members.[163] In this case, a cyclic bromohydrin of the form **59** is treated with a Grignard reagent which, acting as a base, removes the OH proton to give the alkoxide **60**. Refluxing of **60** brings about the ring enlargement. The reaction has been accomplished for **59** in which at least one R group is phenyl or methyl,[164] but fails when both R groups are hydrogen.[165]

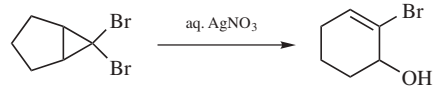


59 **60**

A positive charge generated on a three-membered ring gives ''contraction'' to an allylic cation.[166]



We have previously seen (p. 487) that this is the reason nucleophilic substitutions are not feasible at a cyclopropyl substrate. The reaction is often used to convert cyclopropyl halides and tosylates to allylic products, especially for the purpose of ring expansion, an example being the conversion of **61–62**.[167] The stereochemistry of these cyclopropyl cleavages is governed by the principle of orbital symmetry conservation (for a discussion, see p. 1644).

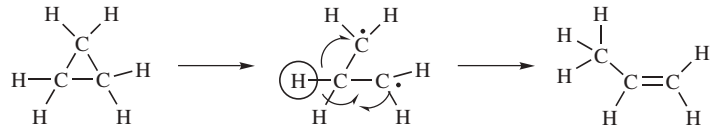


61 **62**

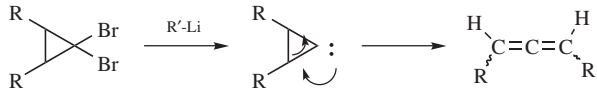
Three-membered rings can also be cleaved to unsaturated products in at least two other ways. (*1*) On pyrolysis, cyclopropanes can undergo ''contraction'' to

[163]Sisti, A.J. *Tetrahedron Lett.* ***1967***, 5327; *J. Org. Chem.* ***1968***, *33*, 453. See also, Sisti, A.J.; Vitale, A.C. *J. Org. Chem.* ***1972***, *37*, 4090.
[164]Sisti, A.J.; Meyers, M. *J. Org. Chem.* ***1973***, *38*, 4431; Sisti, A.J.; Rusch, G.M. *J. Org. Chem.* ***1974***, *39*, 1182.
[165]Sisti, A.J. *J. Org. Chem.* ***1968***, *33*, 3953.
[166]For reviews, see Marvell, E.N. *Thermal Electrocylic Reactions*, Academic Press, NY, ***1980***, pp. 23–53; Sorensen, T.S.; Rauk, A., in Marchand, A.P.; Lehr, R.E. *Pericyclic Reactions*, Vol. 2, Academic Press, NY, ***1977***, pp. 1–78.
[167]Skell, P.S.; Sandler, S.R. *J. Am. Chem. Soc.* ***1958***, *80*, 2024.

propenes.[168] In the simplest case, cyclopropane gives propene when heated to 400–500°C. The mechanism is generally regarded[169] as involving a diradical

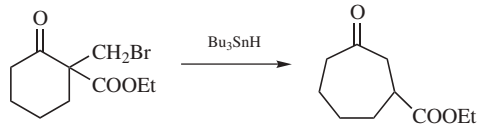


intermediate[170] (recall that free-radical 1,2 migration is possible for diradicals, p. 1574). (*2*) The generation of a carbene or carbenoid carbon in a three-membered ring can lead to allenes, and allenes are often prepared in this



way.[171] Flash vacuum pyrolysis of 1-chlorocyclopropene thermally rearranges to chloroallene.[172] One way to generate, such a species is treatment of a 1,1-dihalocyclopropane with an alkyllithium compound (**12-39**).[173] In contrast, the generation of a carbene or carbenoid at a cyclopropylmethyl carbon gives ring expansion.[174]

Some free-radical ring enlargements are also known, an example being:[175]



[168]For reviews, see Berson, J.A., in de Mayo, P. *Rearrangaements in Ground and Excited States*, Vol. 1, Academic Press, NY, ***1980***, pp. 324–352; *Ann. Rev. Phys. Chem.* ***1977***, *28*, 111; Bergman, R.G., in Kochi, J.K. *Free Radicals*, Vol. 1, Wiley, NY, ***1973***, pp. 191–237; Frey, H.M. *Adv. Phys. Org. Chem.* ***1966***, *4*, 147, see pp. 148–170.

[169]For evidence that diradical intermediates may not be involved, at least in some cases, see Fields, R.; Haszeldine, R.N.; Peter, D. *Chem. Commun.* ***1967***, 1081; Parry, K.A.W.; Robinson, P.J. *Chem. Commun.* ***1967***, 1083; Clifford, R.P.; Holbrook, K.A. *J. Chem. Soc. Perkin Trans. 2* ***1972***, 1972; Baldwin, J.E.; Grayston, M.W. *J. Am. Chem. Soc.* ***1974***, *96*, 1629, 1630.

[170]We have seen before that such diradicals can close up to give cyclopropanes (**17-34**). Therefore, pyrolysis of cyclopropanes can produce not only propenes, but also isomerized (cis → trans or optically active → inactive) cyclopropanes. See, for example, Berson, J.A.; Balquist, J.M. *J. Am. Chem. Soc.* ***1968***, *90*, 7343; Bergman, R.G.; Carter, W.L. *J. Am. Chem. Soc.* ***1969***, *91*, 7411.

[171]For reviews, see Schuster, H.F.; Coppola, G.M. *Allenes in Organic Synthesis*, Wiley, NY, ***1984***, pp. 20–23; Kirmse, W. *Carbene Chemistry*, 2nd ed., Academic Press, NY, ***1971***, pp. 462–467.

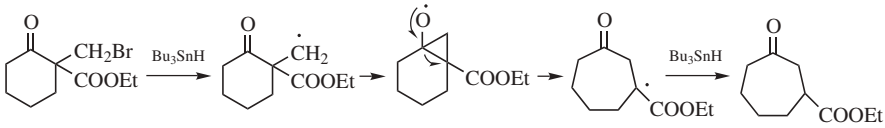
[172]Billups, W.E.; Bachman, R.E. *Tetrahedron Lett.* ***1992***, *33*, 1825.

[173]See Baird, M.S.; Baxter, A.G.W. *J. Chem. Soc. Perkin Trans. 1* ***1979***, 2317, and references cited therein.

[174]For a review, see Gutsche, C.D.; Redmore, D. *Carbocyclic Ring Expansion Reactions*, Academic Press, NY, ***1968***, pp. 111–117.

[175]Dowd, P.; Choi, S. *Tetrahedron Lett.* ***1991***, *32*, 565; *Tetrahedron* ***1991***, *47*, 4847. For a related ring expansion, see Baldwin, J.E.; Adlington, R.M.; Robertson, J. *J. Chem. Soc., Chem. Commun.* ***1988***, 1404.

This reaction has been used to make rings of 6, 7, 8, and 13 members. A possible mechanism is

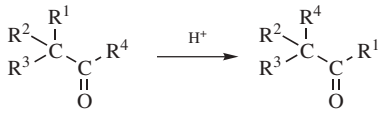


This reaction has been extended to the expansion of rings by three or four carbons, by the use of a substrate containing $(CH_2)_nX$ ($n = 3$ or 4) instead of CH_2Br.[176] By this means, 5-, 6-, and 7-membered rings were enlarged to 18–11-membered rings.

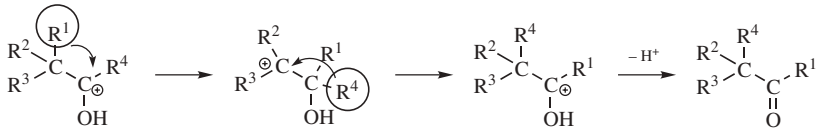
OS **III**, 276; **IV**, 221, 957; **V**, 306, 320; **VI**, 142, 187; **VII**, 12, 114, 117, 129, 135; **VIII**, 179, 467, 556, 578.

18-4 Acid-Catalyzed Rearrangements of Aldehydes and Ketones

1/Alkyl,2/alkyl-interchange, and so on



Rearrangements of this type, where a group α to a carbonyl "changes places" with a group attached to the carbonyl carbon, occur when migratory aptitudes are favorable.[177] The R^2, R^3, and R^4 groups may be alkyl or hydrogen. Certain aldehydes have been converted to ketones, and ketones to other ketones (though more drastic conditions are required for the latter), but no rearrangement of a ketone to an aldehyde ($R^1 = H$) has so far been reported. There are two mechanisms,[178] each beginning with protonation of the oxygen and each involving two migrations. In one pathway, the migrations are in opposite directions:[179]



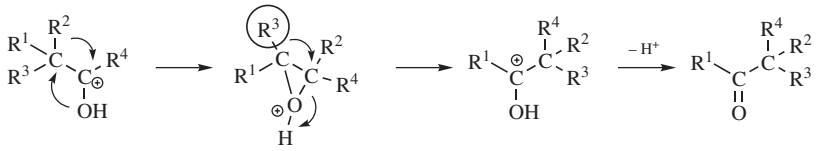
[176]Dowd, P.; Choi, S. *J. Am. Chem. Soc.* ***1987***, *109*, 6548; *Tetrahedron Lett.* ***1991***, *32*, 565.

[177]For reviews, see Fry, A. *Mech. Mol. Migr.* ***1971***, *4*, 113; Collins, C.J.; Eastham, J.F., in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***, pp. 771–790.

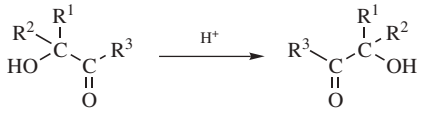
[178]Favorskii, A.; Chilingaren, A. *C. R. Acad. Sci.* ***1926***, *182*, 221.

[179]Kendrick Jr., L.W.; Benjamin, B.M.; Collins, C.J. *J. Am. Chem. Soc.* ***1958***, *80*, 4057; Rothrock, T.S.; Fry, A. *J. Am. Chem. Soc.* ***1958***, *80*, 4349; Collins, C.J.; Bowman, N.S. *J. Am. Chem. Soc.* ***1959***, *81*, 3614.

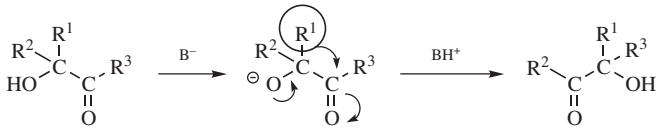
In the other pathway, the migrations are in the same direction. The actual mechanism of this pathway is not certain, but an epoxide (protonated) intermediate[180] is one possibility:[181]



If the reaction is carried out with ketone labeled in the C=O group with ^{14}C, the first pathway predicts that the product will contain all the ^{14}C in the C=O carbon, while in the second pathway the label will be in the α carbon (demonstrating migration of oxygen). The results of such experiments[182] have shown that in some cases only the C=O carbon was labeled, in other cases only the a carbon, while in still others both carbons bore the label, indicating that in these cases both pathways were in operation. With α-hydroxy aldehydes and ketones, the process may stop after only one migration (this is called the α-*ketol* rearrangement).

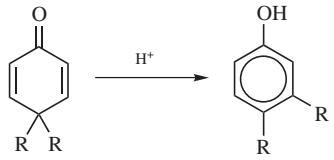


The α-ketol rearrangement can also be brought about by base catalysis, but only if the alcohol is tertiary, since if R^1 or R^2 = hydrogen, enolization of the substrate is more favored than rearrangement.



18-5 The Dienone–Phenol Rearrangement

2/*C* → 5/*O*-Hydro,1/*C* → 2/*C*-alkyl-bis-migration

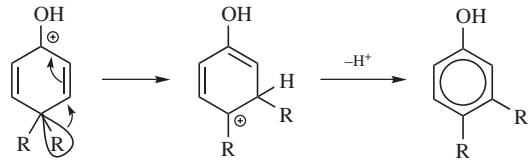


[180]Zook, H.D.; Smith, W.E.; Greene, J.L. *J. Am. Chem. Soc.* ***1957***, *79*, 4436.

[181]Some such pathway is necessary to account for the migration of oxygen that is found. It may involve a protonated epoxide, a 1,2-diol, or simply a [1,2]-shift of an OH group.

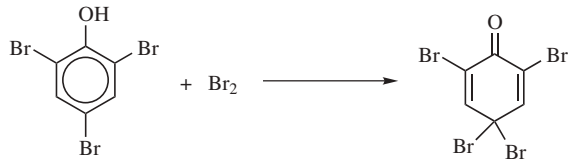
[182]See, for example, Barton, S.; Porter, C.R. *J. Chem. Soc.* ***1956***, 2483; Zalesskaya, T.E.; Remizova, T.B. *J. Gen. Chem. USSR* ***1965***, *35*, 29; Fry, A.; Oka, M. *J. Am. Chem. Soc.* ***1979***, *101*, 6353.

Cyclohexadienone derivatives that have two alkyl groups in the 4 position undergo, on acid treatment,[183] 1,2 migration of one of these groups from **64** to give the phenol. Note that a photochemical version of this reaction has been observed.[184]



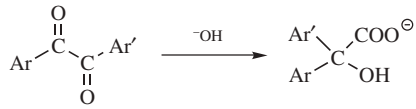
63 **64**

The driving force in the overall reaction (the *dienone–phenol rearrangement*) is of course creation of an aromatic system.[185] Note that **63** and **64** are arenium ions (p. 240), the same as those generated by attack of a phenol on an electrophile.[186] Sometimes, in the reaction of a phenol with an electrophile, a kind of reverse rearrangement (called the *phenol–dienone rearrangement)* takes place, though without an actual migration.[187] An example is



18-6 The Benzil–Benzilic Acid Rearrangement

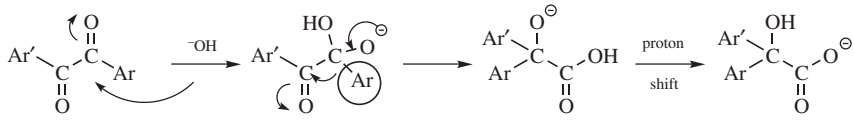
1/*O*-Hydro,3/oxido-(1/ → 2/aryl)-*migro*-addition



When treated with base, α-diketones rearrange to give the salts of α-hydroxy acids, a reaction known as the *benzil-benzilic acid rearrangement* (benzil is

[183]For a reagent that greatly accelerates this reaction, see Chalais, S.; Laszlo, P.; Mathy, A. *Tetrahedron Lett.* ***1986***, *27*, 2627.
[184]Guo, Z.; Schultz, A.G. *Org. Lett.* ***2001***, *3*, 1177.
[185]For reviews, see Perkins, M.J.; Ward, P. *Mech. Mol. Migr.* ***1971***, *4*, 55, 90–103; Miller, B. *Mech. Mol. Migr.* ***1968***, *1*, 247; Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1967***, pp. 55–68; Waring, A.J. *Adv. Alicyclic Chem.* ***1966***, *1*, 129, 207–223. For a review of other rearrangements of cyclohexadienones, see Miller, B. *Acc. Chem. Res.* ***1975***, *8*, 245.
[186]For evidence that these ions are indeed intermediates in this rearrangement, see Vitullo, V.P.; Grossman, N. *J. Am. Chem. Soc.* ***1972***, *94*, 3844; Planas, A.; Tomás, J.; Bonet, J. *Tetrahedron Lett.* ***1987***, *28*, 471.
[187]For a review, see Ershov, V.V.; Volod'kin, A.A.; Bogdanov, G.N. *Russ. Chem. Rev.* ***1963***, *32*, 75.

PhCOCOPh; benzilic acid is $Ph_2COHCOOH$).[188] A rhodium catalyzed version of this reaction has also been reported.[189] Though the reaction is usually illustrated with aryl groups, it can also be applied to aliphatic diketones[190] and to α-keto aldehydes. The use of an alkoxide instead of hydroxide gives the corresponding ester directly,[191] though alkoxide ions that are readily oxidized (e.g., OEt^- or $OCHMe_2^-$) are not useful here, since they reduce the benzil to a benzoin. The mechanism is similar to the rearrangements in **18-1–18-4**, but there is a difference: The migrating group does not move to a carbon with an open sextet. The carbon makes room for the migrating group by releasing a pair of π electrons from the C=O bond to the oxygen. The first step is attack of the base at the carbonyl group, the same as the first step of the tetrahedral mechanism of nucleophilic substitution (p. 1254) and of many additions to the C=O bond (Chapter 16):

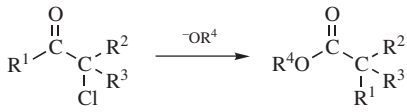


The mechanism has been intensely studied,[188] and there is much evidence for it.[192] The reaction is irreversible.

OS **I**, 89.

18-7 The Favorskii Rearrangement

2/Alkoxy-de-chloro(2/ → 1/alkyl)-*migro*-substitution



The reaction of α-halo ketones (chloro, bromo, or iodo) with alkoxide ions[193] to give rearranged esters is called the *Favorskii rearrangement*.[194] The use of

[188]For a review, see Selman, S.; Eastham, J.F. *Q. Rev. Chem. Soc.* ***1960***, *14*, 221.

[189]Shimizu, I.; Tekawa, M.; Maruyama, Y.; Yamamoto, A. *Chem. Lett.* ***1992***, 1365.

[190]For an example, see Schaltegger, A.; Bigler, P. *Helv. Chim. Acta* ***1986***, *69*, 1666.

[191]Doering, W. von E.; Urban, R.S. *J. Am. Chem. Soc.* ***1956***, *78*, 5938.

[192]However, some evidence for an SET pathway has been reported: Screttas, C.G.; Micha-Screttas, M.; Cazianis, C.T. *Tetrahedron Lett.* ***1983***, *24*, 3287.

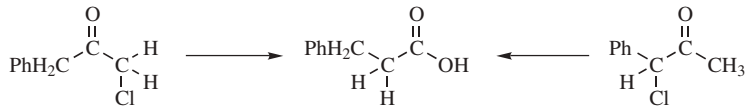
[193]The reaction has also been reported to take place with BF_3–MeOH and Ag^+: Giordano, C.; Castaldi, G.; Casagrande, F.; Abis, L. *Tetrahedron Lett.* ***1982***, *23*, 1385.

[194]For reviews, see Boyer, L.E.; Brazzillo, J.; Forman, M.A.; Zanoni, B. *J. Org. Chem.* ***1996***, *61*, 7611; Hunter, D.H.; Stothers, J.B.; Warnhoff, E.W., in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 1, Academic Press, NY, ***1980***, pp. 437–461; Chenier, P.J. *J. Chem. Educ.* ***1978***, *55*, 286; Rappe, C., in Patai, S. *The Chemistry of the Carbon–Halogen Bond*, pt. 2, Wiley, NY, ***1973***, pp. 1084–1101; Redmore, D.; Gutsche, C.D. *Carbocylcic Ring Expansion Reactions*, Academic Press, NY, ***1968***, pp.46–69; Akhrem, A.A.; Ustynyuk, T.K.; Titov, Yu.A. *Russ. Chem. Rev.* ***1970***, *39*, 732. For an asymmetric version, see Satoh, T.; Motohashi, S.; Kimura, S.; Tokutake, N.; Yamakawa, K. *Tetrahedron Lett.* ***1993***, *34*, 4823.

hydroxide ions or amines as bases leads to the free carboxylic acid (salt) or amide, respectively, instead of the ester. Cyclic α-halo ketones give ring contraction, as in the conversion of **65**–**66**.

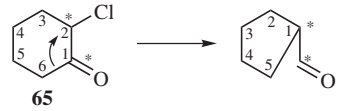
65 **66**

The reaction has also been carried out on α-hydroxy ketones[195] and on α,β-epoxy ketones, which give β-hydroxy acids.[196] The fact that an epoxide gives a reaction analogous to a halide indicates that the oxygen and halogen are leaving groups in a nucleophilic substitution step.



67 **68** **69**

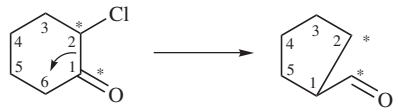
Through the years, the mechanism[197] of the Favorskii rearrangement has been the subject of much investigation; at least five different mechanisms have been proposed. However, the finding[198] that **67** and **68** *both* give **69** (this behavior is typical) shows that any mechanism where the halogen leaves and R^1 takes its place is invalid, since in such a case **67** would be expected to give **69** (with $PhCH_2$ migrating), but **68** should give PhCHMeCOOH (with CH_3 migrating). That is, in the case of **68**, it was PhCH that migrated and not methyl. Another important result was determined by radioactive labeling. **65**, in which C-1 and C-2 were equally labeled with ^{14}C, was converted to **66**. The product was found to contain 50% of the label on the carbonyl carbon, 25% on C-1, and 25% on C-2.[199] Now the carbonyl carbon, which originally carried half of the radioactivity, still had this much, so the rearrangement did not directly affect *it*. However, if the C-6 carbon had migrated to C-2, the other half of the radioactivity would be only on C-1 of the product:



65

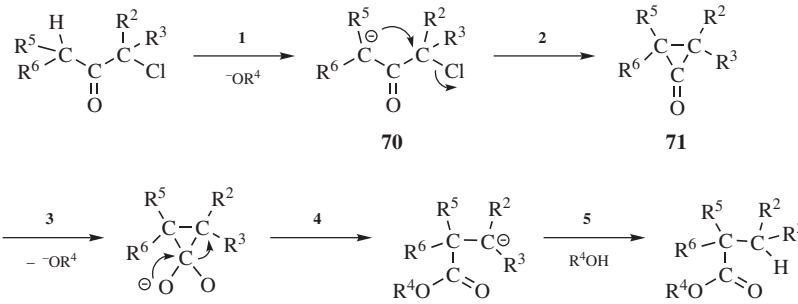
[195]Craig, J.C.; Dinner, A.; Mulligan, P.J. *J. Org. Chem.* ***1972***, *37*, 3539.
[196]See, for example, House, H.O.; Gilmor, W.F. *J. Am. Chem. Soc.* ***1961***, *83*, 3972; Mouk, R.W.; Patel, K.M.; Reusch, W. *Tetrahedron* ***1975***, *31*, 13.
[197]For a review of the mechanism, see Baretta, A.; Waegell, B. *React. Intermed. (Plenum)* ***1982***, *2*, 527.
[198]McPhee, W.D.; Klingsberg, E. *J. Am. Chem. Soc.* ***1944***, *66*, 1132; Bordwell, F.G.; Scamehorn, R.G.; Springer, W.R. *J. Am. Chem. Soc.* ***1969***, *91*, 2087.
[199]Loftfield, R.B. *J. Am. Chem. Soc.* ***1951***, *73*, 4707.

On the other hand, if the migration had gone the other way: If the C-2 carbon had migrated to C-6–then this half of the radioactivity would be found solely on C-2 of the product:



65

The fact that C-1 and C-2 were found to be equally labeled showed that *both migrations occurred*, with equal probability. Since C-2 and C-6 of **65** are not equivalent, this means that there must be a symmetrical intermediate.[200] The type of intermediate that best fits the circumstances is a cyclopropanone,[201] and the mechanism (for the general case) is formulated (replacing R^1 of our former symbolism with CHR^5R^6, since it is obvious that for this mechanism an α hydrogen is required on the non-halogenated side of the carbonyl):



The intermediate corresponding to **71** in the case of **65** is a symmetrical compound, and the three-membered ring can be opened with equal probability on either side of the carbonyl, accounting for the results with ^{14}C. In the general case, **71** is not symmetrical and should open on the side that gives the more stable carbanion.[202] This accounts for the fact that **67** and **68** give the same product. The intermediate in both cases is **70**, which always opens to give the carbanion stabilized by resonance. The cyclopropanone intermediate (**71**) has been isolated in the case where $R^2 = R^5 = t\text{-Bu}$ and $R^3 = R^6 = H$,[203] and it

[200]A preliminary migration of the chlorine from C-2 to C-6 was ruled out by the fact that recovered **65** had the same isotopic distribution as the starting **65**.

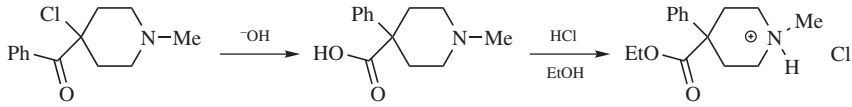
[201]Although cyclopropanones are very reactive compounds, several of them have been isolated. For reviews of cyclopropanone chemistry, see Wasserman, H.H.; Clark, G.M.; Turley, P.C. *Top. Curr. Chem.* ***1974***, *47*, 73; Turro, N.J. *Acc. Chem. Res.* ***1969***, *2*, 25.

[202]Factors other than carbanion stability (including steric factors) may also be important in determining which side of an unsymmetrical **71** is preferentially opened. See, for example, Rappe, C.; Knutsson, L. *Acta Chem. Scand.*, ***1967***, *21*, 2205; Rappe, C.; Knutsson, L.; Turro, N.J.; Gagosian, R.B. *J. Am. Chem. Soc.* ***1970***, *92*, 2032.

[203]Pazos, J.F.; Pacifici, J.G.; Pierson, G.O.; Sclove, D.B.; Greene, F.D. *J. Org. Chem.* ***1974***, *39*, 1990.

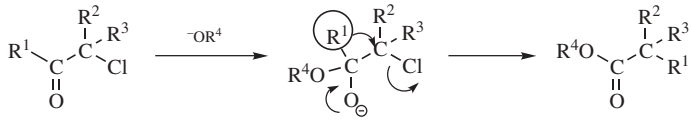
has also been trapped.[204] Also, cyclopropanones synthesized by other methods have been shown to give Favorskii products on treatment with NaOMe or other bases.[205]

The mechanism discussed is in accord with all the facts when the halo ketone contains an α hydrogen on the other side of the carbonyl group. However, ketones that do not have a hydrogen there also rearrange to give the same type of product. This is usually called the *quasi-Favorskii rearrangement*. An example is found in the preparation of Demerol:[206]



Demerol

The quasi-Favorskii rearrangement obviously cannot take place by the cyclopropanone mechanism. The mechanism that is generally accepted (called the *semibenzilic mechanism*[207]) is a base-catalyzed pinacol



rearrangement-type mechanism similar to that of **18-6**. This mechanism requires inversion at the migration terminus and this has been found.[208] It has been shown that even where there *is* an appropriately situated a hydrogen, the semibenzilic mechanism may still operate.[209]

An interesting analog of the Favorskii rearrangement treats a ketone, such as 4-*tert*-butylcyclohexanone, without an α-halogen with $Tl(NO_3)_3$ to give 3-*tert*-butylcyclopentane-1-carboxylic acid.[210]

OS **IV**, 594; **VI**, 368, 711.

[204]Fort, A.W. *J. Am. Chem. Soc.* ***1962***, *84*, 4979; Cookson, R.C.; Nye, M.J. *Proc. Chem. Soc.* ***1963***, 129; Breslow, R.; Posner, J.; Krebs, A. *J. Am. Chem. Soc.* ***1963***, *85*, 234; Baldwin, J.E.; Cardellina, J.H.I. *Chem. Commun.* ***1968***, 558.

[205]Crandall, J.K.; Machleder, W.H. *J. Org. Chem.* ***1968***, *90*, 7347; Turro, N.J.; Gagosian, R.B.; Rappe, C.; Knutsson, L. *Chem. Commun.* ***1969***, 270; Wharton, P.S.; Fritzberg, A.R. *J. Org. Chem.* ***1972***, *37*, 1899.

[206]Smissman, E.E.; Hite, G. *J. Am. Chem. Soc.* ***1959***, *81*, 1201.

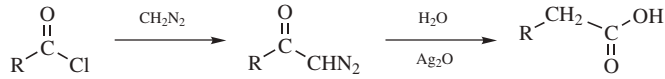
[207]Tchoubar, B.; Sackur, O. *C. R. Acad. Sci.* ***1939***, *208*, 1020.

[208]Baudry, D.; Bégué, J.; Charpentier-Morize, M. *Bull. Soc. Chim. Fr.* ***1971***, 1416; *Tetrahedron Lett.* ***1970***, 2147.

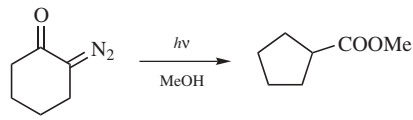
[209]For example, see Salaun, J.R.; Garnier, B.; Conia, J.M. *Tetrahedron* ***1973***, *29*, 2895; Rappe, C.; Knutsson, L. *Acta Chem. Scand.*, ***1967***, *21*, 163; Warnhoff, E.W.; Wong, C.M.; Tai, W.T. *J. Am. Chem. Soc.* ***1968***, *90*, 514.

[210]Ferraz, H.M.; Silva, Jr., J.F. *Tetrahedron Lett.* ***1997***, *38*, 1899.

18-8 The Arndt–Eistert Synthesis



In the *Arndt–Eistert synthesis*, an acyl halide is converted to a carboxylic acid with one additional carbon.[211] The first step of this process is reaction **16-89**. The actual rearrangement occurs in the second step on treatment of the diazo ketone with water and silver oxide or with silver benzoate and triethylamine. This rearrangement is called the *Wolff rearrangement*.[212] It is the best method of increasing a carbon chain by one if a *carboxylic acid* is available (**10-75** and **16-30** begin with alkyl halides). If an alcohol R'OH is used instead of water, the ester RCH_2COOR' is isolated directly.[213] Similarly, ammonia gives the amide. Other catalysts are sometimes used (e.g., colloidal platinum, copper, etc.), but occasionally the diazo ketone is simply heated or photolyzed in the presence of water, an alcohol, or ammonia, with no catalyst at all.[214] The photolysis method[215] often gives better results than the silver catalysis method. Of course, diazo ketones prepared in any other way also give the rearrangement.[216] The reaction is of wide scope. The R group may be alkyl or aryl and may contain many functional groups including unsaturation, but not including groups acidic enough to react with CH_2N_2 or diazo ketones (e.g., **10-5** and **10-19**). Sometimes the reaction is performed with other diazoalkanes (i.e., $R'CHN_2$) to give RCHR'COOH. The reaction has often been used for ring contraction of cyclic diazo ketones,[217] such as **72**.[218]



72

[211]For reviews, see Meier, H.; Zeller, K. *Angew. Chem. Int. Ed.* ***1975***, *14*, 32; Kirmse, W. *Carbene Chemistry*, 2nd ed., Academic Press, NY, ***1971***, pp. 475–493; Rodina, L.L.; Korobitsyna, I.K. *Russ. Chem. Rev.* ***1967***, *36*, 260; For a review of rearrangements of diazo and diazonium compounds, see Whittaker, D., in Patai, S. *The Chemistry of Diazonium and Diazo Compounds*, pt. 2, Wiley, NY, ***1978***, pp. 593–644.

[212]For a review, see Kirmse, W. *Eur. J. Org. Chem.* ***2002***, 2193. For a microwave-induced Wolff rearrangement, see Sudrik, S.G.; Chavan, S.P.; Chandrakumar, K.R.S.; Pal, S.; Date, S.K.; Chavan, S.P.; Sonawane, H.R. *J. Org. Chem.* ***2002***, *67*, 1574.

[213]For an ultrasound-induced version of this variation, see Winum, J.-Y.; Kamal, M.; Leydet, A.; Roque, J.-P.; Montero, J.-L. *Tetrahedron Lett.* ***1996***, *37*, 1781.

[214]For a list of methods, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1850–1851.

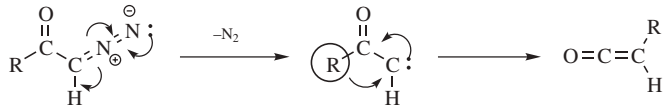
[215]For reviews of the photolysis method, see Regitz, M.; Maas, G. *Diazo Compounds*, Academic Press, NY, ***1986***, pp. 185–195; Ando, W., in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***,78, pp. 458–475.

[216]For a method of conducting the reaction with trimethylsilyldiazomethane instead of CH_2N_2, see Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* ***1980***, *21*, 4461.

[217]For a review, see Redmore, D.; Gutsche, C.D. *Carbocyclic Ring Expansion Reactions*, Academic Press, NY, ***1968***, pp. 125–136.

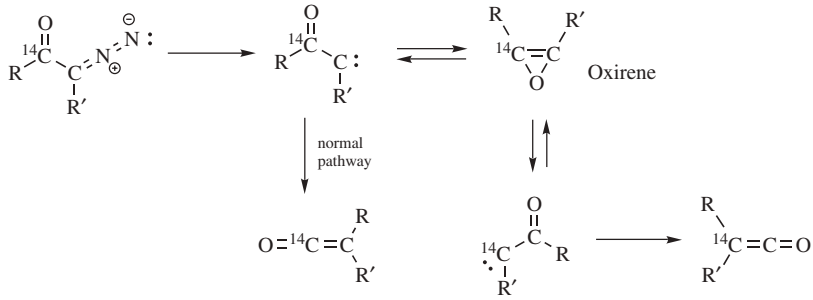
[218]Korobitsyna, I.K.; Rodina, L.L.; Sushko, T.P. *J. Org. Chem. USSR* ***1968***, *4*, 165; Jones, Jr., M.; Ando, W. *J. Am. Chem. Soc.* ***1968***, *90*, 2200. See Lee, Y.R.; Suk, J.Y.; Kim, B.S. *Tetrahedron Lett.* ***1999***, *40*, 8219.

The mechanism is generally regarded as involving formation of a carbene.[219] It is the divalent carbon that has the open sextet and to which the migrating group brings its electron pair:



The actual product of the reaction is thus the ketene, which then reacts with water (**15-3**), an alcohol (**15-5**), or ammonia or an amine (**15-8**). Particularly stable ketenes[220] (e.g., $Ph_2C{=}C{=}O$) have been isolated and others have been trapped in other ways (e.g., as β-lactams,[221] **16-96**). The purpose of the catalyst is not well understood, though many suggestions have been made. This mechanism is strictly analogous to that of the Curtius rearrangement (**18-14**). Although the mechanism as shown above involves a free carbene and there is much evidence to support this,[222] it is also possible that at least in some cases the two steps are concerted and a free carbene is absent.

When the Wolff rearrangement is carried out photochemically, the mechanism is basically the same,[215] but another pathway can intervene. Some of the ketocarbene originally formed can undergo a carbene–carbene rearrangement, through an oxirene intermediate.[223] This was shown by ^{14}C labeling experiments, where



diazo ketones labeled in the carbonyl group gave rise to ketenes that bore the label at both C=C carbons.[224] In general, the smallest degree of scrambling (and thus of

[219]See Scott, A.P.; Platz, M.S.; Radom, L. *J. Am. Chem. Soc.* ***2001***, *123*, 6069.

[220]In some cases, ketenes are subject to rearrangement, see Farlow, R.A.; Thamatloor, D.A.; Sunoj, R.B.; Hadad, C.M. *J. Org. Chem.* ***2002***, *67*, 3257.

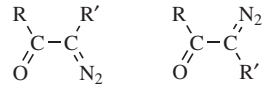
[221]Kirmse, W.; Horner, L. *Chem. Ber.* ***1956***, *89*, 2759; also see, Horner, L.; Spietschka, E. *Chem. Ber.* ***1956***, *89*, 2765.

[222]For a summary of evidence on both sides of the question, see Kirmse, W. *Carbene Chemistry*, 2nd ed., Academic Press, NY, ***1971***, pp. 476–480. See also, Torres, M.; Ribo, J.; Clement, A.; Strausz, O.P. *Can. J. Chem.* ***1983***, *61*, 996; Tomoika, H.; Hayashi, N.; Asano, T.; Izawa, Y. *Bull. Chem. Soc. Jpn.* ***1983***, *56*, 758.

[223]For a review of oxirenes, see Lewars, Y. *Chem. Rev.* ***1983***, *83*, 519.

[224]Fenwick, J.; Frater, G.; Ogi, K.; Strausz, O.P. *J. Am. Chem. Soc.* ***1973***, *95*, 124; Zeller, K. *Chem. Ber.* ***1978***, *112*, 678. See also, Thornton, D.E.; Gosavi, R.K.; Strausz, O.P. *J. Am. Chem. Soc.* ***1970***, *92*, 1768; Russell, R.L.; Rowland, F.S. *J. Am. Chem. Soc.* ***1970***, *92*, 7508; Majerski, Z.; Redvanly, C.S. *J. Chem. Soc., Chem. Commun.* ***1972***, 694.

the oxirene pathway) was found when R′ = H. An intermediate believed to be an oxirene has been detected by laser spectroscopy.[225] The oxirene pathway is not found in the thermal Wolff rearrangement. It is likely that an excited singlet state of the carbene is necessary for the oxirene pathway to intervene.[226] In the photochemical process, ketocarbene intermediates, in the triplet state, have been isolated in an Ar matrix at 10–15 K, where they have been identified by UV–visible, IR, and esr spectra.[227] These intermediates went on to give the rearrangement via the normal pathway, with no evidence for oxirene intermediates.



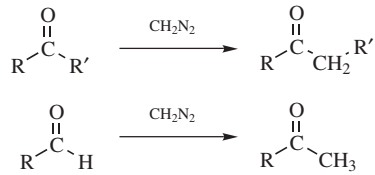
s-(*Z*) *s*-(*E*)

The diazo ketone can exist in two conformations, called *s*-(*E*) and *s*-(*Z*). Studies have shown that Wolff rearrangement takes place preferentially from the *s*-(*Z*) conformation.[228]

OS **III**, 356; **VI**, 613, 840.

18-9 Homologation of Aldehydes and Ketones

Methylene-insertion



Aldehydes and ketones[229] can be converted to their homologs with diazomethane.[230] Several other reagents[231] are also effective, including Me_3SiI, and then silica gel,[232] or $LiCH(B–OCH_2CH_2O–)_2$.[233] With the diazomethane reaction,

[225]Tanigaki, K.; Ebbesen, T.W. *J. Am. Chem. Soc.* ***1987***, *109*, 5883. See also, Bachmann, C.; N'Guessan, T.Y.; Debû, F.; Monnier, M.; Pourcin, J.; Aycard, J.; Bodot, H. *J. Am. Chem. Soc.* ***1990***, *112*, 7488.

[226]Csizmadia, I.G.; Gunning, H.E.; Gosavi, R.K.; Strausz, O.P. *J. Am. Chem. Soc.* ***1973***, *95*, 133.

[227]McMahon, R.J.; Chapman, O.L.; Hayes, R.A.; Hess, T.C.; Krimmer, H. *J. Am. Chem. Soc.* ***1985***, *107*, 7597.

[228]Kaplan, F.; Mitchell, M.L. *Tetrahedron Lett.* ***1979***, 759; Tomioka, H.; Okuno, H.; Izawa, Y. *J. Org. Chem.* ***1980***, *45*, 5278.

[229]For a homologation of carboxylic esters RCOOEt → RCH_2COOEt, which goes by an entirely different pathway, see Kowalski, C.J.; Haque, M.S.; Fields, K.W. *J. Am. Chem. Soc.* ***1985***, *107*, 1429. Also see, Yamamoto, M.; Nakazawa, M.; Kishikawa, K.; Kohmoto, S. *Chem. Commun.* ***1996***, 2353.

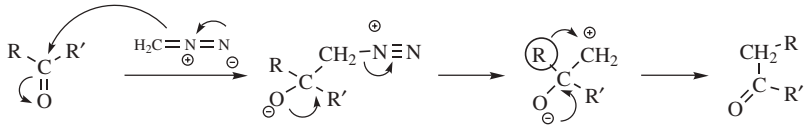
[230]For a review, see Gutsche, C.D. *Org. React.* ***1954***, *8*, 364.

[231]See Taylor, E.C.; Chiang, C.; McKillop, A. *Tetrahedron Lett.* ***1977***, 1827; Villieras, J.; Perriot, P.; Normant, J.F. *Synthesis* ***1979***, 968; Aoyama, T.; Shioiri, T. *Synthesis* ***1988***, 228.

[232]Lemini, C.; Ordoñez, M.; Pérez-Flores, J.; Cruz-Almanza, R. *Synth. Commun.* ***1995***, *25*, 2695.

[233]Schummer, D.; Höfle, G. *Tetrahedron* ***1995***, *51*, 11219.

formation of an epoxide (**16-46**) is a side reaction. Although this reaction appears superficially to be similar to the insertion of carbenes into C–H bonds, **12-21** (and IUPAC names it as an insertion), the mechanism is quite different. This is a true rearrangement and no free carbene is involved. The first step is an addition to the C=O bond:



73

The betaine **73** can sometimes be isolated. As shown in **16-46**, intermediate **73** can also go to the epoxide. The evidence for this mechanism is summarized in the review by Gutsche.[230] Note that this mechanism is essentially the same as in the apparent "insertions" of oxygen (**18-19**) and nitrogen (**18-16**) into ketones.

Aldehydes give fairly good yields of methyl ketones; that is, hydrogen migrates in preference to alkyl. The most abundant side product is not the homologous aldehyde, but the epoxide. However, the yield of aldehyde at the expense of methyl ketone can be increased by the addition of methanol. If the aldehyde contains electron-withdrawing groups, the yield of epoxides is increased and the ketone is formed in smaller amounts, if at all. Ketones give poorer yields of homologous ketones. Epoxides are usually the predominant product here, especially when one or both R groups contain an electron-withdrawing group. The yield of ketones also decreases with increasing length of the chain. The use of a Lewis acid increases the yield of ketone.[234] Cyclic ketones,[235] three-membered[236] and larger, behave particularly well and give good yields of ketones with the ring expanded by one.[237] Aliphatic diazo compounds ($RCHN_2$ and R_2CN_2) are sometimes used instead of diazomethane, with the expected results.[238] Ethyl diazoacetate can be used analogously, in the presence of a Lewis acid or of triethyloxonium fluoroborate,[239] to

[234]For a review of homologations catalyzed by Lewis acids, see Müller, E.; Kessler, H.; Zeeh, B. *Fortschr. Chem. Forsch.* ***1966***, *7*, 128, see pp. 137–150.

[235]For other methods for the ring enlargement of cyclic ketones, see Krief, A.; Laboureur, J.L. *Tetrahedron Lett.* ***1987***, *28*, 1545; Krief, A.; Laboureur, J.L.; Dumont, W. *Tetrahedron Lett.* ***1987***, *28*, 1549; Abraham, W.D.; Bhupathy, M.; Cohen, T. *Tetrahedron Lett.* ***1987***, *28*, 2203; Trost, B.M.; Mikhail, G.K. *J. Am. Chem. Soc.* ***1987***, *109*, 4124.

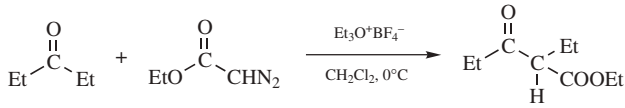
[236]For example, see Turro, N.J.; Gagosian, R.B. *J. Am. Chem. Soc.* ***1970***, *92*, 2036.

[237]For a review, see Gutsche, C.D.; Redmore, D. *Carbocyclic Ring Expansion Reactions*, Academic Press, NY, ***1968***, pp. 81–98. For a review pertaining to bridged bicyclic ketones, see Krow, G.R. *Tetrahedron* ***1987***, *43*, 3.

[238]For example, see Smith, R.F. *J. Org. Chem.* ***1960***, *25*, 453; Warner, C.R.; Walsh, Jr., E.J.; Smith, R.F. *J. Chem. Soc.* ***1962***, 1232; Loeschorn, C.A.; Nakajima, M.; Anselme, J. *Bull. Soc. Chim. Belg.* ***1981***, *90*, 985.

[239]Mock, W.L.; Hartman, M.E. *J. Org. Chem.* ***1977***, *42*, 459, 466; Baldwin, S.W.; Landmesser, N.G. *Synth. Commun.* ***1978***, *8*, 413.

give a β-keto ester, such as **74**.



74

When unsymmetrical ketones were used in this reaction (with BF_3 as catalyst), the less highly substituted carbon preferentially migrated.[240] The reaction can be made regioselective by applying this method to the α-halo ketone, in which case only the other carbon migrates.[241] The ethyl diazoacetate procedure has also been applied to the acetals or ketals of α,β-unsaturated aldehydes and ketones.[242]

Bicyclic ketones can be expanded to form monocyclic ketones in the presence of certain reagents. Treatment of a bicyclo[4.1.0]hexan-4-one derivative with SmI_2 led to a cyclohexanone.[243] The SmI_2 also converts α-halomethyl cyclic ketones to the next larger ring ketone[244] and cyclic ketones to the next larger ring ketone in the presence of CH_2I_2.[245] α-Chloro-α-3-iodopropylcyclobutanones were converted to cycloheptanones using radical conditions (Bu_3SnH/AIBN).[246]

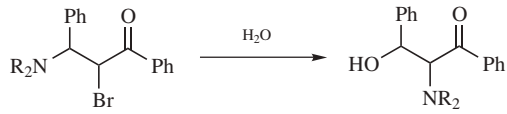
Another homologation reaction converts an aldehyde to its tosyl hydrazone, and subsequent reaction with an aldehyde and NaOEt/EtOH give a ketone.[247] The reaction of an aldehyde with vinyl acetate and barium hydroxide gives the homologated conjugated aldehyde.[248]

OS **IV**, 225, 780. For homologation of carboxyl acid derivatives, see OS **IX**, 426

B. Carbon-to-Carbon Migrations of Other Groups

18-10 Migrations of Halogen, Hydroxyl, Amino, and so on

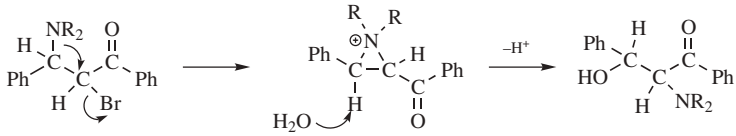
Hydroxy-de-bromo-*cine*-substitution, and so on



When a nucleophilic substitution is carried out on a substrate that has a neighboring group (p. 446) on the adjacent carbon, a cyclic intermediate can be generated

[240]Liu, H.J.; Majumdar, S.P. *Synth. Commun.* ***1975***, *5*, 125.
[241]Dave, V.; Warnhoff, E.W. *J. Org. Chem.* ***1983***, *48*, 2590.
[242]Doyle, M.P.; Trudell, M.L.; Terpstra, J.W. *J. Org. Chem.* ***1983***, *48*, 5146.
[243]Lee, P.H.; Lee, J. *Tetrahedron Lett.* ***1998***, *39*, 7889.
[244]Hasegawa, E.; Kitazume, T.; Suzuki, K.; Tosaka, E. *Tetrahedron Lett.* ***1998***, *39*, 4059.
[245]Fukuzawa, S.; Tsuchimoto, T. *Tetrahedron Lett.* ***1995***, *36*, 5937.
[246]Zhang, W.; Dowd, P. *Tetrahedron Lett.* ***1992***, *33*, 3285. For an example generating larger rings, see Dowd, P.; Choi, S.-C. *Tetrahedron* ***1992***, *48*, 4773.
[247]Angle, S.R.; Neitzel, M.L. *J. Org. Chem.* ***2000***, *65*, 6458.
[248]Mahata, P.K.; Barun, O.; Ila, H.; Junjappa, H. *Synlett* ***2000***, 1345.

that is opened on the opposite side, resulting in migration of the neighboring group. In the example shown above (NR_2 = morpholino),[249] the reaction took place via an aziridinium salt **75** to give an α-amino-β-hydroxy ketone.

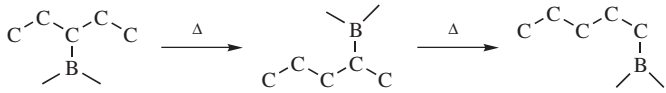


75

Sulfonate esters and halides can also migrate in this reaction.[250] α-Halo and α-acyloxy epoxides undergo ready rearrangement to α-halo and α-acyloxy ketones, respectively.[251] These substrates are very prone to rearrange, and often do so on standing without a catalyst, though in some cases an acid catalyst is necessary. The reaction is essentially the same as the rearrangement of epoxides shown in **18-2**, except that in this case halogen or acyloxy is the migrating group (as shown above; however, it is also possible for one of the R groups (alkyl, aryl, or hydrogen) to migrate instead, and mixtures are sometimes obtained).

18-11 Migration of Boron

Hydro,dialkylboro-interchange, and so on



Boranes are prepared by the reaction of $BH_3(B_2H_6)$ or an alkylborane with an alkene (**15-16**). When a nonterminal borane is heated at temperatures ranging from 100 to 200°C, the boron moves toward the end of the chain.[252] The reaction is catalyzed by small amounts of borane or other species containing B–H bonds.

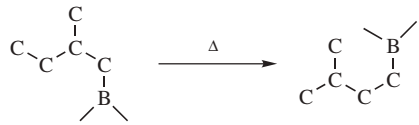
[249]Southwick, P.L.; Walsh, W.L. *J. Am. Chem. Soc.* ***1955***, *77*, 405. See also, Suzuki, K.; Okano, K.; Nakai, K.; Terao, Y.; Sekiya, M. *Synthesis* ***1983***, 723.

[250]For a review of Cl migrations, see Peterson, P.E. *Acc. Chem. Res.* ***1971***, *4*, 407. See also, Loktev, V.F.; Korchagina, D.V.; Shubin, V.G.; Koptyug, V.A. *J. Org. Chem. USSR* ***1977***, *13*, 201; Dobronravov, P.N.; Shteingarts, V.D. *J. Org. Chem. USSR* ***1977***, *13*, 420. For examples of Br migration, see Gudkova, A.S.; Uteniyazov, K.; Reutov, O.A. *Doklad. Chem.* ***1974***, *214*, 70; Brusova, G.P.; Gopius, E.D.; Smolina, T.A.; Reutov, O.A. *Doklad. Chem.* ***1980***, *253*, 334. For a review of F migration (by several mechanisms) see Kobrina, L.S.; Kovtonyuk, V.N. *Russ. Chem. Rev.* ***1988***, *57*, 62. For an example OH migration, see Cathcart, R.C.; Bovenkamp, J.W.; Moir, R.Y.; Bannard, R.A.B.; Casselman, A.A. *Can. J. Chem.* ***1977***, *55*, 3774. For a review of migrations of ArS and $Ar_2P(O)$, see Warren, S. *Acc. Chem. Res.* ***1978***, *11*, 403. See also, Aggarwal, V.K.; Warren, S. *J. Chem. Soc. Perkin Trans. 1* ***1987***, 2579.

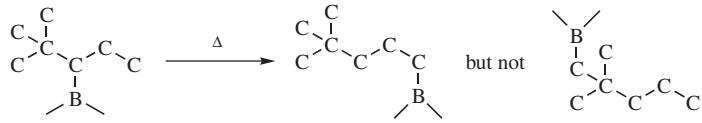
[251]For a review, see McDonald, R.N. *Mech. Mol. Migr.* ***1971***, *3*, 67.

[252]Brown, H.C. *Hydroboration*, W. A. Benjamin, NY, ***1962***, pp. 136–149, Brown, H.C.; Zweifel, G. *J. Am. Chem. Soc.* ***1966***, *88*, 1433. See also, Brown, H.C.; Racherla, U.S. *J. Organomet. Chem.* ***1982***, *241*, C37.

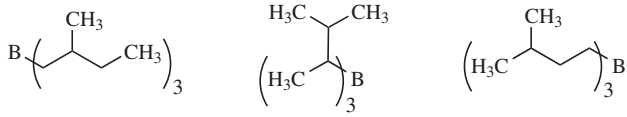
The boron can move past a branch, for example,



but not past a double branch, for example,



The reaction is an equilibrium: **76**, **77**, and **78** each gave a mixture containing ~40% **76**, 1% **77**, and 59% **78**. The migration can go quite a long distance. Thus $(C_{11}H_{23}CHC_{11}H_{23})_3B$ was completely converted to $(C_{23}H_{47})_3B$, involving a migration of 11 positions.[253] If the boron is on a cycloalkyl ring, it can move around

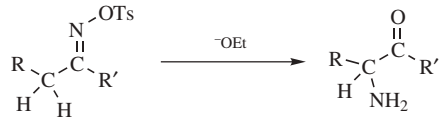


76 **77** **78**

the ring; if any alkyl chain is also on the ring, the boron may move from the ring to the chain, ending up at the end of the chain.[254] The reaction is useful for the migration of double bonds in a controlled way (see **12-2**). The mechanism may involve a π complex, at least partially.[255]

18-12 The Neber Rearrangement

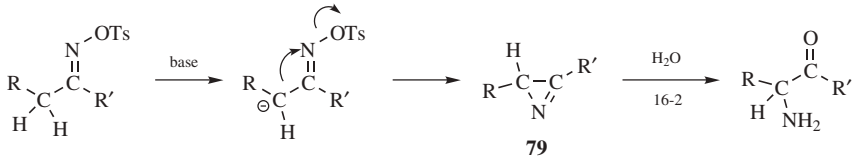
Neber oxime tosylate-amino ketone rearrangement



α-Amino ketones can be prepared by treatment of ketoxime tosylates with a base, such as ethoxide ion or pyridine.[256] This reaction is called the *Neber rearrangement*. The R group is usually aryl, though the reaction has been carried out with

[253]Logan, T.J. *J. Org. Chem.* ***1961***, *26*, 3657.
[254]Brown, H.C.; Zweifel, G. *J. Am. Chem. Soc.* ***1967***, *89*, 561.
[255]See Wood, S.E.; Rickborn, B. *J. Org. Chem.* ***1983***, *48*, 555; Field, L.D.; Gallagher, S.P. *Tetrahedron Lett.* ***1985***, *26*, 6125.
[256]For a review, see Conley, R.T.; Ghosh, S. *Mech. Mol. Migr.* ***1971***, *4*, 197, pp. 289–304.

R = alkyl or hydrogen. The R′ group may be alkyl, or aryl but not hydrogen. The Beckmann rearrangement (**18-17**) and the abnormal Beckmann reaction (elimination to the nitrile, **17-30**) may be side reactions, although these generally occur in acid media. A similar rearrangement is given by *N,N*-dichloroamines of the type $RCH_2CH(NCl_2)R'$, where the product is also $RCH(NH_2)COR'$.[257] The mechanism of the Neber rearrangement is via an azirine intermediate **79**.[258]



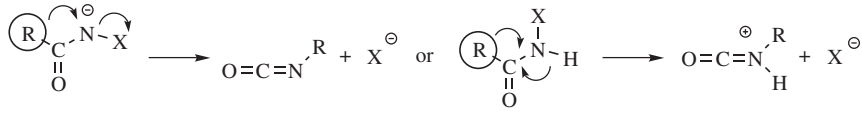
79

The best evidence for this mechanism is that the azirine intermediate has been isolated.[258,259] In contrast to the Beckmann rearrangement, this one is sterically indiscriminate:[260] Both a syn and an anti ketoxime give the same product. The mechanism as shown above consists of three steps. However, it is possible that the first two steps are concerted, and it is also possible that what is shown as the second step is actually two steps: loss of OTs to give a nitrene, and formation of the azirine. In the case of the dichloroamines, HCl is first lost to give $RCH_2C(=NCl)R'$, which then behaves analogously.[261] *N*-Chloroimines prepared in other ways also give the reaction.[262]

OS **V**, 909; **VII**, 149.

C. Carbon-to-Nitrogen Migrations of R and AR

The reactions in this group are nucleophilic migrations from a carbon to a nitrogen atom. In each case the nitrogen atom either has six electrons in its outer shell (and thus invites the migration of a group carrying an electron pair) or else loses a nucleofuge concurrently with the migration (p. 1560). Reactions **18-13**–**18-16** are used to prepare amines from acid derivatives. Reactions **18-16** and **18-17** are used to prepare amines from ketones. The mechanisms of **18-13**–**18-16** (with carboxylic acids) are very similar and follow one of two patterns:



[257]Baumgarten, H.E.; Petersen, H.E. *J. Am. Chem. Soc.* ***1960***, *82*, 459, and references cited therein.
[258]Cram, D.J.; Hatch, M.J. *J. Am. Chem. Soc.* ***1953***, *75*, 33; Hatch, M.J.; Cram, D.J. *J. Am. Chem. Soc.* ***1953***, *75*, 38.
[259]Neber, P.W.; Burgard, A. *Liebigs Ann. Chem.* ***1932***, *493*, 281; Parcell, R.F. *Chem. Ind.* (*London*) ***1963***, 1396.
[260]House, H.O.; Berkowitz, W.F. *J. Org. Chem.* ***1963***, *28*, 2271.
[261]For example, see Nakai, M.; Furukawa, N.; Oae, S. *Bull. Chem. Soc. Jpn.* ***1969***, *42*, 2917.
[262]Baumgarten, H.E.; Petersen, J.M.; Wolf, D.C. *J. Org. Chem.* ***1963***, *28*, 2369.

Some of the evidence[263] is (*1*) configuration is retained in R (p. 1563); (*2*) the kinetics are first order; (*3*) intramolecular rearrangement is shown by labeling; and (*4*) no rearrangement occurs *within* the migrating group, for example, a neopentyl group on the carbon of the starting material is still a neopentyl group on the nitrogen of the product.

In many cases, it is not certain whether the nucleofuge X is lost first, creating an intermediate nitrene[264] or nitrenium ion, or whether migration and loss of the nucleofuge are simultaneous, as shown above.[265] It is likely that both possibilities can exist, depending on the substrate and reaction conditions.

18-13 The Hofmann Rearrangement

Bis(hydrogen)-(2/ 1/*N*-alkyl)-*migro*-detachment (formation of isocyanate)

$$RCONH_2 + NaOBr \longrightarrow R{-}N{=}C{=}O \xrightarrow[\textbf{16-2}]{\text{hydrolysis}} RNH_2$$

In the *Hofmann rearrangement*, an unsubstituted amide is treated with sodium hypobromite (or sodium hydroxide and bromine, which is essentially the same thing) to give a primary amine that has one carbon fewer than the starting amide.[266] The actual product is the isocyanate, but this compound is seldom isolated[267] since it is usually hydrolyzed under the reaction conditions. The R group may be alkyl or aryl, but if it is an alkyl group of more than about six or seven carbons, low yields are obtained unless Br_2 and NaOMe are used instead of Br_2 and NaOH.[268] Another modification uses NBS/NaOMe.[269] Under these conditions the product of addition to the isocyanate is the carbamate RNHCOOMe (**16-8**), which is easily isolated or can be hydrolyzed to the amine. Side reactions when NaOH is the base are formation of ureas RNHCONHR and acylureas RCONHCONHR by addition, respectively, of RNH_2 and $RCONH_2$ to RNCO (**16-20**). If acylureas are desired, they can be made the main products by using only one-half of the usual quantities of Br_2 and NaOH. Another side product, but only from primary R, is the nitrile derived from oxidation of RNH_2 (**19-5**). Imides react to give amino acids, for example, phthalimide gives *o*-aminobenzoic acid. α-Hydroxy and α-halo amides give aldehydes and ketones by way of the unstable α-hydroxy- or α-haloamines. However, a side product with an α-halo amide is a *gem*-dihalide. Ureas analogously give hydrazines.

[263]For a discussion of this mechanism and the evidence for it, see Smith, P.A.S., in de Mayo, P. *Molecular Rearrangements*, Vol. 1, Wiley, NY, ***1963***, Vol. 1, pp. 258–550.

[264]For a review of rearrangements involving nitrene intermediates, see Boyer, J.H. *Mech. Mol. Migr.* ***1969***, *2*, 267. See also, Ref. 282.

[265]The question is discussed by Lwowski, W., in Lwowski *Nitrenes*, Wiley, NY, ***1970***, pp. 217–221.

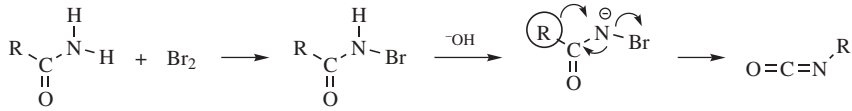
[266]For a review, see Wallis, E.S.; Lane, J.F. *Org. React.* ***1946***, *3*, 267.

[267]If desired, the isocyanate can be isolated by the use of phase-transfer conditions: see Sy, A.O.; Raksis, J.W. *Tetrahedron Lett.* ***1980***, *21*, 2223.

[268]For an example of the use of this method at low temperatures, see Radlick, P.; Brown, L.R. *Synthesis* ***1974***, 290.

[269]Huang, X.; Keillor, J.W. *Tetrahedron Lett.* ***1997***, *38*, 313.

The mechanism follows the pattern outlined on p. 1606.



80

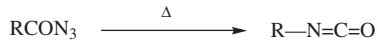
The first step is an example of **12-52** and intermediate *N*-halo amides (**80**) have been isolated. In the second step, **80** lose a proton to the base. Compound **80** is acidic because of the presence of two electron-withdrawing groups (acyl and halo) on the nitrogen. It is possible that the third step is actually two steps: loss of bromide to form a nitrene, followed by the actual migration, but most of the available evidence favors the concerted reaction.[270] A similar reaction can be effected by the treatment of amides with lead tetraacetate.[271] Among other reagents that convert $RCONH_2$ to RNH_2 (R = alkyl, but not aryl) are phenyliodosyl bis(trifluoroacetate) $PhI(OCOCF_3)_2$[272] and hydroxy(tosyloxy)iodobenzene PhI(OH)OTs.[273] A mixture of NBS, $Hg(OAc)_2$, and R'OH is one of several reagent mixtures that convert an amide $RCONH_2$ to the carbamate RNHCOOR' (R = primary, secondary, or tertiary alkyl or aryl) in high yield.[274] A mixture of NBS and DBU (p. 1132) in methanol gives the carbamate,[275] as does electrolysis in methanol.[276]

A variation of the Hofmann rearrangement treated a β-hydroxy primary amide with $PhI(O_2CCF_3)_2$ in aqueous acetonitrile, giving an isocyanate via –CON–I, which reacts with the hydroxyl group intramolecularly to give a cyclic carbamate.[277] Note that carbamates are converted to isocyanates by heating with Montmorillonite K10.[278]

OS **II**, 19, 44, 462; **IV**, 45; **VIII**, 26, 132.

18-14 The Curtius Rearrangement

Dinitrogen-(2/ → 1/*N*-alkyl)-*migro*-detachment



[270]See, for example, Imamoto, T.; Tsuno, Y.; Yukawa, Y. *Bull. Chem. Soc. Jpn.* ***1971***, *44*, 1632, 1639, 1644; Imamoto, T.; Kim, S.; Tsuno, Y.; Yukawa, Y. *Bull. Chem. Soc. Jpn.* ***1971***, *44*, 2776.

[271]Acott, B.; Beckwith, A.L.J.; Hassanali, A. *Aust. J. Chem.* ***1968***, *21*, 185, 197; Baumgarten, H.E.; Smith, H.L.; Staklis, A. *J. Org. Chem.* ***1975***, *40*, 3554.

[272]Loudon, G.M.; Radhakrishna, A.S.; Almond, M.R.; Blodgett, J.K.; Boutin, R.H. *J. Org. Chem.* ***1984***, *49*, 4272; Boutin, R.H.; Loudon, G.M. *J. Org. Chem.* ***1984***, *49*, 4277; Pavlides, V.H.; Chan, E.D.; Pennington, L.; McParland, M.; Whitehead, M.; Coutts, I.G.C. *Synth. Commun.* ***1988***, *18*, 1615.

[273]Vasudevan, A.; Koser, G.F. *J. Org. Chem.* ***1988***, *53*, 5158.

[274]Jew, S.; Park, H.G.; Park, H.; Park, M.; Cho, Y. *Tetrahedron Lett.* ***1990***, *31*, 1559.

[275]Huang, X.; Seid, M.; Keillor, J.W. *J. Org. Chem.* ***1997***, *62*, 7495.

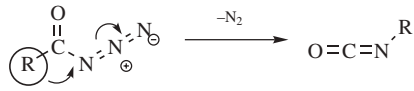
[276]Matsumura, Y.; Maki, T. ; Satoh, Y. *Tetrahedron Lett.* ***1997***, *38*, 8879.

[277]Yu, C.; Jiang, Y.; Liu, B.; Hu, L. *Tetrahedron Lett.* ***2001***, *42*, 1449.

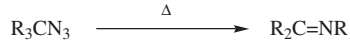
[278]Uriz, P.; Serra, M.; Salagre, P.; Castillon, S.; Claver, C.; Fernandez, E. *Tetrahedron Lett.* ***2002***, *43*, 1673.

The *Curtius rearrangement* involves the pyrolysis of acyl azides to yield isocyanates.[279] The reaction gives good yields of isocyanates, since no water is present to hydrolyze them to the amine. Of course, they can be subsequently hydrolyzed, and indeed the reaction *can* be carried out in water or alcohol, in which case the products are amines, carbamates, or acylureas, as in **18-13**.[280] This is a very general reaction and can be applied to almost any carboxylic acid: aliphatic, aromatic, alicyclic, heterocyclic, unsaturated, and containing many functional groups. Acyl azides can be prepared as in **10-43** or by treatment of acylhydrazines (hydrazides) with nitrous acid (analogous to **12-49**). The Curtius rearrangement is catalyzed by Lewis or protic acids, but these are usually not necessary for good results.

The mechanism is similar to that in **18-13** to give an isocyanate. Also note the exact analogy between this reaction and **18-8**. However, in this case, there is no evidence for a free nitrene and it is probable that the steps are concerted.[281]



Alkyl azides can be similarly pyrolyzed to give imines, in an analogous reaction:[282]



The R groups may be alkyl, aryl, or hydrogen, though if hydrogen migrates, the product is the unstable $R_2C{=}NH$. The mechanism is essentially the same as that of the Curtius rearrangement. However, in pyrolysis of tertiary alkyl azides, there is evidence that free alkyl nitrenes are intermediates.[283] The reaction can also be carried out with acid catalysis, in which case lower temperatures can be used, though the acid may hydrolyze the imine (**16-2**). Cycloalkyl azides give

[279]For a review, see Banthorpe, D.V., in Patai, S. *The Chemistry of the Azido Group*, Wiley, NY, ***1971***, pp. 397–405.

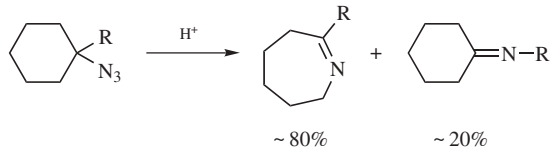
[280]For a variation that conveniently produces the amine directly, see Pfister, J.R.; Wyman, W.E. *Synthesis* ***1983***, 38. See also, Capson, T.L.; Poulter, C.D. *Tetrahedron Lett.* ***1984***, *25*, 3515.

[281]See, for example, Lwowski, W. *Angew. Chem. Int. Ed.* ***1967***, *6*, 897; Linke, S.; Tissue, G.T.; Lwowski, W. *J. Am. Chem. Soc.* ***1967***, *89*, 6308; Smalley, R.K.; Bingham, T.E. *J. Chem. Soc. C* ***1969***, 2481.

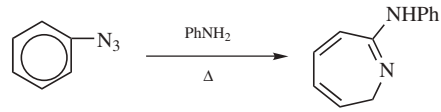
[282]For a treatise on azides, which includes discussion of rearrangement reactions, see Scriven, E.F.V. *Azides and Nitrenes*, Academic Press, NY, ***1984***. For a review of rearrangements of alkyl and aryl azides, see Stevens, T.S.; Watts, W.E. *Selected Molecular Rearrangements*, Van Nostrand-Reinhold, Princeton, NJ, ***1973***, pp. 45–52. For reviews of the formation of nitrenes from alkyl and aryl azides, see, in Lwowski, W. *Nitrenes*, Wiley, NY, ***1970***, the chapters by Lewis, F.D.; Saunders, Jr., W.H. pp. 47–97, 47–78 and by Smith, P.A.S. pp. 99–162.

[283]Abramovitch, R.A.; Kyba, E.P. *J. Am. Chem. Soc.* ***1974***, *96*, 480; Montgomery, F.C.; Saunders, Jr., W.H. *J. Org. Chem.* ***1976***, *41*, 2368.

ring expansion.[284]



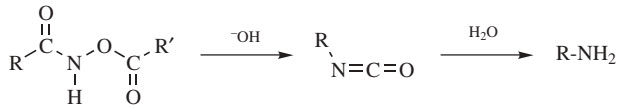
Aryl azides also give ring expansion on heating, for example,[285]



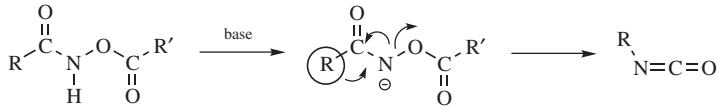
OS **III**, 846; **IV**, 819; **V**, 273; **VI**, 95, 910. Also see, OS **VI**, 210.

18-15 The Lossen Rearrangement

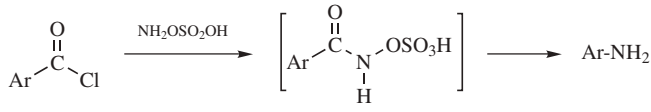
Hydro,acetoxy-(2/ → 1*N*-alkyl)-*migro*-detachment



The *O*-acyl derivatives of hydroxamic acids[286] give isocyanates when treated with bases or sometimes even just on heating, in a reaction known as the *Lossen rearrangement*.[287] The mechanism is similar to that of **18-13** and **18-14**:



In a similar reaction, aromatic acyl halides are converted to amines in one laboratory step by treatment with hydroxylamine-*O*-sulfonic acid.[288]



A chiral Lossen rearrangement is known.[289]

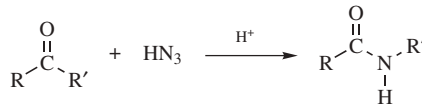
[284]Smith, P.A.S.; Lakritz, J. cited in Smith, P.A.S., in de Mayo, P. *Molecular Rearrangments*, Vol. 1, Wiley, NY, ***1963***, p. 474.
[285]Huisgen, R.; Vossius, D.; Appl, M. *Chem. Ber.* ***1958***, *91*, 1,12.
[286]For a review of hydroxamic acids, see Bauer, L.; Exner, O. *Angew. Chem. Int. Ed.* ***1974***, *13*, 376.
[287]For an example, see Salomon, C.J.; Breuer, E. *J. Org. Chem*, ***1997***, *62*, 3858.
[288]Wallace, R.G.; Barker, J.M.; Wood, M.L. *Synthesis* ***1990***, 1143.
[289]Chandrasekhar, S.; Sridhar, M. *Tetrahedron Asymmetry* ***2000***, *11*, 3467.

18-16 The Schmidt Reaction

$$\text{RCOOH} + \text{HN}_3 \xrightarrow{\text{H}^+} \text{R—N=C=O} \xrightarrow{\text{H}_2\text{O}} \text{RNH}_2$$

There are actually three reactions called by the name *Schmidt reaction*, involving the addition of hydrazoic acid to carboxylic acids, aldehydes and ketones, and alcohols and alkenes.[290] The most common is the reaction with carboxylic acids, illustrated above.[291] Sulfuric acid is the most common catalyst, but Lewis acids have also been used. Good results are obtained for aliphatic R, especially for long chains. When R is aryl, the yields are variable, being best for sterically hindered compounds like mesitoic acid. This method has the advantage over **18-13** and **18-14** in that there is just one laboratory step from the acid to the amine, but conditions are more drastic.[292] Under the acid conditions employed, the isocyanate is virtually never isolated.

The reaction between a ketone and hydrazoic acid is a method for ''insertion'' of NH between the carbonyl group and one R group, converting a ketone into an amide.[293]



Either or both of the R groups may be aryl. In general, dialkyl ketones and cyclic ketones react more rapidly than alkyl aryl ketones, and these more rapidly than diaryl ketones. The latter require sulfuric acid and do not react in concentrated HCl, which is strong enough for dialkyl ketones. Dialkyl and cyclic ketones react sufficiently faster than diaryl or aryl alkyl ketones or carboxylic acids or alcohols so that these functions may be present in the same molecule without interference. Cyclic ketones give lactams:[294]

[290]For a review, see Banthorpe, D.V., in Patai, S. *The Chemistry of the Azido Group*, Wiley, NY, ***1971***, pp. 405–434.

[291]For a review, see Koldobskii, G.I.; Ostrovskii, V.A.; Gidaspov, B.V. *Russ. Chem. Rev.* ***1978***, *47*, 1084.

[292]For a comparision of reactions **18-13**–**18-16** as methods for converting an acid to an amine, see Smith, P.A.S. *Org. React.* ***1946***, *3*, 337, 363–366.

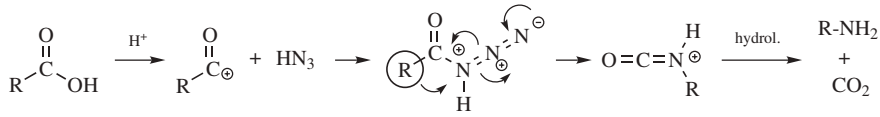
[293]For reviews, see Koldobskii, G.I.; Tereschenko, G.F.; Gerasimova, E.S.; Bagal, L.I. *Russ. Chem. Rev.* ***1971***, *40*, 835; Beckwith, A.L.J., in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 137–145.

[294]For a review with respect to bicyclic ketones, see Krow, G.R. *Tetrahedron* ***1981***, *37*, 1283.

With alkyl aryl ketones, it is the aryl group that generally migrates to the nitrogen, except when the alkyl group is bulky.[295] The reaction has been applied to a few aldehydes, but rarely. With aldehydes the product is usually the nitrile (**16-16**). Even with ketones, conversion to the nitrile is often a side reaction, especially with the type of ketone that gives **17-30**. A useful variation of the Schmidt reaction treats a cyclic ketone with an alkyl azide (RN_3)[296] in the presence of $TiCl_4$, generating a lactam.[297] An intramolecular Schmidt reaction gives bicyclic amines by treatment of a cyclic alkene having a pendant azidoalkyl group with $Hg(ClO_4)_2$, and then $NaBH_4$.[298] Another variation treats a silyl enol ether of a cyclic ketone with $TMSN_3$ and photolyzes the product with UV light to give a lactam.[299] αAzido cyclic ketones rearrangement to lactams under radical conditions (Bu_3SnH/AIBN).[300]

Alcohols and alkenes react with HN_3 to give alkyl azides,[301] which in the course of reaction rearrange in the same way as discussed in reaction **18-14**.[282] The Mitsunobu reaction (**10-17**) can be used to convert alcohols to alkyl azides, and an alternative reagent for azides, $(PhO)_2PON_3$, for use in the Mitsunobu is now available.[302]

There is evidence that the mechanism with carboxylic acids[293] is similar to that of **18-14**, except that it is the protonated azide that undergoes the rearrangement:[303]



The first step is the same as that of the $A_{AC}1$ mechanism (**16-59** which explains why good results are obtained with hindered substrates. The mechanism with ketones

[295]Exceptions to this statement have been noted in the case of cyclic aromatic ketones bearing electron-donating groups in ortho and para positions: Bhalerao, U.T.; Thyagarajan, G. *Can. J. Chem.* ***1968***, *46*, 3367; Tomita, M.; Minami, S.; Uyeo, S. *J. Chem. Soc. C* ***1969***, 183.

[296]See Furness, K.; Aubé, J. *Org. Lett.* ***1999***, *1*, 495.

[297]Desai, P.; Schildknegt, K.; Agrios, K.A.; Mossman, C.; Milligan, G.L.; Aubé, J. *J. Am. Chem. Soc.* ***2000***, *122*, 7226; Sahasrabudhe, K.; Gracias, V.; Furness, K.; Smith, B.T.; Katz, C.E.; Reddy, D.S.; Aubé, J. *J. Am. Chem. Soc.* ***2003***, *125*, 7914. For a variation using a ketal with TMSOTf see Mossman, C.J.; Aubé, J. *Tetrahedron*, ***1996***, *52*, 3403.

[298]Pearson, W.H.; Hutta, D.A.; Fang, W.-k. *J. Org. Chem.* ***2000***, *65*, 8326. See also, Wrobleski, A.; Aubé, J. *J. Org. Chem.* ***2001***, *66*, 886.

[299]Evans, P.A.; Modi, D.P. *J. Org. Chem.* ***1995***, *60*, 6662.

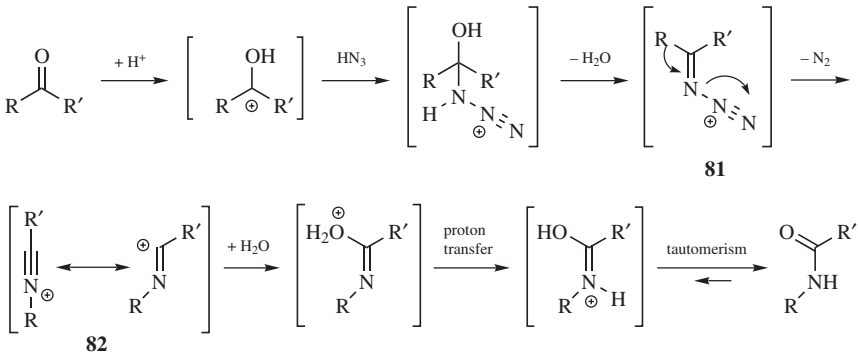
[300]Benati, L.; Nanni, D.; Sangiorgi, C.; Spagnolo, P. *J. Org. Chem.* ***1999***, *64*, 7836.

[301]For an example, see Kumar, H.M.S.; Reddy, B.V.S.; Anjaneyulu, S.; Yadav, J.S. *Tetrahedron Lett.* ***1998***, *39*, 7385. Also see, Saito, A.; Saito, K.; Tanaka, A.; Oritani, T. *Tetrahedron Lett.* ***1997***, *38*, 3955.

[302]Thompson, A.S.; Humphrey, G.R.; DeMarco, A.M.; Mathre, D.J.; Grabowski, E.J.J. *J. Org. Chem.* ***1993***, *58*, 5886.

[303]There has been some controversy about this mechanism. For a discussion, see Vogler, E.A.; Hayes, J.M. *J. Org. Chem.* ***1979***, *44*, 3682.

involves formation of a nitrilium ion **82**, which reacts with water.

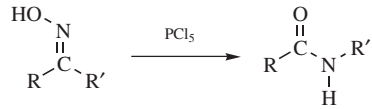


The intermediates **81** have been independently generated in aqueous solution.[304] Note the similarity of this mechanism to those of "insertion" of CH_2 (**18-9**) and of O (**18-19**). The three reactions are essentially analogous, both in products and in mechanism.[293,305] Also note the similarity of the latter part of this mechanism to that of the Beckmann rearrangement (**18-17**).

OS **V**, 408; **VI**, 368; **VII**, 254; **X**, 207. See also, OS **V**, 623.

18-17 The Beckmann Rearrangement

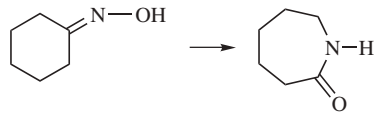
Beckmann oxime-amide rearrangement



When oximes are treated with PCl_5 or a number of other reagents, they rearrange to substituted amides in a reaction called the *Beckmann rearrangement*.[306] Among other reagents used have been concentrated H_2SO_4, formic acid, liquid SO_2, $SOCl_2$,[307] silica gel,[308] MoO_3 on silica gel,[309] $RuCl_3$,[310] $Y(OTf)_3$,[311]

[304]Amyes, T.L.; Richard, J.P. *J. Am. Chem. Soc.* ***1991***, *113*, 1867.
[305]For evidence for this mechanism, see Ostrovskii, V.A.; Koshtaleva, T.M.; Shirokova, N.P.; Koldobskii, G.I.; Gidaspov, B.V. *J. Org. Chem. USSR* ***1974***, *10*, 2365, and references cited therein.
[306]For reviews, see Gawley, R.E. *Org. React.* ***1988***, *35*, 1; McCarty, C.G., in Patai, S. *The Chemistry of the Carbon-Nitrogen Double Bond*, Wiley, NY, ***1970***, pp. 408–439. Also see, Nguyen, M.T.; Raspoet, G.; Vanquickenborne, L.G. *J. Am. Chem. Soc.* ***1997***, *119*, 2552.
[307]Butler, R.N.; O'Donoghue, D.A. *J. Chem. Res. (S)*, ***1983***, 18.
[308]Costa, A.; Mestres, R.; Riego, J.M. *Synth. Commun.* ***1982***, *12*, 1003. On silica with microwave irradiation, see Loupy, A.; Régnier, S. *Tetrahedron Lett.* ***1999***, *40*, 6221.
[309]Dongare, M.K.; Bhagwat, V.V.; Ramana, C.V.; Gurjar, M.K. *Tetrahedron Lett.* ***2004***, *45*, 4759.
[310]De, S.K. *Synth. Commun.* ***2004***, *34*, 3431.
[311]De, S.K. *Org. Prep. Proceed. Int.* ***2004***, *36*, 383.

HCl–HOAc-Ac_2O, $POCl_3$,[312] $BiCl_3$,[313] neat with $FeCl_3$,[314] and polyphosphoric acid.[315] The reaction has been done in supercritical water[316] and in ionic liquids.[317] A polymer-bound Beckman rearrangement has been reported.[318] Simply heating the oxime of benzophenone neat leads to *N*-phenyl benzamide.[319] The oximes of cyclic ketones give ring enlargement and form the lactam,[320] as in the formation of caprolactam (**83**) from the oxime of cyclohexanone. Heating an oxime of a cyclic ketone, *neat*, with $AlCl_3$ also leads to the lactam,[321] as does microwave irradiation of an oxime on Montmorillonite K10 clay.[322] Other solvent-free reactions are known.[323] Treatment of a cyclic ketone with NH_2OSO_3H on silica gel followed by microwave irradiation also gives the lactam.[324] Cyclic ketones can be converted directly to lactams in one laboratory step by treatment with NH_2OSO_2OH and formic acid (**16-14** takes place first, then the Beckmann rearrangement).[325] Heating a ketone with hydroxylamine HCl and oxalic acid also gives the amide.[326] Note that the reaction of an imine with BF_3•OEt_2 and *m*-chloroperoxybenzoic acid leads to a formamide.[327]



83

Of the groups attached to the carbon of the C=N unit, the one that migrates in the Beckman rearrangement is generally the one anti to the hydroxyl, and this is

[312]Majo, V.J.; Venugopal, M.; Prince, A.A.M.; Perumal, P.T. *Synth. Commun.* ***1995***, *25*, 3863.
[313]With microwave irradiation, see Thakur, A.J.; Boruah, A.; Prajapati, D.; Sandhu, J.S. *Synth. Commun.* ***2000***, *30*, 2105.
[314]Khodaei, M.M.; Meybodi, F.A.; Rezai, N.; Salehi, P. *Synth. Commun.* ***2001***, *31*, 2047.
[315]For a review of Beckmann rearrangements with polyphosphoric acid, see Beckwith, A.L.J., in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 131–137.
[316]Ikushima, Y.; Hatakeda, K.; Sato, O.; Yokoyama, T.; Arai, M. *J. Am. Chem. Soc.* ***2000***, *122*, 1908; Boero, M.; Ikeshoji, T.; Liew, C.C.; Terakura, K.; Parrinello, M. *J. Am. Chem. Soc.* ***2004***, *126*, 6280.
[317]In BPy BF_4, butylpyridinium tetrafluoroborate: Peng, J.; Deng, Y. *Tetrahedron Lett.* ***2001***, *42*, 403. In bmim PF_6, 1-butyl-3-methylimidazolium hexafluorophosphate: Ren, R.X.; Zueva, L.D.; Ou, X. *Tetrahedron Lett.* ***2001***, *42*, 8441.
[318]His, S.; Meyer, C.; Cossy, J.; Emeric, G.; Greiner, A. *Tetrahedron Lett.* ***2003***, *44*, 8581.
[319]Chandrasekhar, S.; Gopalaiah, K. *Tetrahedron Lett.* ***2001***, *42*, 8123.
[320]For a review of such ring enlargements, see Vinnik, M.I.; Zarakhani, N.G. *Russ. Chem. Rev.* ***1967***, *36*, 51. For a review with respect to bicyclic oximes, see Krow, G.R. *Tetrahedron* ***1981***, *37*, 1283.
[321]Ghiaci, M.; Imanzadeh, G.H. *Synth. Commun.* ***1998***, *28*, 2275. See Moghaddam, F.M.; Rad, A.A.R.; Zali-Boinee, H. *Synth. Commun.* ***2004***, *34*, 2071.
[322]Bosch, A.I.; de la Cruz, P.; Diez-Barra, E.; Loupy, A.; Langa, F. *Synlett* ***1995***, 1259.
[323]Sharghi, H.; Hosseini, M. *Synthesis* ***2002***, 1057; Eshghi, H.; Gordi, Z. *Synth. Commun.* ***2003***, *33*, 2971.
[324]Laurent, A.; Jacquault, P.; DiMarino, J.-L.; Hamelin, J. *J. Chem. Soc., Chem. Commun.* ***1995***, 1101.
[325]Olah, G.A.; Fung, A.P. *Synthesis* ***1979***, 537. See also, Novoselov, E.F.; Isaev, S.D.; Yurchenko, A.G.; Vodichka, L.; Trshiska, Ya. *J. Org. Chem. USSR* ***1981***, *17*, 2284.
[326]Chandrassekhar, S.; Gopalaiah, K. *Tetrahedron Lett.* ***2003***, *44*, 7437.
[327]An, G.-i.; Kim, M.; Kim. J.Y.; Rhee, H. *Tetrahedron Lett.* ***2003***, *44*, 2183.

often used as a method of determining the configuration of the oxime. However, it is not unequivocal. It is known that with some oximes the syn group migrates and that with others, especially where R and R′ are both alkyl, mixtures of the two possible amides are obtained. However, this behavior does not necessarily mean that the syn group actually undergoes migration. In most cases, the oxime undergoes isomerization under the reaction conditions *before* migration takes place.[328] The scope of the reaction is quite broad and R and R′ may be alkyl, aryl, or hydrogen. However, hydrogen very seldom *migrates*, so the reaction is not generally a means of converting aldoximes to unsubstituted amides ($RCONH_2$). This latter conversion can be accomplished, however, by treatment of the aldoxime with nickel acetate under neutral conditions[329] or by heating the aldoxime for 60 h at 100°C after it has been adsorbed onto silica gel.[330] As in the case of the Schmidt rearrangement, when the oxime is derived from an alkyl aryl ketone, it is generally the aryl group that preferentially migrates.[331]

Not only do oximes undergo the Beckmann rearrangement, but so also do esters of oximes with many acids, organic and inorganic. A side reaction with many substrates is the formation of nitriles (the ''abnormal'' Beckmann rearrangement, **17-30**). The other reagents convert OH to an ester leaving group (e.g., $OPCl_4$ from PCl_5 and OSO_2OH from concentrated H_2SO_4[332]). The *O*-carbonates of imines, such as $Ph_2C{=}N{-}OCO_2Et$, react with $BF_3{\bullet}OEt_2$ to give the corresponding amide, in this case *N*-phenyl benzamide.[333]

In the first step of the mechanism, the OH group is converted by the reagent to a better leaving group, for example, proton acids convert it to OH_2^+. After that, the mechanism[334] follows a course analogous to that for the Schmidt reaction of ketones (**18-16**) from the formation of nitrilium ion **82** on:[335] Alternatively, the attack on **82** can be by the leaving group, if different from H_2O. For example, when PCl_5 is used to induce the reaction, a $N{-}O{-}PCl_4$ species is formed, which generates **82**. Intermediates of the form **82** have been detected by nmr and uv spectroscopy.[336] The rearrangement has also been found to take place by a different mechanism, involving formation of a nitrile by fragmentation, and then addition by

[328]Lansbury, P.T.; Mancuso, N.R. *Tetrahedron Lett.* ***1965***, 2445 have shown that some Beckmann rearrangements are *authentically* nonstereospecific.

[329]Field, L.; Hughmark, P.B.; Shumaker, S.H.; Marshall, W.S. *J. Am. Chem. Soc.* ***1961***, *83*, 1983. See also, Leusink, A.J.; Meerbeek, T.G.; Noltes, J.G. *Recl. Trav. Chim. Pays-Bas* ***1976***, *95*, 123; ***1977***, *96*, 142.

[330]Chattopadhyaya, J.B.; Rama Rao, A.V. *Tetrahedron* ***1974***, *30*, 2899.

[331]See Arisawa, M.; Yamaguchi, M. *Org. Lett.* ***2001***, *3*, 311.

[332]Gregory, B.J.; Moodie, R.B.; Schofield, K. *J. Chem. Soc. B* ***1970***, 338; Kim, S.; Kawakami, T.; Ando, T.; Yukawa, Y. *Bull. Chem. Soc. Jpn.* ***1979***, *52*, 1115.

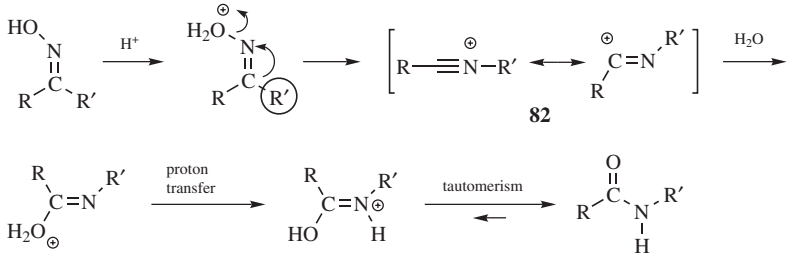
[333]Anilkumar, R.; Chandrasekhar, S. *Tetrahedron Lett.* ***2000***, *41*, 5427.

[334]For a discussion of the gas-phase reaction mechanism, see Nguyen, M.T.; Vanquickenborne, L.G. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 1969.

[335]For summaries of the considerable evidence for this mechanism, see Donaruma, L.G.; Heldt, W.Z. *Org. React.* ***1960***, *11*, 1, 5–14; Smith, P.A.S., in de Mayo, P. *Molecular Rearrangments*, Vol. 1, Wiley, NY, ***1963***, 483–507, p. 488–493.

[336]Gregory, B.J.; Moodie, R.B.; Schofield, K. *J. Chem. Soc. B* ***1970***, 338.

a Ritter reaction (**16-91**).[337] Beckmann rearrangements have also been carried out photochemically.[338]



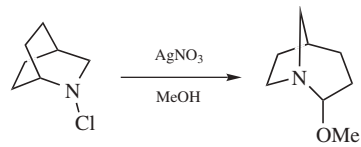
If the rearrangement of oxime sulfonates is induced by organoaluminum reagents,[339] the nitrilium ion intermediate **82** is captured by the nucleophile originally attached to the Al. By this means an oxime can be converted to an imine, an imino thioether (R–N=C–SR), or an imino nitrile (R–N=C–CN).[340] In the last case, the nucleophile comes from added trimethylsilyl cyanide. The imine-producing reaction can also be accomplished with a Grignard reagent in benzene or toluene.[341]

In a related reaction, treatment of spirocyclic oxaziridines with MnCl(TPP)[342] or photolysis[343] leads to a lactam.

OS **II**, 76, 371; **VIII**, 568.

18-18 Stieglitz and Related Rearrangements

Methoxy-de-*N*-chloro-(2/ → 1/*N*-alkyl)-*migro*-substitution, and so on



Besides the reactions discussed at **18-13**–**18-17**, a number of other rearrangements are known in which an alkyl group migrates from C to N. Certain bicyclic *N*-haloamines, for example *N*-chloro-2-azabicyclo[2.2.2]octane (above), undergo

[337]Hill, R.K.; Conley, R.T.; Chortyk, O.T. *J. Am. Chem. Soc.* ***1965***, *87*, 5646; Palmere, R.M.; Conley, R.T.; Rabinowitz, J.L. *J. Org. Chem.* ***1972***, *37*, 4095.

[338]See, for example, Izawa, H.; de Mayo, P.; Tabata, T. *Can. J. Chem.* ***1969***, *47*, 51; Cunningham, M.; Ng Lim, L.S.; Just, T. *Can. J. Chem.* ***1971***, *49*, 2891; Suginome, H.; Yagihashi, F. *J. Chem. Soc. Perkin Trans. 1* ***1977***, 2488.

[339]For a review, see Maruoka, K.; Yamamoto, H. *Angew. Chem. Int. Ed.* ***1985***, *24*, 668.

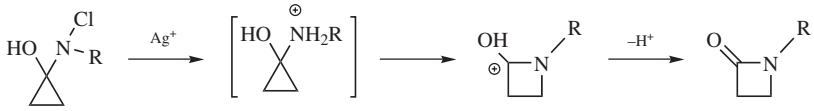
[340]Maruoka, K.; Miyazaki, T.; Ando, M.; Matsumura, Y.; Sakane, S.; Hattori, K.; Yamamoto, H. *J. Am. Chem. Soc.* ***1983***, *105*, 2831; Maruoka, K.; Nakai, S.; Yamamoto, H. *Org. Synth. 66*, 185.

[341]Hattori, K.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* ***1982***, *23*, 3395.

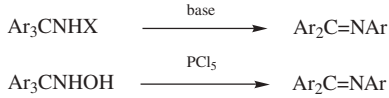
[342]Suda, K.; Sashima, M.; Izutsu, M.; Hino, F. *J. Chem. Soc., Chem. Commun.* ***1994***, 949.

[343]Post, A.J.; Nwaukwa, S.; Morrison, H. *J. Am. Chem. Soc.* ***1994***, *116*, 6439.

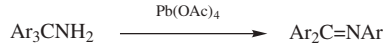
rearrangement when solvolyzed in the presence of silver nitrate.[344] This reaction is similar to the Wagner–Meerwein rearrangement (**18-1**) and is initiated by the silver-catalyzed departure of the chloride ion.[345] Similar reactions have been used for ring expansions and contractions, analogous to those discussed for reaction **18-3**.[346] An example is the conversion of 1-(*N*-chloroamino)cyclopropanols to β-lactams.[347] Methyl prolinate was converted to the lactam 2-piperidone upon treatment with SmI_2 and pivalic acid–THF.[348]



The name *Stieglitz rearrangement* is generally applied to the rearrangements of trityl *N*-haloamines and



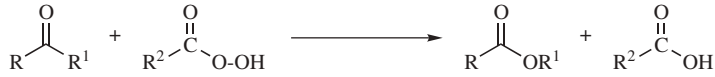
hydroxylamines. These reactions are similar to the rearrangements of alkyl azides (**18-14**), and the name Stieglitz rearrangement is also given to the rearrangement of trityl azides. Another similar reaction is the rearrangement undergone by tritylamines when treated with lead tetraacetate:[349]



D. Carbon-to-Oxygen Migrations of R and AR

18-19 The Baeyer–Villiger Rearrangement[350]

Oxy-insertion



[344]Gassman, P.G.; Fox, B.L. *J. Am. Chem. Soc.* ***1967***, *89*, 338. See also, Schell, F.M.; Ganguly, R.N. *J. Org. Chem.* ***1980***, *45*, 4069; Davies, J.W.; Malpass, J.R.; Walker, M.P. *J. Chem. Soc., Chem. Commun.* ***1985***, 686; Hoffman, R.V.; Kumar, A.; Buntain, G.A. *J. Am. Chem. Soc.* ***1985***, *107*, 4731.

[345]For C → N rearrangements induced by $AlCl_3$, see Kovacic, P.; Lowery, M.K.; Roskos, P.D. *Tetrahedron* ***1970***, *26*, 529.

[346]Gassman, P.G.; Carrasquillo, A. *Tetrahedron Lett.* ***1971***, 109; Hoffman, R.V.; Buntain, G.A. *J. Org. Chem.* ***1988***, *53*, 3316.

[347]Wasserman, H.H.; Adickes, H.W.; Espejo de Ochoa, O. *J. Am. Chem. Soc.* ***1971***, *93*, 5586; Wasserman, H.H.; Glazer, E.A.; Hearn, M.J. *Tetrahedron Lett.* ***1973***, 4855.

[348]Honda, T.; Ishikawa, F. *Chem. Commun.* ***1999***, 1065.

[349]Sisti, A.J.; Milstein, S.R. *J. Org. Chem.* ***1974***, *39*, 3932.

[350]For a review, see Renz, M.; Meunier, B. *Eur. J. Org. Chem.* ***1999***, 737. For a review of green procedures, see Ten Brink, G.-J.; Arends, W.C.E.; Sheldon, R.A. *Chem. Rev.* ***2004***, *104*, 4105.

The treatment of ketones with peroxyacids, such as peroxybenzoic or peroxyacetic acid, or with other peroxy compounds in the presence of acid catalysts, gives carboxylic esters by ''insertion'' of oxygen[351] and the carboxylic acid parent of the peroxyacid as a by-product. The reaction is called the *Baeyer–Villiger rearrangement*.[352] A particularly good reagent is peroxytrifluoroacetic acid. Reactions with this reagent are rapid and clean, giving high yields of product, though it is often necessary to add a buffer, such as Na_2HPO_4, to prevent transesterification of the product with trifluoroacetic acid that is also formed during the reaction. The reaction is often applied to cyclic ketones to give lactones.[353] Hydrogen peroxide has been used to convert cyclic ketones to lactones using a catalytic amount of $MeReO_3$[354] or a diselenide catalyst.[355] Hydrogen peroxide and a $MeReO_3$ catalyst has been used in an ionic liquid.[356] Transition-metal catalysts have been used with peroxyacids to facilitate the oxidation.[357] Hydrogen peroxide and $PhAsO_3H_2$ in hexafluoro-1-propanol can be used.[358] Polymer-supported peroxy acids have been used,[359] and solvent-free Bayer–Villiger reactions are known.[360] Enantioselective synthesis[361] of chiral lactones from achiral ketones has been achieved by the use of enzymes[362]

[351]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*; 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1665–1667.

[352]For reviews, see Hudlický, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC, ***1990***, pp. 186–195; Plesničar, B., in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. C, Academic Press, NY, ***1978***, pp. 254–267; House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 321–329; Lewis, S.N., in Augustine, R.L. *Oxidation*, Vol. 1, Marcel Dekker, NY, ***1969***, pp. 237–244; Lee, J.B.; Uff, B.C. *Q. Rev. Chem. Soc.* ***1967***, *21*, 429, see pp. 449–453. Also see, Mino, T.; Masuda, S.; Nishio, M.; Yamashita, M. *J. Org. Chem.* ***1997***, *62*, 2633. For a discussion of uncatalyzed versus BF_3-assisted reactions, see Carlqvist, P.; Eklund, R.; Brinck, T. *J. Org. Chem.* ***2001***, *66*, 1193.

[353]For a review of the reaction as applied to bicyclic ketones, see Krow, G.R. *Tetrahedron* ***1981***, *37*, 2697.

[354]Phillips, A.M.F.; Romão, C. *Eur. J. Org. Chem.* ***1999***, 1767.

[355]ten Brink, G.-J.; Vis, J.-M.; Arends, I.W.C.E.; Sheldon, R.A. *J. Org. Chem.* ***2001***, *66*, 2429.

[356]In bmim BF_4, 1-butyl-3-methylimidazoliuum tetrafluoroborate: Bernini, R.; Coratti, A.; Fabrizi, G.; Goggiamani, A. *Tetrahedron Lett.* ***2003***, *44*, 8991.

[357]Kotsuki, H.; Arimura, K.; Araki, T.; Shinohara, T. *Synlett* ***1999***, 462; Alam, M.M.; Varala, R.; Adapa, S.R. *Synth. Commun.* ***2003***, *33*, 3035.

[358]Berkessel, A.; Andreae, M.R.M. *Tetrahedron Lett.* ***2001***, *42*, 2293.

[359]Lambert, A.; Elings, J.A.; Macquarrie, D.J.; Carr, G.; Clark, J.H. *Synlett* ***2000***, 1052. For a discussion of selectivity in solid-state Bayer-Villiger reactions, see Hagiwara, H.; Nagatomo, H.; Yoshii, F.; Hoshi, T.; Suzuki, T.; Ando, M. *J. Chem. Soc., Perkin Trans. 1* ***2000***, 2645.

[360]Yakura, T.; Kitano, T.; Ikeda, M.; Uenishi, J. *Tetrahedron Lett.* ***2002***, *43*, 6925.

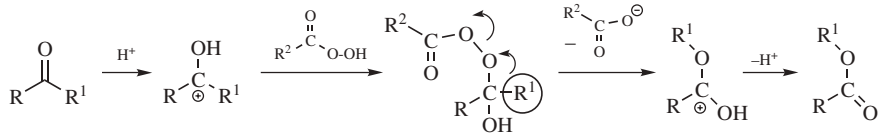
[361]See Bolm, C.; Beckmann, O.; Kühn, T.; Palazzi, C.; Adam, W.; Rao, P.B.; Saha-Möller, C.R. *Tetrahedron Asymmetry* ***2001***, *12*, 2441; Bolm, C.; Frison J.-C.; Zhang, Y.; Wulff, W.D. *Synlett* ***2004***, 1619.

[362]See Taschner, M.J.; Black, D.J. *J. Am. Chem. Soc.* ***1988***, *110*, 6892; Taschner, M.J.; Peddada, L. *J. Chem. Soc., Chem. Commun.* ***1992***, 1384; Pchelka, B.K.; Gelo Pujic, M.; Guibé-Jampel, E. *J. Chem. Soc. Perkin Trans. 1* ***1998***, 2625; Stewart, J.D.; Reed, K.W.; Martinez, C.A.; Zhu, J.; Chen, G.; Kayser, M.M. *J. Am. Chem. Soc.* ***1998***, *120*, 3541; Lemoult, S.C.; Richardson, P.F.; Roberts, S.M. *J. Chem. Soc. Perkin Trans. 1* ***1995***, 89; Mihovilovic, M.D.; Müller, B.; Kayser, M.M.; Stewart, J.D.; Stanetty, P. *Synlett* ***2002***, 703. For a review of enzyme-catalyzed Baeyer–Villiger rearrangements, see Walsh, C.T.; Chen, Y.J. *Angew. Chem. Int. Ed.* ***1988***, *27*, 333. For a review of monooxygenase-mediated Baeyer–Villiger rearrangements, see Mihovilovic, M.D.; Müller, B.; Stanetty, P. *Eur. J. Org. Chem.* ***2002***, 3711. For a reaction using engineered *E. coli* cells, see Mihovilovic, M.D.; Chen, G.; Wang, S.; Kyte, B.; Rochon, F.; Kayser, M.M.; Stewart, J.D. *J. Org. Chem.* ***2001***, *66*, 733.

and other asymmetric reactions are known.[363] Oxidation of chiral substrates with *m*-chloroperoxybenzoic acid (mcpba) also leads to chiral lactones.[364]

For acyclic compounds, R′ must usually be secondary, tertiary, or vinylic, although primary R′ has been rearranged with peroxytrifluoroacetic acid,[365] with BF_3–H_2O_2,[366] and with $K_2S_2O_8$–H_2SO_4.[367] For unsymmetrical ketones the approximate order of migration is tertiary alkyl > secondary alkyl, aryl > primary alkyl > methyl. Since the methyl group has a low migrating ability, the reaction provides a means of cleaving a methyl ketone R'COMe to produce an alcohol or phenol (R'OH) (by hydrolysis of the ester R'OCOMe). The migrating ability of aryl groups is increased by electron-donating and decreased by electron-withdrawing substituents.[368] There is a preference of anti over gauche migration.[369] Enolizable β-diketones do not react. α-Diketones can be converted to anhydrides.[370] With aldehydes, migration of hydrogen gives the carboxylic acid, and this is a way of accomplishing **19-23**. Migration of the other group would give formates, but this seldom happens, though aryl aldehydes have been converted to formates with H_2O_2 and a selenium compound[371] (see also the Dakin reaction in **19-11**).

The mechanism[372] is similar to those of the analogous reactions with hydrazoic acid (**18-16** with ketones) and diazomethane (**18-8**):



One important piece of evidence for this mechanism was that benzophenone–^{18}O gave ester entirely labeled in the carbonyl oxygen, with none in the alkoxyl oxygen.[373] Carbon-14 isotope-effect studies on acetophenones have shown that

[363]For example, see Sugimura, T.; Fujiwara, Y.; Tai, A. *Tetrahedron Lett.* ***1997***, *38*, 6019; Bolm, C.; Schlingloff, G.; Weickhardt, K. *Angew. Chem. Int. Ed.* ***1994***, *33*, 1848; Bolm, C.; Schlingloff, G. *J. Chem. Soc., Chem. Commun.* ***1995***, 1247; Bolm, C.; Beckmann, O.; Cosp, A.; Palazzi, C. *Synlett* ***2001***, 1461; Bolm, C.; Beckmann, O.; Palazzi, C. *Can. J. Chem.* ***2001***, *79*, 1593; Shinohara, T.; Fujioka, S.; Kotsuki, H. *Heterocycles* ***2001***, *55*, 237; Watanabe, A.; Uchida, T.; Ito, K.; Katsuki, T. *Tetrahedron Lett.* ***2002***, *43*, 4481; Murhashi, S.-I.; Ono, S.; Imada, Y. *Angew. Chem. Int. Ed.* ***2002***, *41*, 2366.

[364]Hunt, KW.; Grieco, P.A. *Org. Lett.* ***2000***, *2*, 1717.

[365]Emmons, W.D.; Lucas, G.B. *J. Am. Chem. Soc.* ***1955***, *77*, 2287.

[366]McClure, J.D.; Williams, P.H. *J. Org. Chem.* ***1962***, *27*, 24.

[367]Deno, N.C.; Billups, W.E.; Kramer, K.E.; Lastomirsky, R.R. *J. Org. Chem.* ***1970***, *35*, 3080.

[368]For as report of substituent effects in the α, β, and γ position of alkyl groups, see Noyori, R.; Sato, T.; Kobayashi, H. *Bull. Chem. Soc. Jpn.* ***1983***, *56*, 2661.

[369]Snowden, M.; Bermudez, A.; Kelly, D.R.; Radkiewicz-Poutsma, J.L. *J. Org. Chem.* ***2004***, *69*, 7148.

[370]For a study of the mechanism of this conversion, see Cullis, P.M.; Arnold, J.R.P.; Clarke, M.; Howell, R.; DeMira, M.; Naylor, M.; Nicholls, D. *J. Chem. Soc., Chem. Commun.* ***1987***, 1088.

[371]Syper, L. *Synthesis* ***1989***, 167. See also, Godfrey, I.M.; Sargent, M.V.; Elix, J.A. *J. Chem. Soc. Perkin Trans. 1* ***1974***, 1353.

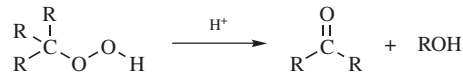
[372]Proposed by Criegee, R. *Liebigs Ann. Chem.* ***1948***, *560*, 127.

[373]Doering, W. von E.; Dorfman, E. *J. Am. Chem. Soc.* ***1953***, *75*, 5595. For summaries of the other evidence, see Smith, P.A.S., in de Mayo, P. *Molecular Rearrangements*, Vol. 1, Wiley, NY, ***1963***, pp. 578–584.

migration of aryl groups takes place in the rate-determining step,[374] demonstrating that migration of Ar is concerted with departure of $OCOR^2$.[375] It is hardly likely that migration would be the slow step if the leaving group departed first to give an ion with a positive charge on an oxygen atom, which would be a highly unstable species.

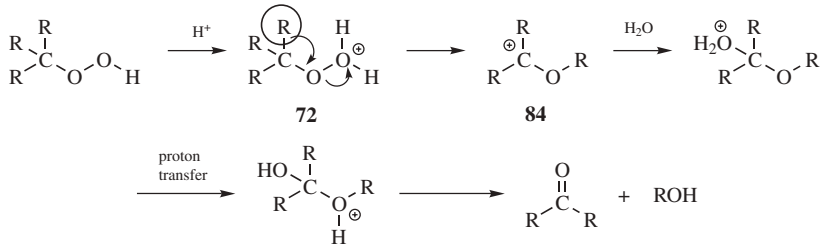
18-20 Rearrangement of Hydroperoxides

C-Alkyl-*O*-hydroxy-elimination



Hydroperoxides (R = alkyl, aryl, or hydrogen) can be cleaved by proton or Lewis acids in a reaction whose principal step is a rearrangement.[376] The reaction has also been applied to peroxy esters ($R_3COOCOR'$), but less often. When aryl and alkyl groups are both present, migration of aryl dominates. It is not necessary actually to prepare and isolate hydroperoxides. The reaction takes place when the alcohols are treated with H_2O_2 and acids. Migration of an alkyl group of a primary hydroperoxide provides a means for converting an alcohol to its next lower homolog ($RCH_2OOH \rightarrow CH_2{=}O + ROH$).

The mechanism is as follows:[377]



The last step is hydrolysis of the unstable hemiacetal. Alkoxycarbocation intermediates (**84**, R = alkyl) have been isolated in super acid solution[378] at

[374]Palmer, B.W.; Fry, A. *J. Am. Chem. Soc.* ***1970***, *92*, 2580. See also, Mitsuhashi, T.; Miyadera, H.; Simamura, O. *Chem. Commun.* ***1970***, 1301. For secondary isotope-effect studies, see Winnik, M.A.; Stoute, V.; Fitzgerald, P. *J. Am. Chem. Soc.* ***1974***, *96*, 1977.

[375]In some cases, the rate-determining step has been shown to be the addition of peracid to the substrate (see, e.g., Ogata, Y.; Sawaki, Y. *J. Org. Chem.* ***1972***, *37*, 2953). Even in these cases it is still highly probable that migration is concerted with departure of the nucleofuge.

[376]For reviews, see Yablokov, V.A. *Russ. Chem. Rev.* ***1980***, *49*, 833; Lee, J.B.; Uff, B.C. *Q. Rev. Chem. Soc.* ***1967***, *21*, 429, 445–449.

[377]For a discussion of the transition state involved in the migration step, see Wistuba, E.; Rüchardt, C. *Tetrahedron Lett.* ***1981***, *22*, 3389.

[378]For a review of peroxy compounds in super acids, see Olah, G.A.; Parker, D.G.; Yoneda, N. *Angew. Chem. Int. Ed.* ***1978***, *17*, 909.

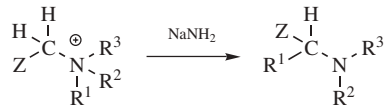
low temperatures, and their structures proved by nmr.[379] The protonated hydroperoxides could not be observed in these solutions, evidently reacting immediately on formation.

OS **V**, 818.

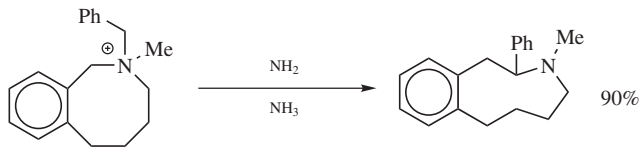
E. Nitrogen-to-Carbon, Oxygen-to-Carbon, and Sulfur-to-Carbon Migration

18-21 The Stevens Rearrangement

Hydron-(2/*N* → 1/alkyl)-*migro*-detachment



In the *Stevens rearrangement*, a quaternary ammonium salt containing an electron-withdrawing group Z on one of the carbons attached to the nitrogen is treated with a strong base (e.g., NaOR or $NaNH_2$) to give a rearranged tertiary amine. The Z group may be RCO, ROOC, or phenyl.[380] The most common migrating groups are allylic, benzylic, benzhydryl, 3-phenylpropargyl, and phenacyl, though even methyl migrates to a sufficiently negative center.[381] When an allylic group migrates, it may or may not involve an allylic rearrangement within the migrating group (see **18-35**), depending on the substrate and reaction conditions. The reaction has been used for ring enlargement,[382] for example:



The mechanism has been the subject of much study.[383] That the rearrangement is intramolecular was shown by crossover experiments, by ^{14}C labeling,[384] and by the

[379]Sheldon, R.A.; van Doorn, J.A. *Tetrahedron Lett.* ***1973***, 1021.

[380]For reviews of the Stevens rearrangement, see Lepley, A.R.; Giumanini, A.G. *Mech. Mol. Migr.* ***1971***, *3*, 297; Pine, S.H. *Org. React.* ***1970***, *18*, 403. For reviews of the Stevens and the closely related Wittig rearrangement (**18-22**), see Stevens, T.S.; Watts, W.E. *Selected Molecular Rearrangements*, Van Nostrand-Reinhold, Princeton, NJ, ***1973***, pp. 81–116; Wilt, J.W., in Kochi, J.K. *Free Radicals*, Vol. 1, Wiley, NY, ***1973***, pp. 448–458; Iwai, I. *Mech. Mol. Migr.* ***1969***, *2*, 73, see pp. 105–113; Stevens, T.S. *Prog. Org. Chem.* ***1968***, *7*, 48.

[381]Migration of aryl is rare, but has been reported: Heaney, H.; Ward, T.J. *Chem. Commun.* ***1969***, 810; Truce, W.E.; Heuring, D.L. *Chem. Commun.* ***1969***, 1499.

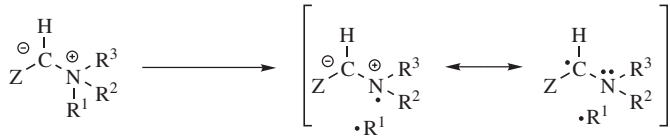
[382]Elmasmodi, A.; Cotelle, P.; Barbry, D.; Hasiak, B.; Couturier, D. *Synthesis* ***1989***, 327.

[383]For example, see Pine, S.H. *J. Chem. Educ.* ***1971***, *48*, 99; Heard, G.L.; Yates, B.F. *Aust. J. Chem.* ***1994***, *47*, 1685.

[384]Stevens, T.S. *J. Chem. Soc.* ***1930***, 2107; Johnstone, R.A.W.; Stevens, T.S. *J. Chem. Soc.* ***1955***, 4487.

fact that retention of configuration is found at R^1.[385] The first step is loss of the acidic proton to give the ylid **85**, which has been isolated.[386] The finding[387] that CIDNP spectra[388] could be obtained in many instances shows that in these cases the product is formed directly from a free-radical precursor. The following radical pair mechanism was proposed:[389]

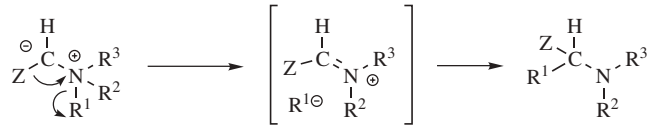
Mechanism *a*



85 Solvent cage

The radicals do not drift apart because they are held together by the solvent cage. According to this mechanism, the radicals must recombine rapidly in order to account for the fact that R^1 does not racemize. Other evidence in favor of mechanism *a* is that in some cases small amounts of coupling products (R^1–R^1) have been isolated,[390] which would be expected if some $\bullet R^1$ leaked from the solvent cage. However, not all the evidence is easily compatible with mechanism *a*.[391] It is possible that another mechanism (*b*) similar to mechanism *a*, but involving

Mechanism *b*



85 Solvent cage

ion pairs in a solvent cage instead of radical pairs, operates in some cases. A third possible mechanism would be a concerted 1,2-shift,[392] but the orbital symmetry

[385]Brewster, J.H.; Kline, M.W. *J. Am. Chem. Soc.* ***1952***, *74*, 5179; Schöllkopf, U.; Ludwig, U.; Ostermann, G.; Patsch, M. *Tetrahedron Lett.* ***1969***, 3415.

[386]Jemison, R.W.; Mageswaran, S.; Ollis, W.D.; Potter, S.E.; Pretty, A.J.; Sutherland, I.O.; Thebtaranonth, Y. *Chem. Commun.* ***1970***, 1201.

[387]Lepley, A.R.; Becker, R.H.; Giumanini, A.G. *J. Org. Chem.* ***1971***, *36*, 1222; Baldwin, J.E.; Brown, J.E. *J. Am. Chem. Soc.* ***1969***, *91*, 3646; Jemison, R.W.; Morris, D.G. *Chem. Commun.* ***1969***, 1226; Schöllkopf, U.; Ludwig, U.; Ostermann, G.; Patsch, M. *Tetrahedron Lett.* ***1969***, 3415.

[388]For a review of the application of CIDNP to rearrangement reactions, see Lepley, A.R., in Lepley, A.R.; Closs, G.L. *Chemically Induced Magnetic Polarization*, Wiley, NY, ***1973***, pp. 323–384.

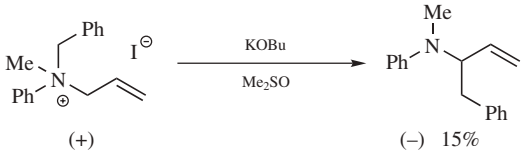
[389]Schöllkopf, U.; Ludwig, U. *Chem. Ber.* ***1968***, *101*, 2224; Ollis, W.D.; Rey, M.; Sutherland, I.O. *J. Chem. Soc. Perkin Trans. 1* ***1983***, 1009, 1049.

[390]Schöllkopf, U.; Ludwig, U.; Ostermann, G.; Patsch, M. *Tetrahedron Lett.* ***1969***, 3415; Hennion, G.F.; Shoemaker, M.J. *J. Am. Chem. Soc.* ***1970***, *92*, 1769.

[391]See, for example, Pine, S.H.; Catto, B.A.; Yamagishi, F.G. *J. Org. Chem.* ***1970***, *35*, 3663.

[392]For evidence against this mechanism, see Jenny, E.F.; Druey, J. *Angew. Chem. Int. Ed.* ***1962***, *1*, 155.

principle requires that this take place with inversion at R^1.[393] (see p. 1654.) Since the actual migration takes place with retention, it cannot, according to this argument, proceed by a concerted mechanism. However, in the case where the migrating group is allylic, a concerted mechanism can also operate (**18-35**). An interesting finding compatible with all three mechanisms is that optically active allylbenzylmethylphenylammonium iodide (asymmetric nitrogen, see p. 142) gave an optically active product:[394]

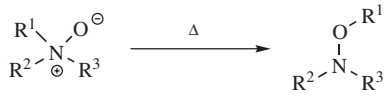


(+) (–) 15%

The *Sommelet–Hauser rearrangement* competes when Z is an aryl group (see **13-31**). *Hofmann elimination* competes when one of the R groups contains a β hydrogen atom (**17-7** and **17-8**).

Sulfur ylids containing a Z group give an analogous rearrangement, often also referred to as a Stevens

rearrangement.[395] In this case too, there is much evidence (including CIDNP) that a radical-pair cage mechanism is operating,[396] except that when the migrating group is allylic, the mechanism may be different (see **18-35**). Another reaction with a similar mechanism[397] is the *Meisenheimer rearrangement*,[398] in which certain tertiary



[393]Woodward, R.B.; Hoffmann, R. *The Conservation of Orbital Symmetry*, Academic Press, NY, ***1970***, p. 131.

[394]Hill, R.K.; Chan, T. *J. Am. Chem. Soc.* ***1966***, *88*, 866.

[395]For a review, see Olsen, R.K.; Currie, Jr., J.O., in Patai, S. *The Chemistry of The Thiol Group*, pt. 2, Wiley, NY, ***1974***, pp. 561–566.

[396]See, for example, Baldwin, J.E.; Erickson, W.F.; Hackler, R.E.; Scott, R.M. *Chem. Commun.* ***1970***, 576; Schöllkopf, U.; Schossig, J.; Ostermann, G. *Liebigs Ann. Chem.* ***1970***, *737*, 158; Iwamura, H.I.; Iwamura, M.; Nishida, T.; Yoshida, M.; Nakayama, T. *Tetrahedron Lett.* ***1971***, 63.

[397]For some of the evidence, see Ostermann, G.; Schöllkopf, U. *Liebigs Ann. Chem.* ***1970***, *737*, 170; Lorand, J.P.; Grant, R.W.; Samuel, P.A.; O'Connell, E.; Zaro, J. *Tetrahedron Lett.* ***1969***, 4087.

[398]For a review, see Johnstone, R.A.W. *Mech. Mol. Migr.* ***1969***, *2*, 249. See Buston, J.E.H.; Coldham, I.; Mulholland, K.R. *J. Chem. Soc., Perkin Trans. 1* ***1999***, 2327.

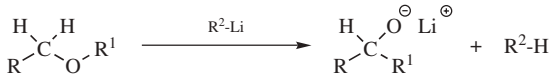
amine oxides rearrange on heating to give substituted hydroxylamines.[399] The migrating group R^1 is almost always allylic or benzilic.[400] R^2 and R^3 may be alkyl or aryl, but if one of the R groups contains a β hydrogen, Cope elimination (**17-9**) often competes. In a related reaction, when 2-methylpyridine *N*-oxides are treated with trifluoroacetic anhydride, the *Boekelheide reaction* occurs to give 2-hydroxymethylpyridines.[401]

Certain tertiary benzylic amines, when treated with BuLi, undergo a rearrangement analogous to the Wittig rearrangement (**18-22**), for example, $PhCH_2NPh_2 \rightarrow Ph_2CHNHPh$.[402] Only aryl groups migrate in this reaction.

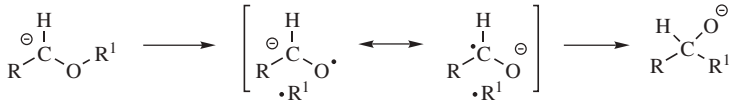
Isocyanides, when heated in the gas phase or in nonpolar solvents, undergo a 1,2-intramolecular rearrangement to nitriles: RNC → RCN.[403] In polar solvents the mechanism is different.[404]

18-22 The Wittig Rearrangement[405]

Hydron-(2/*O* → 1/alkyl)-*migro*-detachment



The rearrangement of ethers with alkyllithium reagents is called the *Wittig rearrangement* (not to be confused with the Wittig reaction, **16-44**) and is similar to **18-21**.[380] However, a stronger base is required (e.g., phenyllithium or sodium amide). The R and R′ groups, may be alkyl,[406] aryl, or vinylic.[407] Also, one of the hydrogens may be replaced by an alkyl or aryl group, in which case the product is the salt of a tertiary alcohol. Migratory aptitudes



[399]For example, see Buston, J.E.H.; Coldham, I.; Mulholland, K.R. *Tetrahedron Asymmetry*, ***1998***, *9*, 1995.

[400]Migration of aryl and of certain alkyl groups has also been reported. See Khuthier, A.; Al-Mallah, K.Y.; Hanna, S.Y.; Abdulla, N.I. *J. Org. Chem.* ***1987***, *52*, 1710, and references cited therein.

[401]Fontenas, C.; Bejan, E.; Haddon, H.A.; Balavoine, G.G.A. *Synth. Commun.* ***1995***, *25*, 629.

[402]Eisch, J.J.; Kovacs, C.A.; Chobe, P. *J. Org. Chem.* ***1989***, *54*, 1275.

[403]See Pakusch, J.; Rüchardt, C. *Chem. Ber.* ***1991***, *124*, 971, and references cited therein.

[404]Meier, M.; Rüchardt, C. *Chimia* ***1986***, *40*, 238.

[405]See Hiersemann, M.; Abraham, L.; Pollex, A. *Synlett* ***2003***, 1088.

[406]See Bailey, W.F.; England, M.D.; Mealy, M.J.; Thongsornkleeb, C.; Teng, L. *Org. Lett.* ***2000***, *2*, 489.

[407]For migration of vinyl, see Rautenstrauch, V.; Büchi, G.; Wüest, H. *J. Am. Chem. Soc.* ***1974***, *96*, 2576. For rearrangment of an α-trimethylsilyl allyl ether, see Maleczka, Jr., R.E.; Geng, F. *Org. Lett.* ***1999***, *1*, 1115.

here are allylic, benzylic > ethyl > methyl > phenyl.[408] The stereospecificity of the 1,2-Wittig rearrangement has been discussed.[409] The following radical-pair mechanism[410] (similar to mechanism *a* of **18-21**) is likely, after removal of the proton by the base. One of the radicals in the radical pair is a ketyl. Among the evidence for this mechanism is (*1*) the rearrangement is largely intramolecular; (*2*) migratory aptitudes are in the order of free-radical stabilities, not of carbanion stabilities[411] (which rules out an ion-pair mechanism similar to mechanism *b* of **18-21**); (*3*) aldehydes are obtained as side products;[412] (*4*) partial racemization of R' has been observed[413] (the remainder of the product retained its configuration); (*5*) crossover products have been detected;[414] and (*6*) when ketyl radicals and R radicals from different precursors were brought together, similar products resulted.[415] However, there is evidence that at least in some cases the radical-pair mechanism accounts for only a portion of the product, and some kind of concerted mechanism can also take place.[416] Most of the above investigations were carried out with systems where R' is alkyl, but a radical-pair mechanism has also been suggested for the case where R' is aryl.[417] When R' is allylic a concerted mechanism can operate (**18-35**).

When R is vinylic it is possible, by using a combination of an alkyllithium and *t*-BuOK, to get migration to the γ carbon (as well as to the α carbon), producing an enolate that, on hydrolysis, gives an aldehyde:[418]

$$CH_2{=}CH{-}CH_2{-}OR' \longrightarrow R'CH_2{-}CH{=}CH{-}OLi \longrightarrow R'CH_2CH_2CHO$$

An aza-Wittig rearrangement is also known.[419]

There are no OS references, but see OS **VIII**, 501, for a related reaction.

[408]Wittig, G. *Angew. Chem.* ***1954***, *66*, 10; Solov'yanov, A.A.; Ahmed, E.A.A.; Beletskaya, I.P.; Reutov, O.A. *J. Chem. Soc., Chem. Commun.* ***1987***, *23*, 1232.

[409]Maleczka Jr., R.E.; Geng, F. *J. Am. Chem. Soc.* ***1998***, *120*, 8551.

[410]For a review of the mechanism, see Schöllkopf, U. *Angew. Chem. Int. Ed.* ***1970***, *9*, 763.

[411]Lansbury, P.T.; Pattison, V.A.; Sidler, J.D.; Bieber, J.B. *J. Am. Chem. Soc.* ***1966***, *88*, 78; Schäfer, H.; Schöllkopf, U.; Walter, D. *Tetrahedron Lett.* ***1968***, 2809.

[412]For example, see Hauser, C.R.; Kantor, S.W. *J. Am. Chem. Soc.* ***1951***, *73*, 1437; Cast, J.; Stevens, T.S.; Holmes, J. *J. Chem. Soc.* ***1960***, 3521.

[413]Schöllkopf, U.; Schäfer, H. *Liebigs Ann. Chem.* ***1963***, *663*, 22; Felkin, H.; Frajerman, C. *Tetrahedron Lett.* ***1977***, 3485; Hebert, E.; Welvart, Z. *J. Chem. Soc., Chem. Commun.* ***1980***, 1035; *Nouv. J. Chim.* ***1981***, *5*, 327.

[414]Lansbury, P.T.; Pattison, V.A. *J. Org. Chem.* ***1962***, *27*, 1933; *J. Am. Chem. Soc.* ***1962***, *84*, 4295.

[415]Garst, J.F.; Smith, C.D. *J. Am. Chem. Soc.* ***1973***, *95*, 6870.

[416]Garst, J.F.; Smith, C.D. *J. Am. Chem. Soc.* ***1976***, *98*, 1526. For evidence against this, see Hebert, E.; Welvart, Z.; Ghelfenstein, M.; Szwarc, H. *Tetrahedron Lett.* ***1983***, *24*, 1381.

[417]Eisch, J.J.; Kovacs, C.A.; Rhee, S. *J. Organomet. Chem.* ***1974***, *65*, 289.

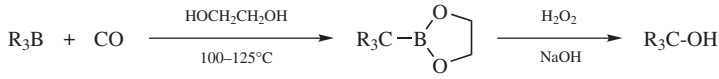
[418]Schlosser, M.; Strunk, S. *Tetrahedron* ***1989***, *45*, 2649.

[419]Coldham, I. *J. Chem. Soc. Perkin Trans. 1* ***1993***, 1275; Anderson, J.C.; Siddons, D.C.; Smith, S.C.; Swarbrick, M.E. *J. Chem. Soc., Chem. Commun.* ***1995***, 1835; Ahman, J.; Somfai, P. *J. Am. Chem. Soc.* ***1994***, *116*, 9781.

F. Boron-to-Carbon Migrations[420]

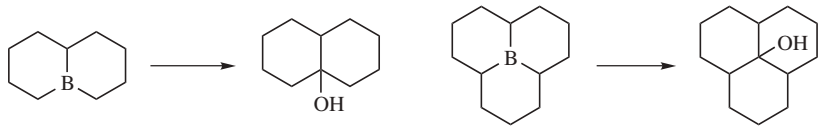
For another reaction involving boron-to-carbon migration, see **10-73**.

18-23 Conversion of Boranes to Alcohols



86

Trialkylboranes (which can be prepared from alkenes by **15-16**) react with carbon monoxide[421] at 100–125°C in the presence of ethylene glycol to give the 2-bora-1,3-dioxolanes (**86**), which are easily oxidized (**12-27**) to tertiary alcohols.[422] The R groups may be primary, secondary, or tertiary, and may be the same or different.[423] Yields are high and the reaction is quite useful, especially for the preparation of sterically hindered alcohols, such as tricyclohexylcarbinol (**87**) and tri-2-norbornylcarbinol (**88**), which are difficult to prepare by **16-24**. Heterocycles in which boron is a ring atom react similarly (except that high CO pressures are required), and cyclic alcohols can be obtained from these substrates.[424] The preparation of such heterocyclic boranes was discussed at **15-16**. The overall conversion of a diene or triene to a cyclic alcohol has been described by H.C. Brown as ''stitching'' with boron and ''riveting'' with carbon.



87 **88**

[420]For reviews, see Matteson, D.S., in Hartley, F.R. *The Chemistry of the Metal-Carbon Bond*, Vol. 4, Wiley, NY, ***1984***, pp. 307–409, 346–387; Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, ***1988***, pp. 256–301; Negishi, E.; Idacavage, M.J. *Org. React*. ***1985***, *33*, 1; Suzuki, A *Top. Curr. Chem.* ***1983***, *112*, 67; Pelter, A., in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 2, Academic Press, NY, ***1980***, pp. 95–147; *Chem. Soc. Rev.* ***1982***, *11*, 191; Cragg, G.M.L.; Koch, K.R. *Chem. Soc. Rev.* ***1977***, *6*, 393; Weill-Raynal, J. *Synthesis* ***1976***, 633; Cragg, G.M.L. *Organoboranes in Organic Synthesis*; Marcel Dekker, NY, ***1973***, pp. 249–300; Paetzold, P.I.; Grundke, H. *Synthesis* ***1973***, 635.

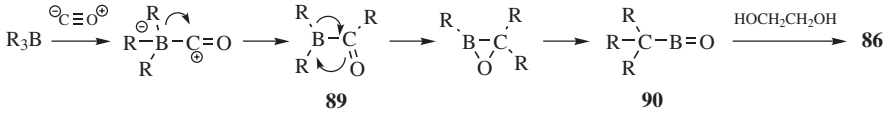
[421]For discussions of the reaction of boranes with CO, see Negishi, E. *Intra-Sci. Chem. Rep.* ***1973***, *7(1)*, 81; Brown, H.C. *Boranes in Organic Chemistry*, Cornell University Press, Ithica, NY, ***1972***, pp. 343–371; *Acc. Chem. Res.* ***1969***, *2*, 65.

[422]Hillman, M.E.D. *J. Am. Chem. Soc.* ***1962***, *84*, 4715; ***1963***, *85*, 982; Brown, H.C.; Rathke, M.W. *J. Am. Chem. Soc.* ***1967***, *89*, 2737; Puzitskii, K.V.; Pirozhkov, S.D.; Ryabova, K.G.; Pastukhova, I.V.; Eidus, Ya.T. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1972***, *21*, 1939; ***1973***, *22*, 1760; Brown, H.C.; Cole, T.E.; Srebnik, M.; Kim, K. *J. Org. Chem.* ***1986***, *51*, 4925.

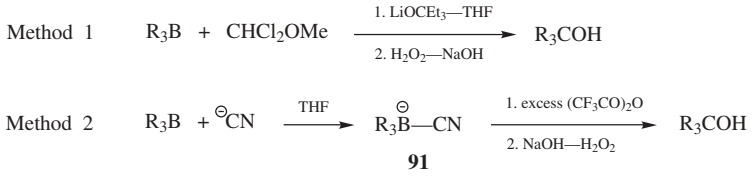
[423]Brown, H.C.; Gupta, S.K. *J. Am. Chem. Soc.* ***1971***, *93*, 1818; Negishi, E.; Brown, H.C. *Synthesis* ***1972***, 197.

[424]Brown, H.C.; Negishi, E.; Dickason, W.C. *J. Org. Chem.* ***1985***, *50*, 520, and references cited therein.

Though the mechanism has not been investigated thoroughly, it has been shown to be intramolecular by the failure to find crossover products when mixtures of boranes are used.[425] The following scheme, involving three boron-to-carbon migrations, has been suggested.



The purpose of the ethylene glycol is to intercept the boronic anhydride **90**, which otherwise forms polymers that are difficult to oxidize. As we will see in **18-23** and **18-24**, it is possible to stop the reaction after only one or two migrations have taken place.



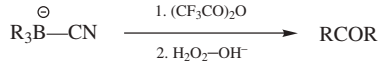
There are two other methods for achieving the conversion $R_3B \rightarrow R_3COH$, which often give better results: (*1*) treatment with α,α-dichloromethyl methyl ether and the base lithium triethylcarboxide[426] (*2*) treatment with a suspension of sodium cyanide in THF followed by reaction of the resulting trialkylcyanoborate **91** with an excess (>2 equivalents) of trifluoroacetic anhydride.[427] All the above migrations take place with retention of configuration at the migrating carbon.[428]

Several other methods for the conversion of boranes to tertiary alcohols are also known.[429]

If the reaction between trialkylboranes and carbon monoxide (**18-23**) is carried out in the presence of water followed by addition of NaOH, the product is a secondary alcohol. If H_2O_2 is added along with the NaOH, the corresponding ketone is obtained instead.[430] Various functional groups (e.g., OAc, COOR, CN) may be

[425]Brown, H.C.; Rathke, M.W. *J. Am. Chem. Soc.* ***1967***, *89*, 4528.
[426]Brown, H.C.; Carlson, B.A. *J. Org. Chem.* ***1973***, *38*, 2422; Brown, H.C.; Katz, J.; Carlson, B.A. *J. Org. Chem.* ***1973***, *38*, 3968.
[427]Pelter, A.; Hutchings, M.G.; Smith, K.; Williams, D.J. *J. Chem. Soc. Perkin Trans. 1* ***1975***, 145, and references cited therein.
[428]See however Pelter, A.; Maddocks, P.J.; Smith, K. *J. Chem. Soc., Chem. Commun.* ***1978***, 805.
[429]See, for example, Brown, H.C.; Lane, C.F. *Synthesis* ***1972***, 303; Yamamoto, Y.; Brown, H.C. *J. Org. Chem.* ***1974***, *39*, 861; Zweifel, G.; Fisher, R.P. *Synthesis* ***1974***, 339; Midland, M.M.; Brown, H.C. *J. Org. Chem.* ***1975***, *40*, 2845; Levy, A.B.; Schwartz, S.J. *Tetrahedron Lett.* ***1976***, 2201; Baba, T.; Avasthi, K.; Suzuki, A. *Bull. Chem. Soc. Jpn.* ***1983***, *56*, 1571; Pelter, A.; Rao, J.M. *J. Organomet. Chem.* ***1985***, *285*, 65; Junchai, B.; Hongxun, D. *J. Chem. Soc., Chem. Commun.* ***1990***, 323.
[430]Brown, H.C.; Rathke, M.W. *J. Am. Chem. Soc.* ***1967***, *89*, 2738.

present in R without being affected,[431] though if they are in the α or β position relative to the boron atom, difficulties may



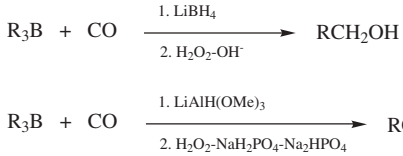
91

be encountered. The use of an equimolar amount of trifluoroacetic anhydride leads to the ketone rather than the tertiary alcohol.[427,432] By this procedure, thexylboranes ($RR'R^2B$, where R^2 = thexyl) can be converted to unsymmetrical ketones (RCOR').[433] Variations of this methodology have been used to prepare optically active alcohols.[434]

For another conversion of trialkylboranes to ketones (see **18-26**).[435] Other conversions of boranes to secondary alcohols are also known.[436]

OS **VII**, 427. Also see, OS **VI**, 137.

18-24 Conversion of Boranes to Primary Alcohols, Aldehydes, or Carboxylic Acids



When the reaction between a trialkylborane and carbon monoxide (**18-23**) is carried out in the presence of a reducing agent such as lithium borohydride or potassium triisopropoxyborohydride, the reduction agent intercepts the intermediate **89**, so that only one boron-to-carbon migration takes place, and the product is hydrolyzed to a primary alcohol or oxidized to an aldehyde.[437] This procedure wastes two of the three R groups, but this problem can be avoided by the use of

[431]Brown, H.C.; Kabalka, G.W.; Rathke, M.W. *J. Am. Chem. Soc.* ***1967***, *89*, 4530.

[432]Pelter, A.; Smith, K.; Hutchings, M.G.; Rowe, K. *J. Chem. Soc. Perkin Trans. 1* ***1975***, 129; See also, Mallison, P.R.; White, D.N.J.; Pelter, A.; Rowe, K.; Smith, K. *J. Chem. Res. (S)*, ***1978***, 234.

[433]This has been done enantioselectively: Brown, H.C.; Bakshi, R.K.; Singaram, B. *J. Am. Chem. Soc.* ***1988***, *110*, 1529.

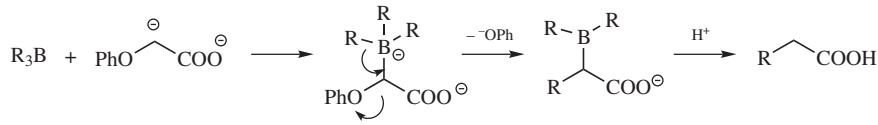
[434]For reviews, see Matteson, D.S. *Mol. Struct. Energ.* ***1988***, *5*, 343; *Acc. Chem. Res.* ***1988***, *21*, 294; *Synthesis* ***1986***, 973, 980–983.

[435]For still other methods, see Brown, H.C.; Levy, A.B.; Midland, M.M. *J. Am. Chem. Soc.* ***1975***, *97*, 5017; Ncube, S.; Pelter, A.; Smith, K. *Tetrahedron Lett.* ***1979***, 1893; Pelter, A.; Rao, J.M. *J. Organomet. Chem.* ***1985***, *285*, 65; Yogo, T.; Koshino, J.; Suzuki, A. *Chem. Lett.* ***1981***, 1059; Brown. H.C.; Bhat, N.G.; Basavaiah, D. *Synthesis* ***1983***, 885; Narayana, C.; Periasamy, M. *Tetrahedron Lett.* ***1985***, *26*, 6361.

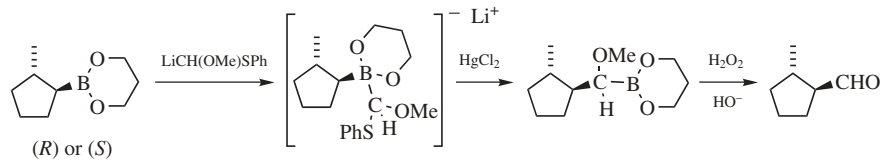
[436]See, for example, Zweifel, G.; Fisher, R.P. *Synthesis* ***1974***, 339; Brown, H.C.; DeLue, N.R. *J. Am. Chem. Soc.* ***1974***, *96*, 311; Hubbard, J.L.; Brown, H.C. *Synthesis* ***1978***, 676; Uguen, D. *Bull. Soc. Chim. Fr.* ***1981***, II-99.

[437]Brown, H.C.; Hubbard, J.L.; Smith, K. *Synthesis* ***1979***, 701, and references cited therein. For discussions of the mechanism, see Brown, H.C.; Hubbard, J.L. *J. Org. Chem.* ***1979***, *44*, 467; Hubbard, J.L.; Smith, K. *J. Organomet. Chem.* ***1984***, *276*, C41.

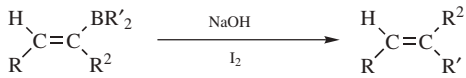
B-alkyl-9-BBN derivatives (p. 1077). Since only the 9-alkyl group migrates, this method permits the conversion in high yield of an alkene to a primary alcohol or aldehyde containing one more carbon.[438] When B-alkyl-9-BBN derivatives are treated with CO and lithium tri-*tert*-butoxyaluminum hydride,[439] other functional groups (e.g., CN and ester) can be present in the alkyl group without being reduced.[440] Boranes can be directly converted to carboxylic acids by reaction with the dianion of phenoxyacetic acid.[441]



Boronic esters $RB(OR')_2$ react with methoxy(phenylthio)methyllithium LiCH(OMe)SPh to give salts, which, after treatment with $HgCl_2$, and then H_2O_2, yield aldehydes.[442] This synthesis has been made enantioselective, with high ee values (>99%), by the use of an optically pure boronic ester,[443] for example:



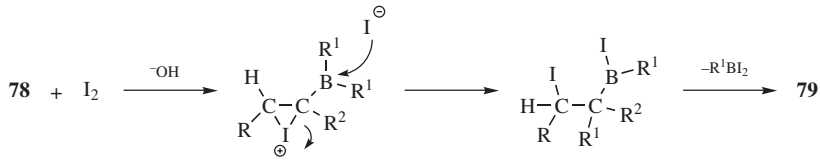
18-25 Conversion of Vinylic Boranes to Alkenes



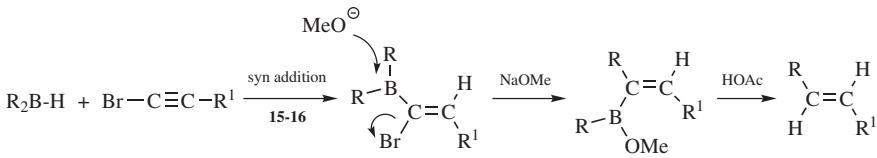
The reaction between trialkylboranes and iodine to give alkyl iodides was mentioned at **12-31**. When the substrate contains a vinylic group, the reaction takes a different course,[444] with one of the R' groups migrating to the carbon, to give alkenes.[445] The reaction is stereospecific in two senses: (*1*) if the groups

[438]Brown, H.C.; Knights, E.F.; Coleman, R.A. *J. Am. Chem. Soc.* ***1969***, *91*, 2144.
[439]Brown, H.C.; Coleman, R.A. *J. Am. Chem. Soc.* ***1969***, *91*, 4606.
[440]For other methods of converting boranes to aldehydes, see Yamamoto, S.; Shiono, M.; Mukaiyama, T. *Chem. Lett.* ***1973***, 961; Negishi, E.; Yoshida, T.; Silveira, Jr., A.; Chiou, B.L. *J. Org. Chem.* ***1975***, *40*, 814.
[441]Hara, S.; Kishimura, K.; Suzuki, A.; Dhillon, R.S. *J. Org. Chem.* ***1990***, *55*, 6356. See also, Brown, H.C.; Imai, T. *J. Org. Chem.* ***1984***, *49*, 892.
[442]Brown, H.C.; Imai, T. *J. Am. Chem. Soc.* ***1983***, *105*, 6285. For a related method that produces primary alcohols, see Brown, H.C.; Imai, T.; Perumal, P.T.; Singaram, B. *J. Org. Chem.* ***1985***, *50*, 4032.
[443]Brown, H.C.; Imai, T.; Desai, M.C.; Singaram, B. *J. Am. Chem. Soc.* ***1985***, *107*, 4980.
[444]Zweifel, G.; Fisher, R.P. *Synthesis* ***1975***, 376; Brown, H.C.; Basavaiah, D.; Kulkarni, S.U.; Bhat, N.G.; Vara Prasad, J.V.N. *J. Org. Chem.* ***1988***, *53*, 239.
[445]For a list of methods of preparing alkenes using boron reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 421–427.

R and R″ are cis in the starting compound, they will be trans in the product; (*2*) there is retention of configuration within the migrating group R′.[446] Since vinylic boranes can be prepared from alkynes (**15-16**), this is a method for the addition of R′ and H to a triple bond. If $R^2 = H$, the product is a (*Z*)-alkene. The mechanism is believed to involve an iodonium intermediate, such as **92**, and attack by iodide on boron. When R′ is vinylic, the product is a conjugated diene.[447]



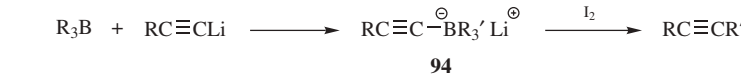
In another procedure, the addition of a dialkylborane to a 1-haloalkyne produces an α-halo vinylic borane (**93**).[448] Treatment of this with NaOMe gives the rearrangement shown, and protonolysis of the product



produces the (*E*)-alkene.[446] If R is a vinylic group the product is a 1,3-diene.[449] If one of the groups is thexyl, the other migrates.[450] This extends the scope of the synthesis, since dialkylboranes where one R group is thexyl are easily prepared. A combination of both of the procedures described above results in the preparation of trisubstituted alkenes.[451] The entire conversion of haloalkyne to alkene can be carried out in one reaction vessel, without isolation of intermediates. An aluminum counterpart of the α-halo vinylic borane procedure has been reported.[452]

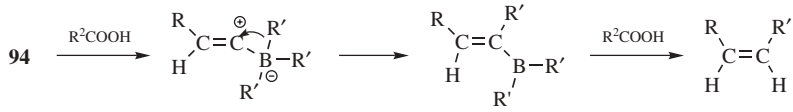
[446]Zweifel, G.; Fisher, R.P.; Snow, J.T.; Whitney, C.C. *J. Am. Chem. Soc.* ***1971***, *93*, 6309.
[447]Zweifel, G.; Polston, N.L.; Whitney, C.C. *J. Am. Chem. Soc.* ***1968***, *90*, 6243; Brown, H.C.; Ravindran, N. *J. Org. Chem.* ***1973***, *38*, 1617; Hyuga, S.; Takinami, S.; Hara, S.; Suzuki, A. *Tetrahedron Lett.* ***1986***, *27*, 977.
[448]For improvements in this method, see Brown, H.C.; Basavaiah, D.; Kulkarni, S.U.; Lee, H.D.; Negishi, E.; Katz, J. *J. Org. Chem.* ***1986***, *51*, 5270.
[449]Negishi, E.; Yoshida, T. *J. Chem. Soc. Chem. Commun.* ***1973***, 606; See also, Negishi, E.; Yoshida, T.; Abramovitch, A.; Lew, G.; Williams, R.H. *Tetrahedron* ***1991***, *47*, 343.
[450]Corey, E.J.; Ravindranathan, T. *J. Am. Chem. Soc.* ***1972***, *94*, 4013; Negishi, E.; Katz, J.; Brown, H.C. *Synthesis* ***1972***, 555.
[451]Zweifel, G.; Fisher, R.P. *Synthesis* ***1972***, 557.
[452]Miller, J.A. *J. Org. Chem.* ***1989***, *54*, 998.

18-26 Formation of Alkynes, Alkenes, and Ketones from Boranes and Acetylides



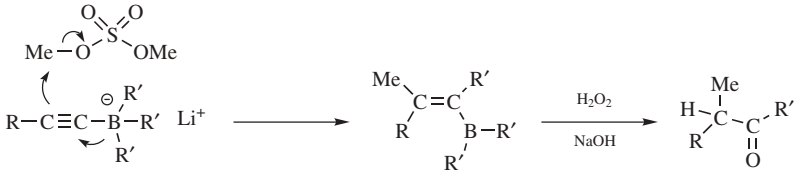
94

A hydrogen directly attached to a triple-bond carbon can be replaced in high yield by an alkyl or an aryl group, by treatment of the lithium acetylide with a trialkyl- or triarylborane, followed by reaction of the lithium alkynyltrialkylborate **94** with iodine.[453] The R′ group may be primary or secondary alkyl as well as aryl, so the reaction has a broader scope than the older reaction **10-74**.[454] The R group may be alkyl, aryl, or hydrogen, though in the last-mentioned case satisfactory yields are obtained only if lithium acetylide–ethylenediamine is used as the starting



compound.[455] Optically active alkynes can be prepared by using optically active thexylborinates (RR^2BOR', R^2 = thexyl), where R is chiral, and $LiC{\equiv}CSiMe_3$.[456] The reaction can be adapted to the preparation of alkenes[414] by treatment of **94** with an electrophile such as propanoic acid[457] or tributyltin chloride.[458] The reaction with Bu_3SnCl produces the (*Z*)-alkene stereoselectively.

Treatment of **94** with an electrophile, such as methyl sulfate, allyl bromide, or triethyloxonium borofluoride, followed by oxidation of the resulting vinylic borane gives a ketone (illustrated for methyl sulfate):[459]



[453]Suzuki, A.; Miyaura, N.; Abiko, S.; Itoh, M.; Brown, H.C.; Sinclair, J.A.; Midland, M.M. *J. Org. Chem.* ***1986***, *51*, 4507; Sikorski, J.A.; Bhat, N.G.; Cole, T.E.; Wang, K.K.; Brown, H.C. *J. Org. Chem.* ***1986***, *51*, 4521. For a review of reactions of organoborates, see Suzuki, A. *Acc. Chem. Res.* ***1982***, *15*, 178.

[454]For a study of the relative migratory aptitudes of R', see Slayden, S.W. *J. Org. Chem.* ***1981***, *46*, 2311.

[455]Midland, M.M.; Sinclair, J.A.; Brown, H.C. *J. Org. Chem.* ***1974***, *39*, 731.

[456]Brown, H.C.; Mahindroo, V.K.; Bhat, N.G.; Singaram, B. *J. Org. Chem.* ***1991***, *56*, 1500.

[457]Miyaura, N.; Yoshinari, T.; Itoh, M.; Suzuki, A. *Tetrahedron Lett.* ***1974***, 2961; Pelter, A.; Gould, K.J.; Harrison, C.R. *Tetrahedron Lett.* ***1975***, 3327.

[458]Hooz, J.; Mortimer, R. *Tetrahedron Lett.* ***1976***, 805; Wang, K.K.; Chu, K. *J. Org. Chem.* ***1984***, *49*, 5175.

[459]Pelter, A.; Drake, R.A. *Tetrahedron Lett.* ***1988***, *29*, 4181.

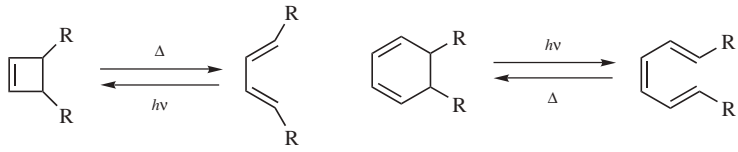
Note that there are reactions that involve N → O rearrangements, including those mediated by silicon.[460]

NON-1,2 REARRANGEMENTS

A. Electrocyclic Rearrangements

18-27 Electrocyclic Rearrangements of Cyclobutenes and 1,3-Cyclohexadienes

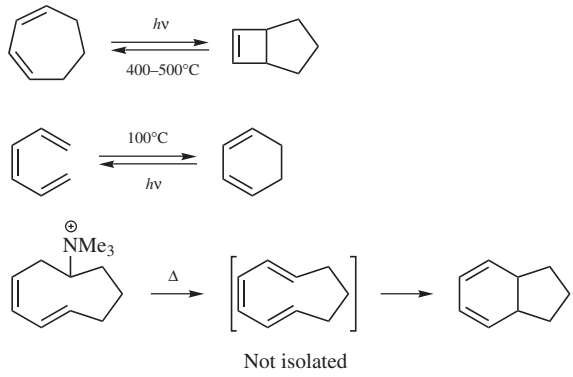
(4)*seco*-1/4/Detachment; (4)*cyclo*-1/4/Attachment
(6)*seco*-1,6/Detachment; (6)*cyclo*-1/6/Attachment



Cyclobutenes and 1,3-dienes can be interconverted by treatment with uv light or with heat.[461] The thermal reaction is generally not reversible (although exceptions[462] are known), and many cyclobutenes have been converted to 1,3-dienes by heating at temperatures between 100 and 200°C. The photochemical conversion can in principle be carried out in either direction, but most often 1,3-dienes are converted to cyclobutenes rather than the reverse, because the dienes are stronger absorbers of light at the wavelengths used.[463] In a similar reaction, 1,3-cyclohexadienes interconvert with 1,3,5-trienes, but in this case the ring-closing process is generally favored thermally and the ring-opening process photochemically, though exceptions are known in both directions.[464] Substituent effects can lead to acceleration of the electrocyclization process.[465] Torquoselectivity in cyclobutene ring opening reaction has been examined.[466]

[460]Talami, S.; Stirling, C.J.M. *Can. J. Chem.* ***1999***, *77*, 1105.
[461]See Dolbier Jr., W.R.; Koroniak, H.; Houk, K.N.; Sheu, C. *Acc. Chem. Res.* ***1996***, *29*, 471; Niwayama, S.; Kallel, E.A.; Spellmeyer, D.C.; Sheu, C.; Houk, K.N. *J. Org. Chem.* ***1996***, *61*, 2813. The effect of pressure on this reaction has been discussed, see Jenner, G. *Tetrahedron* ***1998***, *54*, 2771.
[462]For example; see Shumate, K.M.; Neuman, P.N.; Fonken, G.J. *J. Am. Chem. Soc.* ***1965***, *87*, 3996; Gil-Av, E.; Herling, J. *Tetrahedron Lett.* ***1967***, 1; Doorakian, G.A.; Freedman, H.H. *J. Am. Chem. Soc.* ***1968***, *90*, 3582; Brune, H.A.; Schwab, W. *Tetrahedron* ***1969***, *25*, 4375; Steiner, R.P.; Michl, J. *J. Am. Chem. Soc.* ***1978***, *100*, 6413.
[463]For examples of photochemical conversion of a cylcobutene to a 1,3-diene, see Scerer, Jr., K.V. *J. Am. Chem. Soc.* ***1968***, *90*, 7352; Saltiel, J.; Lim, L.N. *J. Am. Chem. Soc.* ***1969***, *91*, 5404; Adam, W.; Oppenländer, T.; Zang, G. *J. Am. Chem. Soc.* ***1985***, *107*, 3921; Dauben, W.G.; Haubrich, J.E. *J. Org. Chem.* ***1988***, *53*, 600.
[464]For a review of photochemical rearrangements in trienes, see Dauben, W.G.; McInnis, E.L.; Michno, D.M., in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 3, Academic Press, NY, ***1980***, pp. 91–129. For an *ab initio* study see Rodríguez-Otero, J. *J. Org. Chem.* ***1999***, *64*, 6842.
[465]Tanaka, K.; Mori, H.; Yamamoto, M.; Katsumura, S. *J. Org. Chem.* ***2001***, *66*, 3099.
[466]Yasui, M.; Naruse, Y.; Inagaki, S. *J. Org. Chem.* ***2004***, *69*, 7246.

Some examples are



Ref.[467]

An interesting example of 1,3-cyclohexadiene–1,3,5-triene interconversion is the reaction of norcaradienes to give cycloheptatrienes.[468] Norcaradienes give this reaction so readily (because they are *cis*-1,2-divinylcyclopropanes, see p. 1661) that they cannot generally be isolated, though some exceptions are known[469,470] (see also, p. 1239).

Norcaradiene

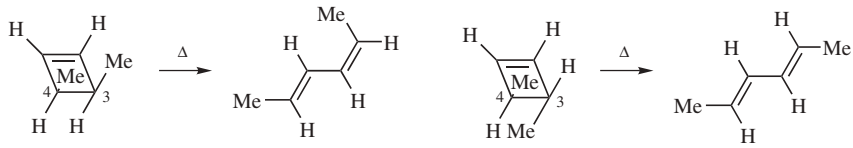
[467]Dauben, W.G.; Cargill, R.L. *Tetrahedron* ***1961***, *12*, 186; Chapman, O.L.; Pasto, D.J.; Borden, G.W.; Griswold, A.A. *J. Am. Chem. Soc.* ***1962***, *84*, 1220.

[468]For reviews of the norcaradiene-cycloheptatriene interconversion and the analogous benzene oxide–oxepin interconversion, see Maier, G. *Angew. Chem. Int. Ed.* ***1967***, *6*, 402; Vogel, E.; Günther, H. *Angew. Chem. Int. Ed.* ***1967***, *6*, 385; Vogel, E. *Pure Appl. Chem.* ***1969***, *20*, 237.

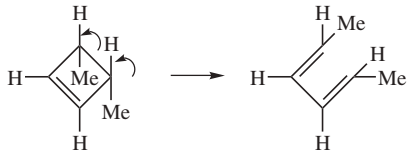
[469]Ciganek, E. *J. Am. Chem. Soc.* ***1967***, *89*, 1454; Mukai, T.; Kubota, H.; Toda, T. *Tetrahedron Lett.* ***1967***, 3581; Maier, G.; Heep, U. *Chem. Ber.* ***1968***, *101*, 1371; Ciganek, E. *J. Am. Chem. Soc.* ***1971***, *93*, 2207; Dürr, H.; Kober, H. *Tetrahedron Lett.* ***1972***, 1255, 1259; Vogel, E.; Wiedemann, W.; Roth, H.D.; Eimer, J.; Günther, H. *Liebigs Ann. Chem.* ***1972***, *759*, 1; Bannerman, C.G.F.; Cadogan, J.I.G.; Gosney, I.; Wilson, N.H. *J. Chem. Soc., Chem. Commun.* ***1975***, 618; Takeuchi, K.; Kitagawa, T.; Senzaki, Y.; Okamoto, K. *Chem. Lett.* ***1983***, 73; Kawase, T.; Iyoda, M.; Oda, M. *Angew. Chem. Int. Ed.* ***1987***, *26*, 559.

[470]See, for example, Ciganek, E. *J. Am. Chem. Soc.* ***1967***, *89*, 1454; Mukai, T.; Kubota, H.; Toda, T. *Tetrahedron Lett.* ***1967***, 3581; Maier, G.; Heep, U. *Chem. Ber.* ***1968***, *101*, 1371; Ciganek, E. *J. Am. Chem. Soc.* ***1971***, *93*, 2207; Dürr, H.; Kober, H. *Tetrahedron Lett.* ***1972***, 1255, 1259; Vogel, E.; Wiedemann, W.; Roth, H.D.; Eimer, J.; Günther, H. *Liebigs Ann. Chem.* ***1972***, *759*, 1; Bannerman, C.G.F.; Cadogan, J.I.G.; Gosney, I.; Wilson, N.H. *J. Chem. Soc., Chem. Commun.* ***1975***, 618; Takeuchi, K.; Kitagawa, T.; Senzaki, Y.; Okamoto, K. *Chem. Lett.* ***1983***, 73; Kawase, T.; Iyoda, M.; Oda, M. *Angew. Chem. Int. Ed.* ***1987***, *26*, 559.

These reactions, called *electrocyclic rearrangements*,[471] take place by pericyclic mechanisms. The evidence comes from stereochemical studies, which show a remarkable stereospecificity whose direction depends on whether the reaction is induced by heat or light. For example, it was found for the thermal reaction that *cis*-3,4-dimethylcyclobutene gave only *cis*,*trans*-2,4-hexadiene, while the trans isomer gave only the trans–trans diene:[472]



This is evidence for a four-membered cyclic transition state and arises from conrotatory motion about the C-3–C-4 bond.[473] It is called conrotatory because both movements are clockwise (or both counterclockwise). Because both rotate in the same direction, the cis isomer gives the cis–trans diene:[474]



The other possibility (*disrotatory* motion) would have one moving clockwise while the other moves counterclockwise; the cis isomer would have given the cis–cis

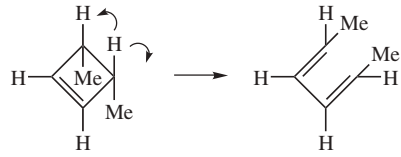
[471]For a monograph on thermal isomerizations, which includes electrocyclic and sigmatropic rearrangements, as well as other types, see Gajewski, J.J. *Hydrocarbon Thermal Isomerizations*, Academic Press, NY, ***1981***. For a monograph on electrocyclic reactions, see Marvell, E.N. *Thermal Electrocyclic Reactions*, Academic Press, NY, ***1980***. For reviews, see Dolbier, W.R.; Koroniak, H. *Mol. Struct. Energ.*, ***1988***, *8*, 65; Laarhoven, W.H. *Org. Photochem.* ***1987***, *9*, 129; George, M.V.; Mitra, A.; Sukumaran, K.B. *Angew. Chem. Int. Ed.* ***1980***, *19*, 973; Jutz, J.C. *Top. Curr. Chem.* ***1978***, *73*, 125; Gilchrist, T.L.; Storr, R.C. *Organic Reactions and Orbital Symmetry*, Cambridge University Press, Cambridge, ***1972***, pp. 48–72; DeWolfe, R.H. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9, Elsevier, NY, ***1973***; pp. 461–470; Crowley, K.J.; Mazzocchi, P.H., in Zabicky, J. *The Chemistry of Alkenes*, Vol. 2, Wiley, NY, ***1970***, pp. 284–297; Criegee, R. *Angew. Chem. Int. Ed.* ***1968***, *7*, 559; Vollmer, J.J.; Servis, K.L. *J. Chem. Educ.* ***1968***, *45*, 214. For a review of isotope effects in these reactions, see Gajewski, J.J. *Isot. Org. Chem.* ***1987***, *7*, 115. For a related review, see Schultz, A.G.; Motyka, L. *Org. Photochem.* ***1983***, *6*, 1.

[472]Winter, R.E.K. *Tetrahedron Lett.* ***1965***, 1207. Also see, Vogel, E. *Liebigs Ann. Chem.* ***1958***, *615*, 14; Criegee, R.; Noll, K. *Liebigs Ann. Chem.* ***1959***, *627*, 1.

[473]The mechanism of cyclobutene thermal isomerization has been examined. See Baldwin, J.E.; Gallagher, S.S.; Leber, P.A.; Raghavan, A.S.; Shukla, R. *J. Org. Chem.* ***2004***, *69*, 7212.

[474]This picture is from Woodward, R.B.; Hoffmann, R. *J. Am. Chem. Soc.* ***1965***, *87*, 395, who coined the terms, *conrotatory* and *disrotatory.*

diene (shown) or the trans–trans diene:



If the motion had been disrotatory, this would still have been evidence for a cyclic mechanism. If the mechanism were a diradical or some other kind of noncyclic process, it is likely that no stereospecificity of either kind would have been observed. The reverse reaction is also conrotatory. In contrast, the photochemical cyclobutene: 1,3-Diene interconversion is *disrotatory* in either direction.[475] On the other hand, the cyclohexadiene: 1,3,5-Triene interconversion shows precisely the opposite behavior. The thermal process is *disrotatory*, while the photochemical process is *conrotatory* (in either direction). These startling results are a consequence of the symmetry rules mentioned in Chapter 15 (p. 1208).[476] As in the case of cycloaddition reactions, we will use the frontier orbital and Möbius–Hückel approaches.[477]

The Frontier Orbital Method[478]

As applied to these reactions, the frontier orbital method may be expressed: *A* σ *bond will open in such a way that the resulting p orbitals will have the symmetry of the highest occupied* π *orbital of the product*. In the case of cyclobutenes, the HOMO of the product in the thermal reaction is the χ_2 orbital (Fig. 18.1).

[475]Photochemical ring opening of cyclobutenes can also be nonstereospecific. See Leigh, W.J.; Zheng, K. *J. Am. Chem. Soc.* ***1991***, *113*, 4019; Leigh, W.J.; Zheng, K.; Nguyen, N.; Werstiuk, N.H.; Ma, J. *J. Am. Chem. Soc.* ***1991***, *113*, 4993, and references cited therein.

[476]Woodward, R.B.; Hoffmann, R. *J. Am. Chem. Soc.* ***1965***, *87*, 395. Also see, Longuet-Higgins, H.C.; Abrahamson, E.W. *J. Am. Chem. Soc.* ***1965***, *87*, 2045; Fukui, K. *Tetrahedron Lett.* ***1965***, 2009.

[477]For the correlation diagram method, see Jones, R.A.Y. *Physical and Mechanistic Organic Chemistry*, 2nd ed., Cambridge University Press, Cambridge, ***1984***, pp. 352–359; Yates, K. *Hückel Molecular Orbital Theory*, Academic Press, NY, ***1978***, pp. 250–263. Also see, Zimmerman, H.E., in Marchand, A.P.; Lehr, R.E. *Pericyclic Reactions*, Vol. 2, Academic Press, NY, ***1977***, pp. 53–107; *Acc. Chem. Res.* ***1971***, *4*, 272; *J. Am. Chem. Soc.* ***1966***, *88*, 1564, 1566; Dewar, M.J.S. *Angew. Chem. Int. Ed.* ***1971***, *10*, 761; Jefford, C.W.; Burger, U. *Chimia* ***1971***, *25*, 297; Herndon, W.C. *J. Chem. Educ.* ***1981***, *58*, 371.

[478]Fukui, K.; Fujimoto, H. *Bull. Chem. Soc. Jpn.* ***1967***, *40*, 2018; ***1969***, *42*, 3399; Fukui, K. *Fortschr. Chem. Forsch.* ***1970***, *15*, 1; *Acc. Chem. Res.* ***1971***, *4*, 57; Houk, K.N. *Acc. Chem. Res.* ***1975***, *8*, 361. See also, Chu, S. *Tetrahedron* ***1978***, *34*, 645. For a monograph on frontier orbitals see Fleming, I. *Pericyclic Reactions*, Oxford University Press, Oxford, ***1999***. For reviews, see Fukui, K. *Angew. Chem. Int. Ed.* ***1982***, *21*, 801; Houk, K.N., in Marchand, A.P.; Lehr, R.F. *Pericyclic Reactions*, Vol. 2, Academic Press, NY, ***1977***, pp. 181–271.

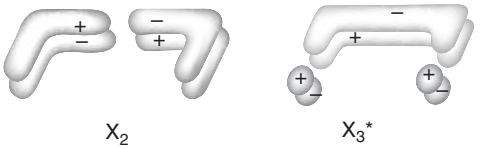


Fig. 18.1. Symmetries of the X_2 and X_3* orbitals of a conjugated diene.

Therefore, in a thermal process, the cyclobutene must open so that on one side the positive lobe lies above the plane, and on the other side below it. Thus the substituents are forced into conrotatory motion (Fig. 18.2). On the other hand, in the photochemical process, the HOMO of the product is now the χ_3 orbital (Fig. 18.1), and in order for the *p* orbitals to achieve this symmetry (the two plus lobes on the same side of the plane), the substituents are forced into disrotatory motion.

We may also look at this reaction from the opposite direction (ring closing). For this direction, the rule is that *those lobes of orbitals that overlap (in the HOMO) must be of the same sign*. For thermal cyclization of butadienes, this requires conrotatory motion (Fig. 18.3). In the photochemical process the HOMO is the χ_3 orbital, so that disrotatory motion is required for lobes of the same sign to overlap.

The Möbius–Hückel Method[481]

As we saw on p. 1210, in this method we choose a basis set of *p* orbitals and look for sign inversions in the transition state. Figure 18.4 shows a basis set for a 1,3-diene. It is seen that disrotatory ring closing (Fig. 18.4*a*) results in overlap of plus lobes only, while in conrotatory closing (Fig. 18.4*b*) there is one overlap of a plus

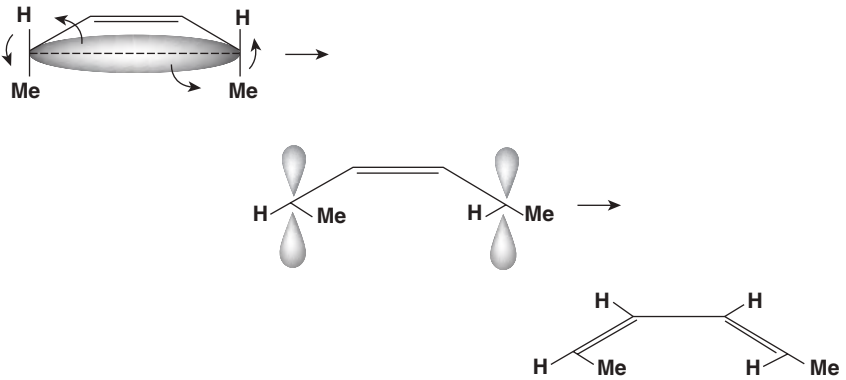


Fig. 18.2. Thermal opening of 1,2-dimethylcyclobutene. The two hydrogens and two methyls are forced into conrotatory motion so that the resulting *p* orbitals have the symmetry of the HOMO of the diene.

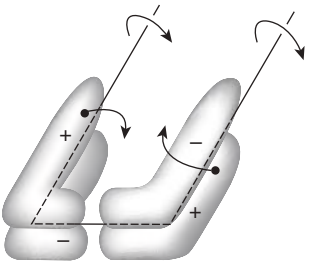


Fig. 18.3. Thermal ring closing of a 1,3-diene. Conrotatory motion is required for two + lobes to overlap.

with a minus lobe. In the first case, we have zero sign inversions, while in the second there is one sign inversion. With zero (or an even number of) sign inversions, the disrotatory transition state is a Hückel system, and so is allowed thermally only if the total number of electrons is $4n + 2$ (p. 1211). Since the total here is 4, the

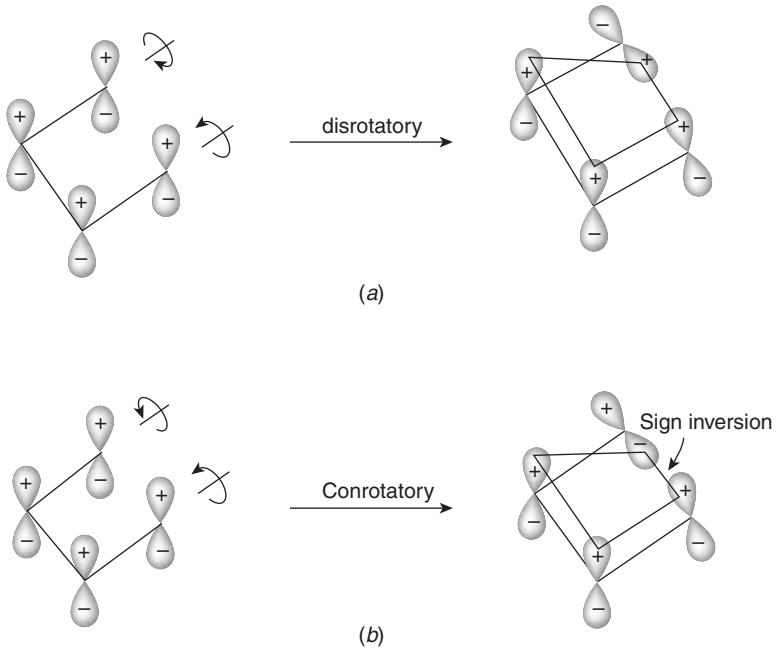
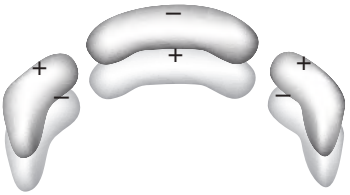


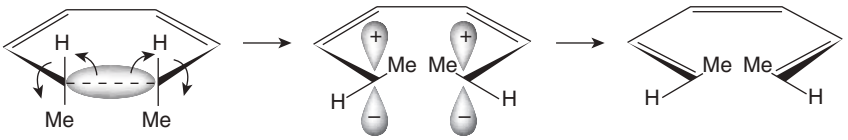
Fig. 18.4. The 1,3-diene–cyclobutene interconversion. The orbitals shown are *not* molecular orbitals, but a basis set of *p*-atomic orbitals. (*a*) Disrotatory ring closure gives zero sign inversion. (*b*) Conrotatory ring closure gives one sign inversion. We could have chosen to show any other basis set (e.g., another basis set would have two plus lobes above the plane and two below, etc.). This would change the number of sign inversion, but the disrotatory mode would still have an even number of sign inversions, and the conrotatory mode an odd number, whichever basis set was chosen.

disrotatory process is not allowed. On the other hand, the conrotatory process, with one sign inversion, is a Möbius system, which is thermally allowed if the total number is $4n$. The conrotatory process is therefore allowed thermally. For the photochemical reactions, the rules are reversed: A reaction with $4n$ electrons requires a Hückel system, so only the disrotatory process is allowed.

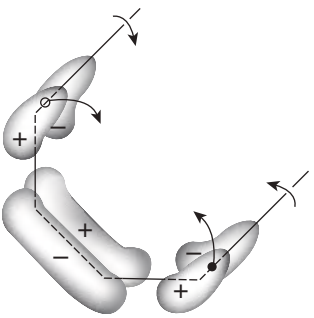
Both the frontier orbital and the Möbius–Hückel methods can also be applied to the cyclohexadiene: 1,3,5-triene reaction;[479] in either case the predicted result is that for the thermal process, only the disrotatory pathway is allowed, and for the photochemical process, only the conrotatory. For example, for a 1,3,5-triene, the symmetry of the HOMO is



In the thermal cleavage of cyclohexadienes, then, the positive lobes must lie on the same side of the plane, requiring disrotatory motion:



Disrotatory motion is also necessary for the reverse reaction, in order that the orbitals that overlap may be of the same sign:

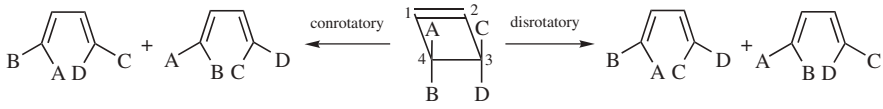


[479]For a discussion of the transition structures and energy, see Zora, M. *J. Org. Chem.* ***2004***, *69*, 1940.

All these directions are reversed for photochemical processes, because in each case a higher orbital, with inverted symmetry, is occupied.

In the Möbius–Hückel approach, diagrams similar to Fig. 18.4 can be drawn for this case. Here too, the disrotatory pathway is a Hückel system and the conrotatory pathway a Möbius system, but since six electrons are now involved, the thermal reaction follows the Hückel pathway and the photochemical reaction the Möbius pathway.

In the most general case, there are four possible products that can arise from a given cyclobutene or cyclohexadiene: two from the conrotatory and two from the disrotatory pathway. For example, conrotatory ring opening of **95** gives either **96** or **97**, while disrotatory opening gives either **98** or **99**. The orbital-symmetry rules tell us when a given reaction will operate by the conrotatory and when by the disrotatory mode, but they do not say which of the two possible conrotatory or disrotatory pathways will be followed. It is often possible,



96 **97** **95** **98** **99**

however, to make such predictions on steric grounds. For example, in the opening of **95** by the disrotatory pathway, **98** arises when groups A and C swing in toward each other (clockwise motion around C-4, counterclockwise around C-3), while **99** is formed when groups B and D swing in and A and C swing out (clockwise motion around C-3, counterclockwise around C-4). We therefore predict that when A and C are larger than B and D, the predominant or exclusive product will be **99**, rather than **98**. Predictions of this kind have largely been borne out.[480] There is evidence, however, that steric effects[481] are not the only factor, and that electronic effects also play a role, which may be even greater.[482] An electron-donating group stabilizes the transition state when it rotates *outward*, because it mixes with the LUMO; if it rotates *inward*, it mixes with the HOMO, destabilizing the transition state.[483] The compound 3-formylcyclobutene provided a test. Steric factors would cause the CHO

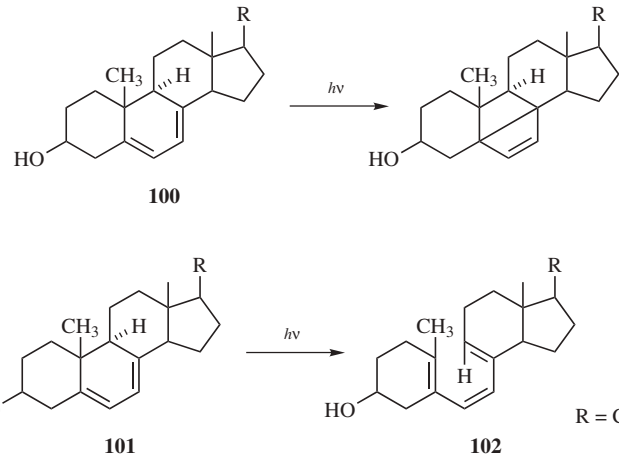
[480]For example, see Baldwin, J.E.; Krueger, S.M. *J. Am. Chem. Soc.* ***1969***, *91*, 6444; Spangler, C.W.; Hennis, R.P. *J. Chem. Soc., Chem. Commun.* ***1972***, 24; Gesche, P.; Klinger, F.; Riesen, A.; Tschamber, T.; Zehnder, M.; Streith, J. *Helv. Chim. Acta* ***1987***, *70*, 2087.

[481]Leigh, W.J.; Postigo, J.A. *J. Am. Chem. Soc.* ***1995***, *117*, 1688.

[482]Kirmse, W.; Rondan, N.G.; Houk, K.N. *J. Am. Chem. Soc.* ***1984***, *106*, 7989; Dolbier, Jr., W.R.; Gray, T.A.; Keaffaber, J.J.; Celewicz, L.; Koroniak, H. *J. Am. Chem. Soc.* ***1990***, *112*, 363; Hayes, R.; Ingham, S.; Saengchantara, S.T.; Wallace, T.W. *Tetrahedron Lett.* ***1991***, *32*, 2953.

[483]For theoretical studies, see Buda, A.B.; Wang, Y.; Houk, K.N. *J. Org. Chem.* ***1989***, *54*, 2264; Kallel, E.A.; Wang, Y.; Spellmeyer, D.C.; Houk, K.N. *J. Am. Chem. Soc.* ***1990***, *112*, 6759.

(an electron-withdrawing group) to rotate outward; electronic effects would cause it to rotate inward. The experiment showed inward rotation.[484]



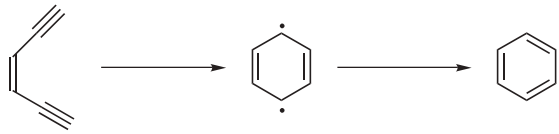
Cyclohexadienes are of course 1,3-dienes, and in certain cases it is possible to convert them to cyclobutenes instead of to 1,3,5-trienes.[485] An interesting example is found in the pyrocalciferols. Photolysis of the syn isomer **100** (or of the other syn isomer, not shown) leads to the corresponding cyclobutene,[486] while photolysis of the anti isomers (one of them is **101**) gives the ring-opened 1,3,5-triene, **102**. This difference in behavior is at first sight remarkable, but is easily explained by the orbital-symmetry rules. Photochemical ring opening to a 1,3,5-triene must be conrotatory. If **100** were to react by this pathway, the product would be the triene **102**, but this compound would have to contain a *trans*-cyclohexene ring (either the methyl group or the hydrogen would have to be directed inside the ring). On the other hand, photochemical conversion to a cyclobutene must be disrotatory, but if **101** were to give this reaction, the product would have to have a trans-fused ring junction. Compounds with such ring junctions are known (p. 188), but are very strained. Stable *trans*-cyclohexenes are unknown (p. 226). Thus, **100** and **101** give the products they do owing to a combination of orbital-symmetry rules and steric influences.

[484]Rudolf, K.; Spellmeyer, D.C.; Houk, K.N. *J. Org. Chem.* ***1987***, *52*, 3708; Piers, E.; Lu, Y.-F. *J. Org. Chem.* ***1989***, *54*, 2267.

[485]For a discussion of the factors favoring either direction, see Dauben, W.G.; Kellogg, M.S.; Seeman, J.I.; Vietmeyer, N.D.; Wendschuh, P.H. *Pure Appl. Chem.* ***1973***, *33*, 197.

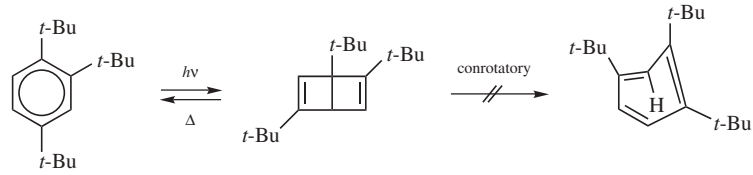
[486]Dauben, W.G.; Fonken, G.J. *J. Am. Chem. Soc.* ***1959***, *81*, 4060. This was the first reported example of the conversion of a 1,3-diene to a cyclobutene.

A variation of this process is the *Bergmann cyclization*,[487] where an ene-diyne cyclizes to a biradical (**103**) and then aromatizes as shown.



103

Simply heating the en-diyne will usually lead to aromatization via this pathway.[488] Quinones can be formed via Bergman cyclization[489] and there are other synthetic applications.[490] The role of vinyl substitution has been examined.[491] An aza-Bergman cyclization is known.[492]



104 **105** **106**

The 1,3-diene-cyclobutene interconversion can even be applied to benzene rings. For example,[493] photolysis of 1,2,4-tri-*tert*-butylbenzene (**104**) gives

[487]Bergman, R.G. *Accts. Chem. Res*. ***1973***, *6*, 25; Darby, N.; Kim, C.U.; Shelton, K.W.; Takada, S.; Masamune, S. *J. Chem. Soc. (D)*, ***1971***, *23*, 1516; Adam, W.; Krebs, O. *Chem. Rev*. ***2003***, *103*, 4131. For a discussion of electronic and stereoelectronic effects see Pourde II, G.W.; Warner, P.M.; Parrish, D.A.; Jones, G.B. *J. Org. Chem*. ***2002***, *67*, 5369; Jones, G.B.; Wright, J.M.; Hynd, G.; Wyatt, J.K.; Warner, P.M.; Huber, R.S.; Li, A.; Kilgore, M.W.; Sticca, R.P.; Pollenz, R.S. *J. Org. Chem*. ***2002***, *67*, 5727. For polar effects, see Schmittel, M.; Kiau, S. *Chem. Lett*, ***1995***, 953; Grissom, J.W.; Calkins, T.L.; McMillen, H.A.; Jiang, Y. *J. Org. Chem*. ***1994***, *59*, 5833. For free-energy relationships see Choy, N.; Kim, C.-S.; Ballestero, C.; Artigas, L.; Diez, C.; Lichtenberger, F.; Shapiro, J.; Russell, K.C. *Tetrahedron Lett*. ***2000***, *41*, 6955.

[488]For examples, see Grissom, J.W.; Klingberg, D. *Tetrahedron Lett.* ***1995***, *36*, 6607; Danheiser, R.L.; Gould, A.E.; de la Pradilla, R.F.; Helgason, A.L. *J. Org. Chem.* ***1994***, *59*, 5514; Grissom, J.W.; Calkins, T.L.; McMillen, H.A. *J. Org. Chem.* ***1993***, *58*, 6556; Tanaka, H.; Yamada, H.; Matsuda, A.; Takahashi, T. *Synlett* ***1997***, 381.

[489]Jones, G.B.; Warner, P.M. *J. Org. Chem.* ***2001***, *66*, 8669.

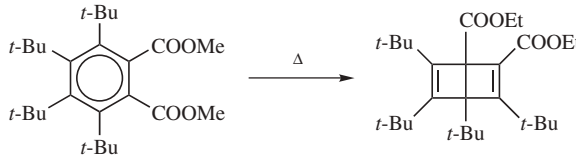
[490]Bowles, D.M.; Palmer, G.J.; Landis, C.A.; Scott, J.L.; Anthony, J.E. *Tetrahedron* ***2001***, *57*, 3753.

[491]Jones, G.B.; Warner, P.M. *J. Am. Chem. Soc.* ***2001***, *123*, 2134.

[492]Feng, L.; Kumar, D.; Kerwin, S.M. *J. Org. Chem.* ***2003***, *68*, 2234.

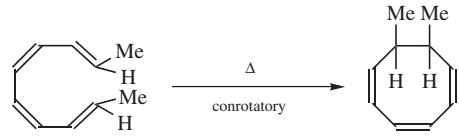
[493]Unsubstituted Dewar benzene has been obtained, along with other photoproducts, by photolysis of benzene: Ward, H.R.; Wishnok, J.S. *J. Am. Chem. Soc.* ***1968***, *90*, 1085; Bryce-Smith, D.; Gilbert, A.; Robinson, D.A. *Angew. Chem. Int. Ed.* ***1971***, *10*, 745. For other examples, see Arnett, E.M.; Bollinger, J.M. *Tetrahedron Lett.* ***1964***, 3803; Camaggi, G.; Gozzo, F.; Cevidalli, G. *Chem. Commun.* ***1966***, 313; Haller, I. *J. Am. Chem. Soc.* ***1966***, *88*, 2070; *J. Chem. Phys.* ***1967***, *47*, 1117; Barlow, M.G.; Haszeldine, R.N.; Hubbard, R. *Chem. Commun.* ***1969***, 202; Lemal, D.M.; Staros, J.V.; Austel, V. *J. Am. Chem. Soc.* ***1969***, *91*, 3373.

1,2,5-tri-*tert*-butyl[2.2.0]hexadiene (**105**, a Dewar benzene).[494] The reaction owes its success to the fact that once **105** is formed, it cannot, under the conditions used, revert to **104** by either a thermal or a photochemical route. The orbital-symmetry rules prohibit thermal conversion of **105** to **104** by a pericyclic mechanism, because thermal conversion of a cyclobutene to a 1,3-diene must be conrotatory, and conrotatory reaction of **105** would result in a 1,3,5-cyclohexatriene containing one trans double bond (**106**), which is of course too strained to exist. Compound **105** cannot revert to **104** by a photochemical pathway either, because light of the frequency used to excite **104** would not be absorbed by **105**. This is thus another example of a molecule that owes its stability to the orbital-symmetry rules (see p. 1232). Pyrolysis of **105** does give **104** , probably by a diradical mechanism.[495] In the case of **107** and **108**, the Dewar benzene is actually more stable than the benzene. Compound **107** rearranges to **108** in 90% yield at 120°C.[496] In this case, thermolysis of the benzene gives the Dewar benzene (rather than the reverse), because of the strain of four adjacent *tert*-butyl groups on the ring.



107 **108**

A number of electrocyclic reactions have been carried out with systems of other sizes, for example, conversion of the 1,3,5,7-octatetraene **109** to the cyclooctatriene **110**.[497] The stereochemistry of these reactions can be predicted in a



109 **110**

[494]Wilzbach, K.E.; Kaplan, L. *J. Am. Chem. Soc.* ***1965***, *87*, 4004; van Tamelen, E.E.; Pappas, S.P.; Kirk, K.L. *J. Am. Chem. Soc.* ***1971***, *93*, 6092; van Tamelen, E.E. *Acc. Chem. Res.* ***1972***, *5*, 186. As mentioned on p. $$$ (Lemal, D.M.; Lokensgard, J.P. *J. Am. Chem. Soc.* ***1966***, *88*, 5934; Schäfer, W.; Criegee, R.; Askani, R.; Grüner, H. *Angew. Chem. Int. Ed.* ***1967***, *6*, 78), Dewar benzenes can be photolyzed further to give prismanes.

[495]See, for example, Oth, J.F.M. *Recl. Trav. Chim. Pays-Bas* ***1968***, *87*, 1185; Adam, W.; Chang, J.C. *Int. J. Chem. Kinet.*, ***1969***, *1*, 487; Lechtken, P.; Breslow, R.; Schmidt, A.H.; Turro, N.J. *J. Am. Chem. Soc.* ***1973***, *95*, 3025; Wingert, H.; Irngartinger, H.; Kallfass, D.; Regitz, M. *Chem. Ber.* ***1987***, *120*, 825.

[496]Maier, G.; Schneider, K. *Angew. Chem. Int. Ed.* ***1980***, *19*, 1022. See also, Wingert, H.; Maas, G.; Regitz, M. *Tetrahedron* ***1986***, *42*, 5341.

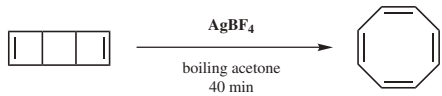
[497]Marvell, E.N.; Seubert, J. *J. Am. Chem. Soc.* ***1967***, *89*, 3377; Huisgen, R.; Dahmen, A.; Huber, H. *J. Am. Chem. Soc.* ***1967***, *89*, 7130, *Tetrahedron Lett.* ***1969***, 1461; Dahmen, A.; Huber, H. *Tetrahedron Lett.* ***1969***, 1465.

similar manner. The results of such predictions can be summarized according to whether the number of electrons involved in the cyclic process is of the form $4n$ or $4n + 2$ (where n is any integer including zero).

	Thermal Reaction	Photochemical Reaction
$4n$	Conrotatory	Disrotatory
$4n + 2$	Disrotatory	Conrotatory

Although the orbital-symmetry rules predict the stereochemical results in almost all cases, it is necessary to recall (p. 1210) that they only say what is allowed and what is forbidden, but the fact that a reaction is allowed does not necessarily mean that the reaction takes place, and if an allowed reaction does take place, it does not *necessarily* follow that a concerted pathway is involved, since other pathways of lower energy may be available.[498] Furthermore, a ''forbidden'' reaction might still be made to go, if a method of achieving its high activation energy can be found. This was, in fact, done for the cyclobutene butadiene interconversion (*cis*-3,4-dichlorocyclobutene gave the forbidden *cis*,-*cis*- and *trans*,*trans*-1,4-dichloro-1,3-butadienes, as well as the allowed cis, trans isomer) by the use of ir laser light.[499] This is a thermal reaction. The laser light excites the molecule to a higher vibrational level (p. 330), but not to a higher electronic state.

As is the case for [2+2]-cycloaddition reactions (**15-63**), certain forbidden electrocyclic reactions can be made to take place by the use of metallic catalysts.[500] An example is the silver ion-catalyzed conversion of tricyclo[4.2.0.0^{2,5}]octa-3,7-diene to cyclooctatetraene:[501]

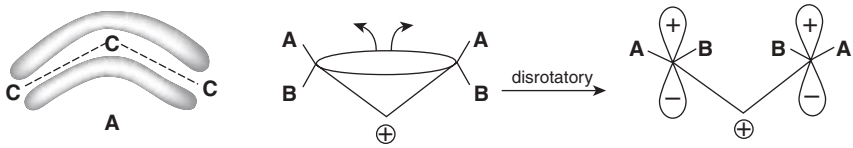


This conversion is very slow thermally (i.e., without the catalyst) because the reaction must take place by a disrotatory pathway, which is disallowed thermally.[502] In another example, the major thermal product from the barrelene anion is a

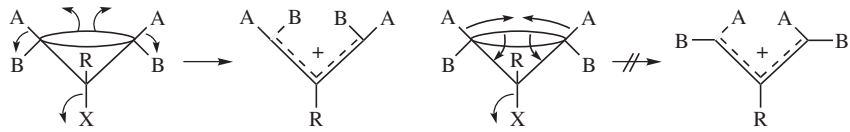
[498]For a discussion, see Baldwin, J.E.; Andrist, A.H.; Pinschmidt Jr., R.K. *Acc. Chem. Res.* ***1972***, *5*, 402.
[499]Mao, C.; Presser, N.; John, L.; Moriarty, R.M.; Gordon, R.J. *J. Am. Chem. Soc.* ***1981***, *103*, 2105.
[500]For a review, see Pettit, R.; Sugahara, H.; Wristers, J.; Merk, W. *Discuss. Faraday Soc.* ***1969***, *47*, 71. See also, Labunskaya, V.I.; Shebaldova, A.D.; Khidekel', M.L. *Russ. Chem. Rev.* ***1974***, *43*, 1; Mango, F.D. *Top. Curr. Chem.* ***1974***, *45*, 39; *Tetrahedron Lett.* ***1973***, 1509; *Intra-Sci. Chem. Rep.* ***1972***, *6 (3)*, 171; *CHEMTECH* ***1971***, *1*, 758; *Adv. Catal.* ***1969***, *20*, 291; Mango, F.D.; Schachtschneider, J.H. *J. Am. Chem. Soc.* ***1971***, *93*, 1123; ***1969***, *91*, 2484; van der Lugt, W.T.A.M. *Tetrahedron Lett.* ***1970***, 2281; Wristers, J.; Brener, L.; Pettit, R. *J. Am. Chem. Soc.* ***1970***, *92*, 7499.
[501]Merk, W.; Pettit, R. *J. Am. Chem. Soc.* ***1967***, *89*, 4788.
[502]For discussions of how these reactions take place, see Slegeir, W.; Case, R.; McKennis, J.S.; Pettit, R. *J. Am. Chem. Soc.* ***1974***, *96*, 287; Pinhas, A.R.; Carpenter, B.K. *J. Chem. Soc., Chem. Commun.* ***1980***, 15.

rearranged allyl anion that is formed by disrotatory cleavage of the cyclopropyl ring, a formally Woodward–Hoffmann-forbidden process.[503]

The ring opening of cyclopropyl cations (pp. 486, 1591) is an electrocyclic reaction and is governed by the orbital symmetry rules.[504] For this case, we invoke the rule that the *s* bond opens in such a way that the resulting *p* orbitals have the symmetry of the highest occupied orbital of the product, in this case, an allylic cation. We may recall that an allylic system has three molecular orbitals (p. 42). For the cation, with only two electrons, the highest occupied orbital is the one of the lowest energy (A). Thus, the cyclopropyl cation must undergo a



disrotatory ring opening in order to maintain the symmetry. (Note that, in contrast, ring opening of the cyclopropyl *anion* must be conrotatory,[505] since in this case it is the next orbital of the allylic system that is the highest occupied, and this has the opposite symmetry.[506]) However, it is very difficult to generate a free cyclopropyl cation (p. 487), and it is likely that in most cases, cleavage of the σ bond is concerted with departure of the leaving group in the original cyclopropyl substrate. This, of course, means that the σ bond provides anchimeric assistance to the removal of the leaving group (an S_N2-type process), and we would expect that such assistance should come from the back side. This has an important effect on the direction of ring opening. The orbital-symmetry rules require that the ring opening be disrotatory, but as we have seen, there are two disrotatory pathways and the rules do not tell us which is preferred. But the fact that the *s* orbital provides assistance from the backside means that the two substituents that are trans to the leaving group must move *outward*, not inward.[507] Thus, the disrotatory pathway that is followed is the one shown in B, not the one shown in C, because the former puts the electrons of the σ bond on the



[503]Leivers, M.; Tam, I.; Groves, K.; Leung, D.; Xie, Y.; Breslow, R. *Org. Lett.* ***2003***, *5*, 3407.

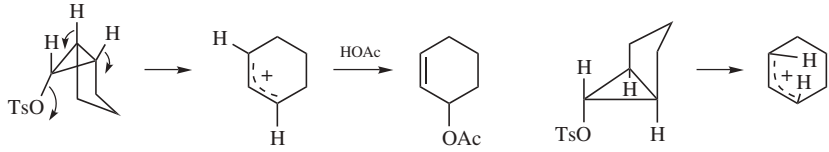
[504]For discussions, see DePuy, C.H. *Acc. Chem. Res.* ***1968***, *1*, 33; Schöllkopf, U. *Angew. Chem. Int. Ed.* ***1968***, *7*, 588.

[505]For a review of ring opening of cyclopropyl anions and related reactions, see Boche, G. *Top. Curr. Chem.* ***1988***, *146*, 1.

[506]For evidence that this is so, see Newcomb, M.; Ford, W.T. *J. Am. Chem. Soc.* ***1974***, *96*, 2968; Boche, G.; Buckl, K.; Martens, D.; Schneider, D.R.; Wagner, H. *Chem. Ber.* ***1979***, *112*, 2961; Coates, R.M.; Last, L.A. *J. Am. Chem. Soc.* ***1983***, *105*, 7322. For a review of the analogous ring opening of epoxides, see Huisgen, R. *Angew. Chem. Int. Ed.* ***1977***, *16*, 572.

[507]This was first proposed by DePuy, C.H.; Schnack, L.G.; Hausser, J.W.; Wiedemann, W. *J. Am. Chem. Soc.* ***1965***, *87*, 4006.

side opposite that of the leaving group.[508] Strong confirmation of this picture[509] comes from acetolysis of *endo*- (**111**) and *exo*-bicyclo[3,1,0]hexyl-6-tosylate (**112**). The groups trans to the tosylate must move outward. For **111**, this means that the two hydrogens can go outside the framework of the six-membered ring, but for **112** they



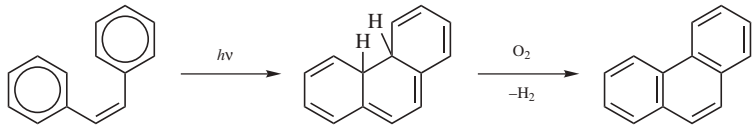
111 **112**

are forced to go inside. Consequently, it is not surprising that the rate ratio for solvolysis of **111/112** was found to be $>2.5 \times 10^6$ and that at 150°C **112** did not solvolyze at all.[510] This evidence is kinetic. Unlike the cases of the cyclobutene (1,3-diene and cyclohexadiene) 1,3,5-triene interconversions, the direct product here is a cation, which is not stable but reacts with a nucleophile and loses some of its steric integrity in the process, so that much of the evidence has been of the kinetic type rather than from studies of product stereochemistry. However, it has been shown by investigations in superacids, where it is possible to keep the cations intact and to study their structures by NMR, that in all cases studied the cation that is predicted by these rules is in fact formed.[511]

OS **V**, 235, 277, 467; **VI**, 39, 145, 196, 422, 427, 862; **IX**, 180.

18-28 Conversion of One Aromatic Compound to Another

(6)*cyclo*-de-hydrogen-coupling (Overall transformation)



Stilbenes can be converted to phenanthrenes by irradiation with UV light[512] in the presence of an oxidizing agent, such as dissolved molecular oxygen, $FeCl_3$,

[508]It has been suggested that the pathway shown in **C** is possible in certain cases: Hausser, J.W.; Grubber, M.J. *J. Org. Chem.* ***1972***, *37*, 2648; Hausser, J.W.; Uchic, J.T. *J. Org. Chem.* ***1972***, *37*, 4087.

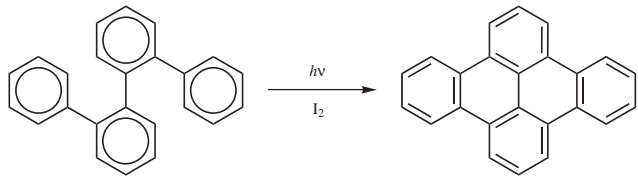
[509]There is much other evidence. For example, see Jefford, C.W.; Medary, R. *Tetrahedron Lett.* ***1966***, 2069; Jefford, C.W.; Wojnarowski, W. *Tetrahedron Lett.* ***1968***, 199; Sliwinski, W.F.; Su, T.M.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1972***, *94*, 133; Sandler, S.R. *J. Org. Chem.* ***1967***, *32*, 3876; Ghosez, L.; Slinckx, G.; Glineur, M.; Hoet, P.; Laroche, P. *Tetrahedron Lett.* ***1967***, 2773; Parham, W.E.; Yong, K.S. *J. Org. Chem.* ***1968***, *33*, 3947; Reese, C.B.; Shaw, A. *J. Am. Chem. Soc.* ***1970***, *92*, 2566; Dolbier, Jr., W.R.; Phanstiel, O. *Tetrahedron Lett.* ***1988***, *29*, 53.

[510]Schöllkopf, U.; Fellenberger, K.; Patsch, M.; Schleyer, P.v.R.; Su, T.M.; Van Dine, G.W. *Tetrahedron Lett.* ***1967***, 3639.

[511]Schleyer, P.v.R.; Su, T.M.; Saunders, M.; Rosenfeld, J.C. *J. Am. Chem. Soc.* ***1969***, *91*, 5174.

[512]For reviews, see Mallory, F.B.; Mallory, C.W. *Org. React.* ***1984***, *30*, 1; Laarhoven, W.H. *Recl. Trav. Chim. Pays-Bas* ***1983***, *102*, 185, 241; Blackburn, E.V.; Timmons, C.J. *Q. Rev. Chem. Soc.* ***1969***, *23*, 482; Stermitz, L.F. *Org. Photochem.* ***1967***, *1*, 247. For a review of electrocyclizations of conjugated aryl olefins in general, see Laarhoven, W.H. *Org. Photochem.* ***1989***, *10*, 163.

Pd–C,[513] or iodine.[514] The reaction is a photochemically allowed conrotatory[515] conversion of a 1,3,5-hexatriene to a cyclohexadiene, followed by removal of two hydrogen atoms by the oxidizing agent. The intermediate dihydrophenanthrene has been isolated.[516] The use of substrates containing heteroatoms (e.g., PhN=NPh) allows the formation of heterocyclic ring systems. The actual reacting species must be the *cis*-stilbene, but *trans*-stilbenes can often be used, because they are isomerized to the cis isomers under the reaction conditions. The reaction can be extended to the preparation of many fused aromatic systems, for example,[517]



though not all such systems give reaction.[518]

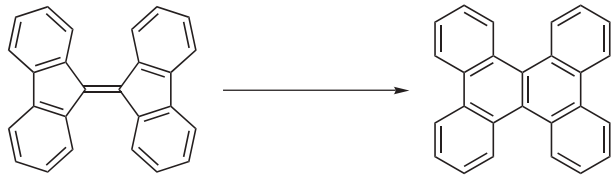
Isomerization of biphenylene to benzo[*a*]pentalene[519] is a well-known benzene ring contraction rearrangement,[520] driven by relief of strain in the four-membered ring. Related to this process is the FVP of the alternant polycyclic aromatic hydrocarbon benzo[*b*]biphenylene at 1100°C, which gives fluoranthene, a nonalternant polycyclic aromatic hydrocarbon, as the major product at 1100°C in the gas phase.[521] The mechanism used explain that this isomerization involves equilibrating diradicals of 2-phenylnaphthalene, which rearrange by the net migration of a phenyl group to give equilibrating diradicals of 1-phenylnaphthalene, one isomer of which then cyclizes to fluoranthene.

Another transformation of one aromatic compound to another is the *Stone–Wales rearrangement* of pyracyclene (**113**),[522] which is a bond-switching reaction. The rearrangement of bifluorenylidene (**114**) to dibenzo[*g,p*]chrysene (**115**) occurs at temperatures as low as 400°C and is accelerated in the presence of decomposing iodomethane, a convenient source of methyl radicals.[523] This result suggested a

[513]Rawal, V.H.; Jones, R.J.; Cava, M.P. *Tetrahedron Lett.* ***1985***, *26*, 2423.
[514]For the use of iodine plus propylene oxide in the absence of air, see Liu, L.; Yang, B.; Katz, T.J.; Poindexter, M.K. *J. Org. Chem.* ***1991***, *56*, 3769.
[515]Cuppen, T.J.H.M.; Laarhoven, W.H. *J. Am. Chem. Soc.* ***1972***, *94*, 5914.
[516]Doyle, T.D.; Benson, W.R.; Filipescu, N. *J. Am. Chem. Soc.* ***1976***, *98*, 3262.
[517]Sato, T.; Shimada, S.; Hata, K. *Bull. Chem. Soc. Jpn.* ***1971***, *44*, 2484.
[518]For a discussion and lists of photocyclizing and nonphotocyclizing compounds, see Laarhoven, W.H. *Recl. Trav. Chim. Pays-Bas* ***1983***, *102*, 185, 185–204.
[519]Wiersum, U.E.; Jenneskens, L.W. *Tetrahedron Lett.* ***1993***, *34*, 6615; Brown, R.F.C.; Choi, N.; Coulston, K.J.; Eastwood, F.W.; Wiersum, U.E.; Jenneskens, L.W. *Tetrahedron Lett.* ***1994***, *35*, 4405.
[520]Scott, LT.; Roelofs, N.H. *J. Am. Chem. Soc.* ***1987***, *109*, 5461; Scott, L.T.; Roelofs, N.H. *Tetrahedron Lett.* ***1988***, *29*, 6857; Anderson, M.R.; Brown, R.F.C.; Coulston, K.J.; Eastwood, F.W.; Ward, A. *Aust. J. Chem.* ***1990***, *43*, 1137; Brown, R F.C.; Eastwood, F.W.; Wong, N.R. *Tetrahedron Lett.* ***1993***, *34*, 3607.
[521]Preda, D.V.; Scott, L.T. *Org. Lett.* ***2000***, *2*, 1489.
[522]Stone, A.J.; Wales, D.J. *Chem. Phys. Lett.* ***1986***, *128*, 501.
[523]Alder, R.W.; Whittaker, G. *J. Chem. Soc., Perkin Trans. 2* ***1975***, 712

radical rearrangement. This rearrangement is believed to occur by a radical-promoted mechanism consisting of a sequence of homoallyl–cyclopropylcarbinyl rearrangement steps.[524]

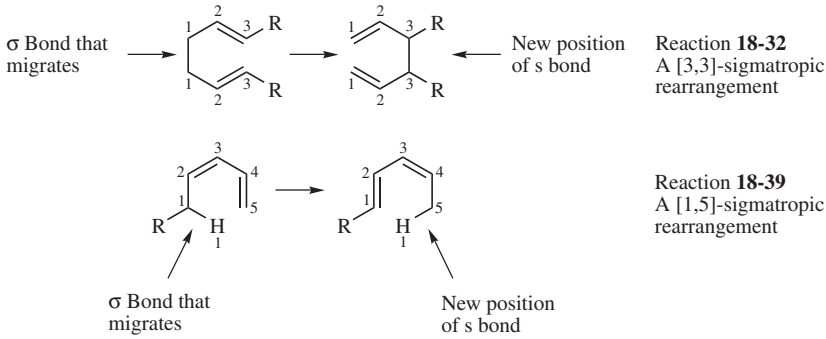
113



114 **115**

B. Sigmatropic Rearrangements

A sigmatropic rearrangement is defined[525] as migration, in an uncatalyzed intramolecular process, of a σ bond, adjacent to one or more π systems, to a new position in a molecule, with the π systems becoming reorganized in the process. Examples are



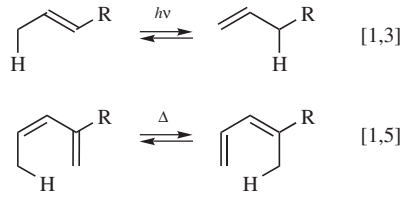
The *order* of a sigmatropic rearrangement is expressed by two numbers set in brackets: [*i*,*j*]. These numbers can be determined by counting the atoms over which each end of the σ bond has moved. Each of the original termini is given the number 1. Thus in the first example above, each terminus of the σ bond has

[524]Alder, R.W.; Harvey, J. N. *J. Am. Chem. Soc.* ***2004***, *126*, 2490.
[525]Woodward, R.B.; Hoffmann, R. *The Conservation of Orbital Symmetry*, Academic Press, NY, ***1970***, p. 114.

migrated from C-1 to C-3, so the order is [3,3]. In the second example, the carbon terminus has moved from C-1 to C-5, but the hydrogen terminus has not moved at all, so the order is [1,5].

18-29 [1,*j*]-Sigmatropic Migrations of Hydrogen

1/ → 3/Hydrogen-migration; 1/ → 5/Hydrogen-migration



Many examples of thermal or photochemical rearrangements in which a hydrogen atom migrates from one end of a system of π bonds to the other have been reported,[526] although the reaction is subject to geometrical conditions. Isotope effects play a role in sigmatropic rearrangements, and there is evidence for a kinetic silicon isotope effect.[527] Pericyclic mechanisms are involved,[528] and the hydrogen must, in the transition state, be in contact with both ends of the chain at the same time. This means that for [1,5] and longer rearrangements, the molecule must be able to adopt the cisoid conformation. Furthermore, there are two geometrical pathways by which any sigmatropic rearrangement can take place, which we illustrate for the case of a [1,5]-sigmatropic rearrangement,[529] starting with a substrate of the form **116**, where the migration origin is an asymmetric carbon atom and U ≠ V. In one of the two pathways, the hydrogen moves along the top or bottom face of the π system. This is called *suprafacial migration*. In the other pathway, the hydrogen moves *across* the π system, from top to bottom, or vice versa. This is *antarafacial* migration. Altogether, a single isomer like **116** (different rotamers) can give four products. In a suprafacial migration, H can move across the top of the π system (as drawn above) to give the (*R*,*Z*) isomer, or it can rotate 180° and move across the bottom of the π system to give the (*S*,*E*) isomer.[530] The antarafacial migration can similarly lead to two diastereomers, in

[526]For a monograph, see Gajewski, J.J. *Hydrocarbon Thermal Isomerizations*, Academic Press, NY, ***1981***. For reviews, see Mironov, V.A.; Fedorovich, A.D.; Akhrem, A.A. *Russ. Chem. Rev.* ***1981***, *50*, 666; Spangler, C.W. *Chem. Rev.* ***1976***, *76*, 187; DeWolfe, R.H., in Bamford, C.H.; Tipper, C.F.H. *Comprehensieve Chemical Kinetics*, Vol. 9, Elsevier, NY, ***1973***, pp. 474–480; Woodward, R.B.; Hoffmann, R. *The Conservation of Orbital Symmetry*, Academic Press, NY, ***1970***, pp. 114–140; Hansen, H.; Schmid, H. *Chimia*, ***1970***, *24*, 89; Roth, W.R. *Chimia*, ***1966***, *20*, 229.

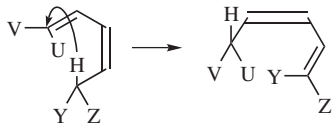
[527]Lin, Y.-L.; Turos, E. *J. Am. Chem. Soc.* ***1999***, *121*, 856.

[528]For a discussion of catalysts that induce pericyclic rearrangements, see Moss, S.; King, B.T.; de Meijere, A.; Kozhushkov, S.I.; Eaton, P.E.; Michl, J. *Org. Lett.* ***2001***, *3*, 2375.

[529]Note that a [1,5]-sigmatropic rearrangement of hydrogen is also an internal ene synthesis (**15-20**).

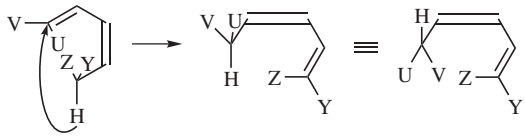
[530]Since we are using the arbitrary designations U, V, Y, and Z, we have been arbitrary in which isomer to call (*R*,*Z*) and which to call (*S*,*E*).

this case the (*S*,*Z*) and (*R*,*E*) isomers.



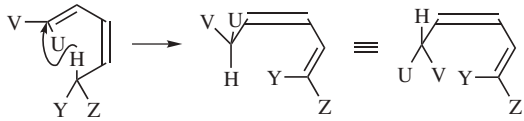
Suprafacial

116 (*R*, *Z*) Isomer



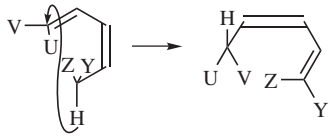
Suprafacial

116 (*S*,*E*) Isomer



Antarafacial

116 (*S*, *Z*) Isomer



Antarafacial

116 (*R*,*E*) Isomer

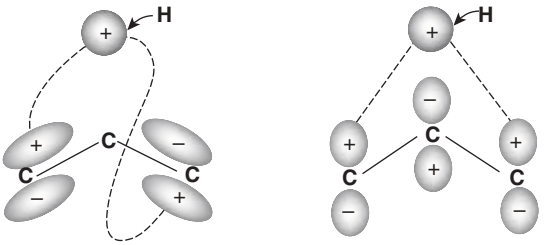
In any given sigmatropic rearrangement, only one of the two pathways is allowed by the orbital-symmetry rules; the other is forbidden. To analyze this situation, first we use a modified frontier orbital approach.[531] We will imagine that in the transition state **C**, the migrating H atom breaks away from the rest of the system, which we may treat as if it were a free radical.

C

Imaginary transition state for a [1,3]-sigmatropic rearrangement

[531]See Woodward, R.B.; Hoffmann, R. *The Conservation of Orbital Symmetry*, Academic Press, NY, ***1970***, pp. 114–140.

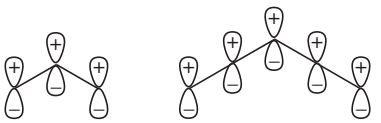
Note that this is not what actually takes place; we merely imagine it in order to be able to analyze the process. In a [1,3]-sigmatropic rearrangement, the imaginary transition state consists of a hydrogen atom and an allyl radical. The latter species (p. 42) has three π orbitals, but the only one that concerns us here is the HOMO which, in a thermal rearrangement is **D**. The electron of the hydrogen atom is of course in a 1*s* orbital, which has only one lobe. The rule governing sigmatropic migration of hydrogen is *the H must move from a plus to a plus or from a minus to a minus*



D **E**

lobe, of the HOMO; it cannot move to a lobe of opposite sign.[532] Obviously, the only way this can happen in a thermal [1,3]-sigmatropic rearrangement is if the migration is antarafacial. Consequently, the rule predicts that antarafacial thermal [1,3]-sigmatropic rearrangements are allowed, but the suprafacial pathway is forbidden. However, in a photochemical reaction, promotion of an electron means that **E** is now the HOMO; the suprafacial pathway is now allowed and the antarafacial pathway forbidden.

A similar analysis of [1,5]-sigmatropic rearrangements shows that in this case the thermal reaction must be suprafacial and the photochemical process antarafacial. For the general case, with odd-numbered *j*, we can say that [1,*j*]-suprafacial migrations are allowed thermally when *j* is of the form $4n + 1$, and photochemically when *j* has the form $4n - 1$; the opposite is true for antarafacial migrations.



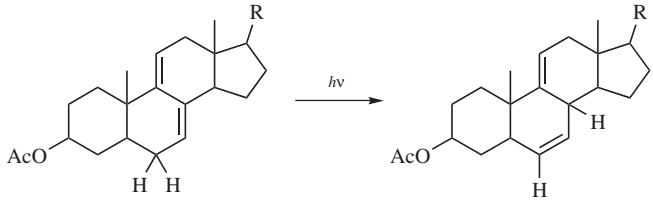
F **G**

As expected, the Möbius–Hückel method leads to the same predictions. Here, we look at the basis set of orbitals shown in **F** and **G** for [1,3]- and [1,5]-rearrangements, respectively. A [1,3]-shift involves four electrons, so an allowed thermal pericyclic reaction must be a Möbius system (p. 1210) with one or an odd number

[532]This follows from the principle that bonds are formed only by overlap of orbitals of the same sign. Since this is a concerted reaction, the hydrogen orbital in the transition state must overlap simultaneously with one lobe from the migration origin and one from the terminus. It is obvious that both of these lobes must have the same sign.

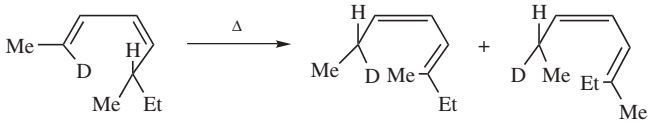
of sign inversions. As can be seen in **F**, only an antarafacial migration can achieve this. A [1,5]-shift, with six electrons, is allowed thermally only when it is a Hückel system with zero or an even number of sign inversions; hence it requires a suprafacial migration.[533]

The actual reported results bear out this analysis. Thus a thermal [1,3] migration is allowed to take place only antarafacially, but such a transition state would be extremely strained, and thermal [1,3]-sigmatropic migrations of hydrogen are unknown.[534] On the other hand, the photochemical pathway allows suprafacial [1,3]-shifts, and a few such reactions are known, an example being the photochemical rearrangement of **117** to **118**.[535] Substituents influence the efficacy of the [1,3]-hydrogen shift.[536]

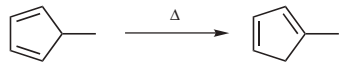


117 **118**

The situation is reversed for [1,5]-hydrogen shifts. In this case the thermal rearrangements, being suprafacial, are quite common, while photochemical rearrangements are rare.[537] Two examples of the thermal reaction are



Ref. [538]



Ref. [539]

[533]For a discussion of the origins for the preference for orbital-symmetry forbidden reactions and the stereochemistry of [1,5]-sigmatropic shifts, see Kless, A.; Nendel, M.; Wilsey, S.; Houk, K.N. *J. Am. Chem. Soc.* ***1999***, *121*, 4524.

[534]A possible [1,3]-migration of hydrogen has been reported. See Yeh, M.; Linder, L.; Hoffman, D.K.; Barton, T.J. *J. Am. Chem. Soc.* ***1986***, *108*, 7849. See also, Pasto, D.J.; Brophy, J.E. *J. Org. Chem.* ***1991***, *56*, 4554.

[535]Dauben, W.G.; Wipke, W.T. *Pure Appl. Chem.* ***1964***, *9*, 539, 546. For another example, see Kropp, P.J.; Fravel, Jr., H.G.; Fields, T.R. *J. Am. Chem. Soc.* ***1976***, *98*, 840.

[536]Hudson, C.E.; McAdoo, D.J. *J. Org. Chem.* ***2003***, *68*, 2735.

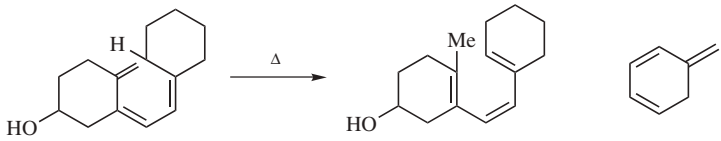
[537]For examples of photochemical [1,5]-antarafacial reactions, see Kiefer, E.F.; Tanna, C.H. *J. Am. Chem. Soc.* ***1969***, *91*, 4478; Kiefer, E.F.; Fukunaga, J.Y. *Tetrahedron Lett.* ***1969***, 993; Dauben, W.G.; Poulter, C.D.; Suter, C. *J. Am. Chem. Soc.* ***1970***, *92*, 7408.

[538]Roth, W.R.; König, J.; Stein, K. *Chem. Ber.* ***1970***, *103*, 426.

[539]McLean, S.; Haynes, P. *Tetrahedron* ***1965***, *21*, 2329. For a review of such rearrangements, see Klärner, F. *Top. Stereochem.* ***1984***, *15*, 1. For a discussion of [1,5]-sigmatropic hydrogen shifts in cyclic 1,3-dienes, see Hess, Jr., B.A.; Baldwin, J.E. *J. Org. Chem.* ***2002***, *67*, 6025.

Note that the first example bears out the stereochemical prediction made earlier. Only the two isomers shown were formed. In the second example, migration can continue around the ring. Migrations of this kind are called *circumambulatory rearrangements*.[540] Such migrations are known for cyclopentadiene, pyrrole, and phosphole derivatives.[541] Geminal bond participation has been observed in pentadienes,[542] the effects of phenyl substituents have been studied,[543] and the kinetics and activation parameters of [1,5] hydrogen shifts have been examined.[544] The [1,5] hydrogen shifts are also known with vinyl aziridines.[545]

The rare [1,4]-hydrogen transfer has been observed in radical cyclizations.[546] With respect to [1,7]-hydrogen shifts, the rules predict the thermal reaction to be antarafacial.[547] Unlike the case of [1,3]-shifts, the transition state is not too greatly strained, and an example of such rearrangements is the formation of **119** and **120**.[548] Photochemical [1,7]-shifts are suprafacial and, not surprisingly, many of these have been observed.[549]



119 **120**

The orbital symmetry rules also help us to explain, as on pp. 1232 and 1642, the unexpected stability of certain compounds. Thus, **120** could, by a thermal [1,3]-sigmatropic rearrangement, easily convert to toluene, which of course is far more stable because it has an aromatic sextet. Yet, **120** has been prepared and is stable at dry ice temperature and in dilute solutions.[550]

[540]For a review, see Childs, R.F. *Tetrahedron* ***1982***, *38*, 567. See also, Minkin, V.I.; Mikhailov, I.E.; Dushenko, G.A.; Yudilevich, J.A.; Minyaev, R.M.; Zschunke, A.; Mügge, K. *J. Phys. Org. Chem.* ***1991***, *4*, 31. For a study of [1,5]-sigmatropic shiftamers, see Tantillo, D.J.; Hoffmann, R. *Eur. J. Org. Chem.* ***2004***, 273.

[541]Bachrach, S.M. *J. Org. Chem.* ***1993***, *58*, 5414.

[542]Ikeda, H.; Ushioda, N.; Inagaki, S. *Chem. Lett.* ***2001***, 166.

[543]Hayase, S.; Hrovat, D.A.; Borden, W.T. *J. Am. Chem. Soc.* ***2004***, *126*, 10028.

[544]Baldwin, J.E.; Raghavan, A.S. *J. Org. Chem.* ***2004***, *69*, 8128.

[545]Åhman, J.; Somfai, P.; Tanner, D. *J. Chem. Soc., Chem. Commun.* ***1994***, 2785; Somfai, P.; Åhman, J. *Tetrahedron Lett.* ***1995***, *36*, 1953.

[546]Journet, M.; Malacria, M. *Tetrahedron Lett.* ***1992***, *33*, 1893.

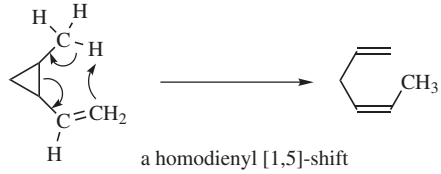
[547]For a computational study that supports tunneling in thermal [1,7]-hydrogen shifts see Hess, Jr., B.A. *J. Org. Chem.* ***2001***, *66*, 5897.

[548]Gurskii, M.E.; Gridnev, I.D.; Il'ichev, Y.V.; Ignatenko, A.V.; Bubnov, Y.N. *Angew. Chem. Int. Ed.* ***1992***, *31*, 781; Baldwin, J.E.; Reddy, V.P. *J. Am. Chem. Soc.* ***1987***, *109*, 8051; ***1988***, *110*, 8223.

[549]See Murray, R.W.; Kaplan, M.L. *J. Am. Chem. Soc.* ***1966***, *88*, 3527; ter Borg, A.P.; Kloosterziel, H. *Recl. Trav. Chim. Pays-Bas* ***1969***, *88*, 266; Tezuka, T.; Kimura, M.; Sato, A.; Mukai, T. *Bull. Chem. Soc. Jpn.* ***1970***, *43*, 1120.

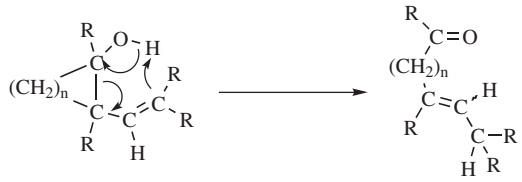
[550]Bailey, W.J.; Baylouny, R.A. *J. Org. Chem.* ***1962***, *27*, 3476.

Analogs of sigmatropic rearrangements in which a cyclopropane ring replaces one of the double bonds are also known, for example,[551]



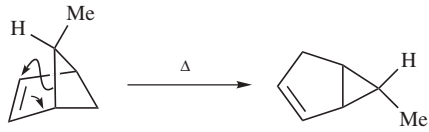
a homodienyl [1,5]-shift

The reverse reaction has also been reported.[552] 2-Vinylcycloalkanols[553] undergo an analogous reaction, as do cyclopropyl ketones (see p. 1673 for this reaction).



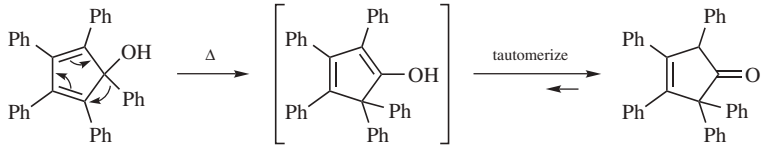
18-30 [1,*j*]-Sigmatropic Migrations of Carbon

[1,3] migration of alkyl



Ref. [554]

[1,5] migration of phenyl



Ref. [555]

[551]Frey, H.M.; Solly, R.K. *Int. J. Chem. Kinet.*, ***1969***, *1*, 473; Roth, W.R.; König, J. *Liebigs Ann. Chem.* ***1965***, *688*, 28; Ohloff, G. *Tetrahedron Lett.* ***1965***, 3795; Jorgenson, M.J.; Thacher, A.F. *Tetrahedron Lett.* ***1969***, 4651; Corey, E.J.; Yamamoto, H.; Herron D.K.; Achiwa, K. *J. Am. Chem. Soc.* ***1970***, *92*, 6635; Loncharich, R.J.; Houk, K.N. *J. Am. Chem. Soc.* ***1988***, *110*, 2089; Parziale, P.A.; Berson, J.A. *J. Am. Chem. Soc.* ***1990***, *112*, 1650; Pegg, G.G.; Meehan, G.V. *Aust. J. Chem.* ***1990***, *43*, 1009, 1071.

[552]Roth, W.R.; König, J. *Liebigs Ann. Chem.* ***1965***, *688*, 28. Also see, Grimme, W. *Chem. Ber.* ***1965***, *98*, 756.

[553]Arnold, R.T.; Smolinsky, G. *J. Am. Chem. Soc.* ***1960***, *82*, 4918; Leriverend, P.; Conia, J.M. *Tetrahedron Lett.* ***1969***, 2681; Conia, J.M.; Barnier, J.P. *Tetrahedron Lett.* ***1969***, 2679.

[554]Roth, W.R.; Friedrich, A. *Tetrahedron Lett.* ***1969***, 2607.

[555]Youssef, A.K.; Ogliaruso, M.A. *J. Org. Chem.* ***1972***, *37*, 2601.

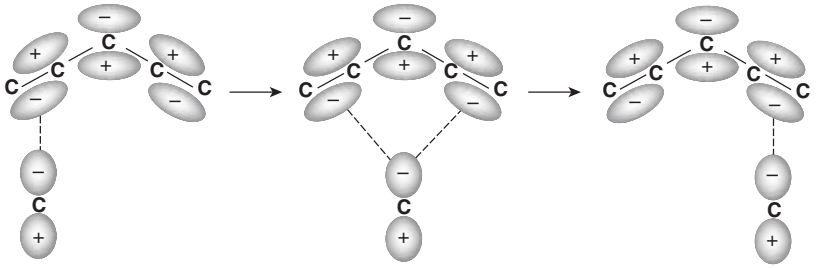


Fig. 18.5. Hypothetical orbital movement for a thermal [1,5]-sigmatropic migration of carbon. To move from one negative lobe, the migrating carbon uses only its own negative lobe, retaining its configuration.

Sigmatropic migrations of alkyl or aryl groups[556] are less common than the corresponding hydrogen migrations.[557] When they do take place, there is an important difference. Unlike a hydrogen atom, whose electron is in a 1*s* orbital with only one lobe, a carbon free radical has its odd electron in a *p* orbital that has *two lobes of opposite sign*. Therefore, if we draw the imaginary transition states for this case (see p. 1650), we see that in a thermal suprafacial [1,5] process (Fig. 18.5), symmetry can be conserved only if the migrating carbon moves in such a way that the lobe which was originally attached to the π system remains attached to the π system.

This can happen only if configuration is *retained within the migrating group*. On the other hand, thermal suprafacial [1,3] migration (Fig. 18.6) *can* take place if the migrating carbon switches lobes. If the migrating carbon was originally bonded by its minus lobe, it must now use its plus lobe to form the new C–C bond. Thus, configuration in the migrating group will be *inverted*. From these considerations we predict that suprafacial [1,*j*]-sigmatropic rearrangements in which carbon is the migrating group are always allowed, both thermally and photochemically, but that thermal [1,3] migrations will proceed with inversion and thermal [1,5]

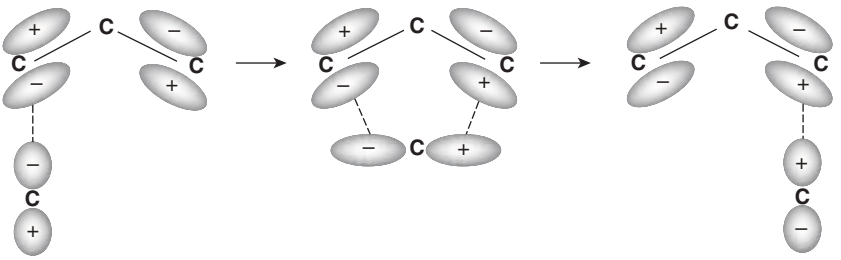
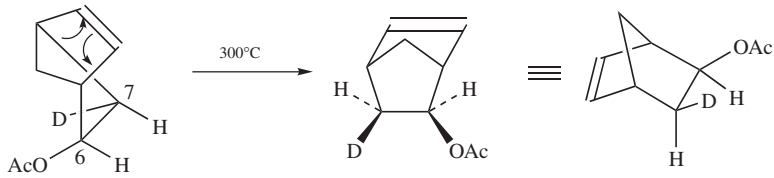


Fig. 18.6. Hypothetical orbital movement for a thermal [1,3]-sigmatropic migration of carbon. The migrating carbon moves a negative to a positive lobe, requiring it to switch its own bonding lobe from negative to positive, inverting its configuration.

[556]For reviews, see Mironov, V.A.; Fedorovich, A.D.; Akhrem, A.A. *Russ. Chem. Rev.* ***1981***, *50*, 666; Spangler, C.W. *Chem. Rev.* ***1976***, *76*, 187

[557]It has been shown that methyl and phenyl have lower migratory aptitudes than hydrogen in thermal sigmatropic rearrangements: Shen, K.; McEwen, W.E.; Wolf, A.P. *Tetrahedron Lett.* ***1969***, 827; Miller, L.L.; Greisinger, R.; Boyer, R.F. *J. Am. Chem. Soc.* ***1969***, *91*, 1578.

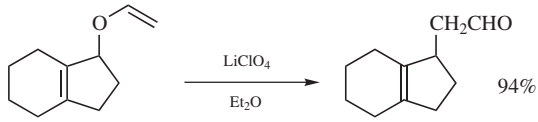
migrations with retention of configuration within the migrating group. More generally, we can say that suprafacial [1,*j*] migrations of carbon in systems where $j = 4n - 1$ proceed with inversion thermally and retention photochemically, while systems where $j = 4n + 1$ show the opposite behavior. Where antarafacial migrations take place, all these predictions are of course reversed.



121 **122**

The first laboratory test of these predictions was the pyrolysis of deuterated *endo*-bicyclo[3.2.0]hept-2-en-6-yl acetate (**121**), which gave the *exo*-deuterio-*exo*-norbornyl acetate **122**.[558] Thus, as predicted by the orbital symmetry rules, this thermal suprafacial [1,3]-sigmatropic reaction took place with complete inversion at C-7. Similar results have been obtained in a number of other cases.[559] However, similar studies of the pyrolysis of the parent hydrocarbon of **121**, labeled with D at C-6 and C-7, showed that while most of the product was formed with inversion at C-7, a significant fraction (11–29%) was formed with retention.[560] Other cases of lack of complete inversion are also known.[561] A diradical mechanism has been invoked to explain such cases.[562] There is strong evidence for a radical mechanism for some [1,3]-sigmatropic rearrangements.[563] Photochemical suprafacial [1,3] migrations of carbon have been shown to proceed with retention, as predicted.[564]

Although allylic vinylic ethers generally undergo [3,3]-sigmatropic rearrangements (**18-33**), they can be made to give the [1,3] kind, to give aldehydes, for example,



[558]Berson, J.A.; Nelson, G.L. *J. Am. Chem. Soc.* ***1967***, *89*, 5503; Berson, J.A. *Acc. Chem. Res.* ***1968***, *1*, 152.

[559]See Roth, W.R.; Friedrich, A. *Tetrahedron Lett.* ***1969***, 2607; Berson, J.A. *Acc. Chem. Res.* ***1972***, *5*, 406; Bampfield, H.A.; Brook, P.R.; Hunt, K. *J. Chem. Soc., Chem. Commun.* ***1976***, 146; Franzus, B.; Scheinbaum, M.L.; Waters, D.L.; Bowlin, H.B. *J. Am. Chem. Soc.* ***1976***, *98*, 1241; Klärner, F.; Adamsky, F. *Angew. Chem. Int. Ed.* ***1979***, *18*, 674.

[560]Baldwin, J.E.; Belfield, K.D. *J. Am. Chem. Soc.* ***1988***, *110*, 296; Klärner, F.; Drewes, R.; Hasselmann, D. *J. Am. Chem. Soc.* ***1988***, *110*, 297.

[561]See, for example, Berson, J.A.; Holder, R.W. *J. Am. Chem. Soc.* ***1973***, *95*, 2037; Pikulin, S.; Berson, J.A. *J. Am. Chem. Soc.* ***1988***, *110*, 8500.

[562]See Newman-Evans, R.H.; Carpenter, B.K. *J. Am. Chem. Soc.* ***1984***, *106*, 7994; Pikulin, S.; Berson, J.A. *J. Am. Chem. Soc.* ***1988***, *110*, 8500. See also, Berson, J.A. *Chemtracts: Org. Chem.* ***1989***, *2*, 213.

[563]See, for example, Bates, G.S.; Ramaswamy, S. *Can. J. Chem.* ***1985***, *63*, 745; Dolbier, W.B.; Phanstiel IV, O. *J. Am. Chem. Soc.* ***1989***, *111*, 4907.

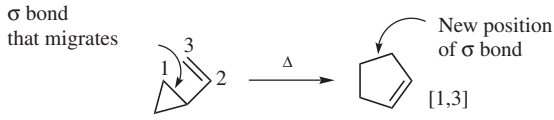
[564]Cookson, R.C.; Hudec, J.; Sharma, M. *Chem. Commun.* ***1971***, 107, 108.

by treatment with $LiClO_4$ in diethyl ether.[565] In this case, the C–O bond undergoes a 1,3 migration from the O to the end vinylic carbon. When the vinylic ether is of the type $ROCR'{=}CH_2$, ketones RCH_2COR' are formed. There is evidence that this [1,3]-sigmatropic rearrangement is not concerted, but involves dissociation of the substrate into ions.[565]

Thermal suprafacial [1,5] migrations of carbon have been found to take place with retention,[566] but also with inversion.[567] A diradical mechanism has been suggested for the latter case.[567]

Simple nucleophilic, electrophilic, and free-radical 1,2-shifts can also be regarded as sigmatropic rearrangements (in this case, [1,2]-rearrangements). We have already (p. $$$) applied similar principles to such rearrangements to show that nucleophilic 1,2-shifts are allowed, but the other two types are forbidden unless the migrating group has some means of delocalizing the extra electron or electron pair. The mechanism of the forbidden [3s,5s]-sigmatropic shift has been examined.[568]

18-31 Conversion of Vinylcyclopropanes to Cyclopentenes



The thermal expansion of a vinylcyclopropane to a cyclopentene ring[569] is a special case of a [1,3]-sigmatropic migration of carbon, although it can also be considered an internal $[_\pi 2 + _\sigma 2]$-cycloaddition reaction (see **15-63**). It is known as a *vinylcyclopropane rearrangement*.[570] The reaction has been carried out on many vinylcyclopropanes bearing various substituents in the ring[571] or

[565]Grieco, P.A.; Clark, J.D.; Jagoe, C.T. *J. Am. Chem. Soc.* ***1991***, *113*, 5488; Palani, N.; Balasubramanian, K.K. *Tetrahedron Lett.* ***1995***, *36*, 9527.

[566]Boersma, M.A.M.; de Haan, J.W.; Kloosterziel, H.; van de Ven, L.J.M. *Chem. Commun.* ***1970***, 1168.

[567]Klärner, F.; Yaslak, S.; Wette, M. *Chem. Ber.* ***1979***, *112*, 1168; Klärner, F.; Brassel, B. *J. Am. Chem. Soc.* ***1980***, *102*, 2469; Gajewski, J.J.; Gortva, A.M.; Borden, J.E. *J. Am. Chem. Soc.* ***1986***, *108*, 1083; Baldwin, J.E.; Broline, B.M. *J. Am. Chem. Soc.* ***1982***, *104*, 2857.

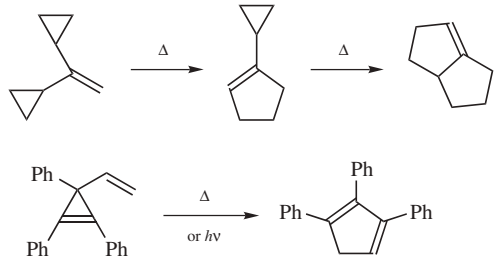
[568]Leach, A.G.; Catak, S.; Houk, K.N. *Chem. Eur. J.* ***2002***, *8*, 1290.

[569]For reviews, see Baldwin, J.E. *Chem. Rev.* ***2003***, *103*, 1197; Wong, H.N.C.; Hon, M.; Tse, C.; Yip, Y.; Tanko, J.; Hudlicky, T. *Chem. Rev.* ***1989***, *89*, 165, see pp. 169–172; Hudlicky, T.; Kutchan, T.M.; Naqvi, S.M. *Org. React.* ***1985***, *33*, 247; DeWolfe, R.H., in Bamford, C.H.; Tipper, C.F.H. *Comprehenseive Chemical Kintetics*, Vol. 9, Elseiver, NY, ***1973***, pp. 470–474; Gutsche, C.D.; Redmore, D. *Carbocyclic Ring Expansion Reactions*, Academic Press, NY, ***1968***, pp. 163–170.

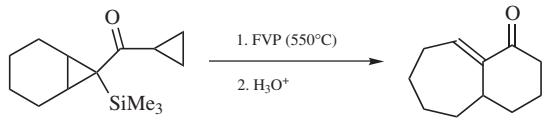
[570]For a novel vinylcyclopropane rearrangement, see Armesto, D.; Ramos, A.; Mayoral, E.P.; Ortiz, M.J.; Agarrabeitia, A.R. *Org. Lett.* ***2000***, *2*, 183.

[571]For a study of substituent effects, see McGaffin, G.; Grimm, B.; Heinecke, U.; Michaelsen, H.; de Meijere, A.; Walsh, R. *Eur. J. Org. Chem.* ***2001***, 3559.

on the vinyl group and has been extended to 1,1-dicyclopropylethene[572]

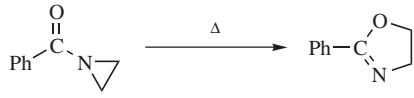


and (both thermally[573] and photochemically[574]) to vinylcyclopropenes. This rearrangement can be catalyzed by rhodium and silver compounds, and has been used to form rings.[575] Another variation converts α-trimethylsilylcyclopropyl ketones to ring-expanded ketones, such as **123**, via FVP at 550°C.[576] Flash vacuum pyrolysis of the trimethylsilyl ether of cyclopropylcarbinyl alcohols gives similar results.[577] A variation uses flash vacuum pyrolysis at 600°C to convert α-trimethylsilyloxy-α-vinyl cyclic ketones to ring expanded ketones.[578]



123

Various heterocyclic analogs[579] are also known, as in the rearrangement of aziridinyl amides (**124**).[580] Cyclopropyl ketones can be treated with tosylamine and a zirconium catalyst, which converts the imine formed *in situ* to a pyrroline.[581]



124

[572]Ketley, A.D. *Tetrahedron Lett.* ***1964***, 1687; Branton, G.R.; Frey, H.M. *J. Chem. Soc. A* ***1966***, 1342.
[573]Small, A.; Breslow, R. cited in Breslow, R. in de Mayo, P. *Molecular Rearrangments*, Vol. 1, Wiley, NY, ***1963***, p. 236.
[574]Padwa, A.; Blacklock, T.J.; Getman, D.; Hatanaka, N.; Loza, R. *J. Org. Chem.* ***1978***, *43*, 1481; Zimmerman, H.E.; Kreil, D.J. *J. Org. Chem.* ***1982***, *47*, 2060.
[575]Wender, P.A.; Husfeld, C.O.; Langkopf, E.; Love, J.A. *J. Am. Chem. Soc.* ***1998***, *120*, 1940.
[576]Liu, H.; Shook, C.A.; Jamison, J.A.; Thiruvazhi, M.; Cohen, T. *J. Am. Chem. Soc.* ***1998***, *120*, 605.
[577]Rüedi, G.; Nagel, M.; Hansen, H.-J. *Org. Lett.* ***2004***, *6*, 2989.
[578]Rüedi, G.; Oberli, M.A.; Nagel, M.; Hansen, H.-J. *Org. Lett.* ***2004***, *6*, 3179.
[579]For a review of a nitrogen analog, see Boeckman, Jr., R.K.; Walters, M.A. *Adv. Heterocycl. Nat. Prod. Synth.* ***1990***, *1*, 1.
[580]For reviews of ring expansions of aziridines, see Heine, H.W. *Mech. Mol. Migr.* ***1971***, *3*, 145; Dermer, O.C.; Ham, G.E. *Ethylenimine and Other Aziridines*, Academic Press, NY, ***1969***, pp. 282–290. See also, Wong, H.N.C.; Hon, M.; Tse, C.; Yip, Y.; Tanko, J.; Hudlicky, T. *Chem. Rev.* ***1989***, *89*, 165, 190–192.
[581]Shi, M.; Yang, Y.-H.; Xu, B. *Synlett* ***2004***, 1622.

Two competing reactions are the homodienyl [1,5]-shift (if a suitable H is available, see **18-29**), and simple cleavage of the cyclopropane ring, leading in this case to a diene (see **18-3**).

Vinylcyclobutanes can be similarly converted to cyclohexenes,[582] but larger ring compounds do not generally give the reaction.[583] Bicyclo[2.1.0]pentane derivatives undergo this reaction, and tricyclo[4.1.0.$0^{2,5}$]heptanes rearrange to give nonconjugated cycloheptadienes.[584] Though high temperatures (as high as 500°C) are normally required for the thermal reaction, the lithium salts of 2-vinylcyclopropanols rearrange to the lithium salt of cyclopent-3-enols at 25°C.[585] Salts of 2-vinylcyclobutanols behave analogously.[586]

The reaction rate has also been greatly increased by the addition of a one-electron oxidant tris-(4-bromophenyl)aminium hexafluoroantimonate $Ar_3N^{\bullet+}$ SbF_6^- (Ar = *p*-bromophenyl).[587] This reagent converts the substrate to a cation radical, which undergoes ring expansion much faster.[588]

The mechanisms of these ring expansions are not certain. Both concerted[589] and diradical[590] pathways have been proposed,[591] and it is possible that both pathways operate, in different systems.

For the conversion of a vinylcyclopropane to a cyclopentene in a different way, see OS **68**, 220.

[582]See, for example, Overberger, C.G.; Borchert, A.E. *J. Am. Chem. Soc.* ***1960***, *82*, 1007; Gruseck, U.; Heuschmann, M. *Chem. Ber.* ***1990***, *123*, 1911. The kinetics of gas-phase fragmentation of propenylmethyl cyclobutanes has been examined, see Baldwin, J.E.; Burrell, R.C. *J. Org. Chem.* ***2002***, *67*, 3249. Thermal [1,3]-carbon sigmatropic rearrangements of vinylcyclobutanes have been reviewed. See Leber, P.A.; Baldwin, J.E. *Acc. Chem. Res.* ***2002***, *35*, 279.

[583]For an exception, see Thies, R.W. *J. Am. Chem. Soc.* ***1972***, *94*, 7074.

[584]Deak, H.L.; Stokes, S.S.; Snapper, M.L. *J. Am. Chem. Soc.* ***2001***, *123*, 5152.

[585]Danheiser, R.L.; Bronson, J.J.; Okano, K. *J. Am. Chem. Soc.* ***1985***, *107*, 4579.

[586]Danheiser, R.L.; Martinez-Davila, C.; Sard, H. *Tetrahedron* ***1981***, *37*, 3943.

[587]Dinnocenzo, J.P.; Conlan, D.A. *J. Am. Chem. Soc.* ***1988***, *110*, 2324.

[588]For a review of ring expansion of vinylcyclobutane cation radicals, see Bauld, N.L. *Tetrahedron* ***1989***, *45*, 5307.

[589]For evidence favoring the concerted mechanism, see Billups, W.E.; Leavell, K.H.; Lewis, E.S.; Vanderpool, S. *J. Am. Chem. Soc.* ***1973***, *95*, 8096; Berson, J.A.; Dervan, P.B.; Malherbe, R.; Jenkins, J.A. *J. Am. Chem. Soc.* ***1976***, *98*, 5937; Andrews, G.D.; Baldwin, J.E. *J. Am. Chem. Soc.* ***1976***, *98*, 6705, 6706; Dolbier, Jr., W.R.; Al-Sader, B.H.; Sellers, S.F.; Koroniak, H. *J. Am. Chem. Soc.* ***1981***, *103*, 2138; Gajewski, J.J.; Olson, L.P. *J. Am. Chem. Soc.* ***1991***, *113*, 7432.

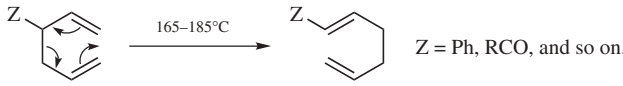
[590]For evidence favoring the diradical mechanism, see Willcott, M.R.; Cargle, V.H. *J.Am.Chem.Soc.* ***1967***, *89*, 723; Doering, W. von E.; Schmidt, E.K.G. *Tetrahedron* ***1971***, *27*, 2005; Roth, W.R.; Schmidt, E.K.G. *Tetrahedron Lett.* ***1971***, 3639; Simpson, J.M.; Richey Jr., H.G. *Tetrahedron Lett.* ***1973***, 2545; Gilbert, J.C.; Higley, D.P. *Tetrahedron Lett.* ***1973***, 2075; Caramella, P.; Huisgen, R.; Schmolke, B. *J.Am.Chem.Soc.* ***1974***, *96*, 2997, 2999; Mazzocchi, P.H.; Tamburin, H.J. *J.Am.Chem. Soc.* ***1975***, *97*, 555; Zimmerman, H.E.; Fleming, S.A. *J. Am. Chem. Soc.* ***1983***, *105*, 622; Klumpp, G.W.; Schakel, M. *Tetrahedron Lett.* ***1983***, *24,* 4595; McGaffin, G.; de Meijere, A.; Walsh, R. *Chem. Ber.* ***1991***, *124*, 939. A "continuous diradical transition state" has also been proposed: Roth, W.R.; Lennartz, H.; Doering, W. von E.; Birladeanu, L.; Guyton, C.A.; Kitagawa, T. *J. Am. Chem. Soc.* ***1990***, *112*, 1722, and references cited therein.

[591]For a discussion concerning whether or not this [1,3]-shift is a concerted reaction, see Gajewski, J.J.; Olson, L.P.; Willcott III, M.R. *J. Am. Chem. Soc.* ***1996***, *118*, 299. For a discussion of the mechanism of this reaction, see Su, M.-D. *Tetrahedron* ***1995***, *51*, 5871.

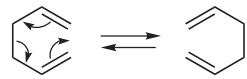
N-Cyclopropylimines undergo rearrangement to cyclic imines (pyrrolines) under photochemical conditions.[592] P-Vinyl phosphiranes (the P analog of cyclopropanes with P in the ring) under a similar rearrangement, and the mechanism has been studied.[593]

18-32 The Cope Rearrangment

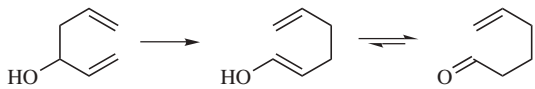
(3/4/) → (1/6/)-*sigma*-Migration



When 1,5-dienes are heated, a [3,3] sigmatropic rearrangement known as the *Cope rearrangement* (not to be confused with the Cope elimination reaction, **17-9**) occurs to generate an isomeric 1,5-diene.[594] When the diene is symmetrical about the 3,4 bond, we have the unusual situation where a reaction gives a product identical with the starting material:[595]

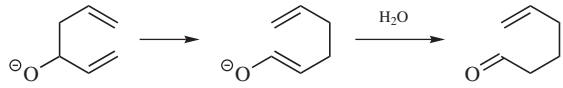


Therefore, a Cope rearrangement can be detected only when the diene is not symmetrical about this bond. Any 1,5-diene gives the rearrangement; for example, 3-methyl-1,5-hexadiene heated to 300°C gives 1,5-heptadiene.[596] However, the reaction takes place more easily (lower temperature required) when there is a group on the 3- or 4-carbon with leads to the new double bond being substituted. The reaction is obviously reversible[597] and produces an equilibrium mixture of the two 1,5-dienes, which is richer in the thermodynamically more stable isomer. However, the equilibrium can be shifted to the right for 3-hydroxy-1,5-dienes,[598] because the product tautomerizes to the ketone or aldehyde:



[592]Campos, P.J.; Soldevilla, A.; Sampedro, D.; Rodrguez, M.A. *Org. Lett.* ***2001***, *3*, 4087.
[593]Mátrai, J.; Dransfeld, A.; Veszprém, T.; Nguyen, M.T. *J. Org. Chem.* ***2001***, *66*, 5671.
[594]For reviews, see Bartlett, P.A. *Tetrahedron* ***1980***, *36*, 2, 28–39; Rhoads, S.J.; Raulins, N.R. *Org. React.* ***1975***, *22*, 1; Smith, G.G.; Kelly, F.W. *Prog. Phys. Org. Chem.* ***1971***, *8*, 75, 153–201; DeWolfe, R.H., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9, Elsevier, NY, ***1973***, pp. 455–461.
[595]Note that the same holds true for [1,*j*]-sigmatropic reactions of symmetrical substrates (**18-28**, **18-29**).
[596]Levy, H.; Cope, A.C. *J. Am. Chem. Soc.* ***1944***, *66*, 1684.
[597]For a review of the reverse Cope cyclization, see Cooper, N.J.; Knight, D.W. *Tetrahedron* ***2004***, *60*, 243.
[598]For an exception, see Elmore, S.W.; Paquette, L.A. *Tetrahedron Lett.* ***1991***, *32*, 319.

The reaction of 3-hydroxy-1,5-dienes is called the *oxy-Cope rearrangement*,[599] and has proved highly useful in synthesis.[600] The oxy-Cope rearrangement is greatly accelerated (by factors of 10^{10}–10^{17}) if the alkoxide is used rather than the alcohol (the *anionic oxy-Cope rearrangement*),[601] where the direct product is the enolate ion, which is hydrolyzed to the ketone. A metal free reaction using a phosphazene base has been reported.[602] The silyloxy-Cope rearrangement has proven to be quite useful.[603] An antibody-catalyzed oxy-Cope reaction is known,[604] and the mechanism and origins of catalysis for this reaction have been studied.[605] Sulfur substitution also leads to rate enhancement of the oxy-Cope rearrangement.[606] Note that 2-oxonia Cope rearrangements have been implicated in Prins cyclization reactions (**16-54**).[607]



aza-Cope rearrangements are also known.[608] In amino-Cope rearrangements, the solvent plays a role in the regioselectivity of the reaction.[609] It has been suggested that this latter reaction does not proceed solely by a concerted [3.3]-sigmatropic rearrangement.[610]

[599]Berson, J.A.; Walsh, Jr., E.J. *J. Am. Chem. Soc.* ***1968***, *90*, 4729; Warrington, J.M.; Yap, G.P.A.; Barriault, L. *Org. Lett.* ***2000***, *2*, 663; Ovaska, T.V.; Roses, J.B. *Org. Lett.* ***2000***, *2*, 2361. For reviews, see Paquette, L.A. *Angew. Chem. Int. Ed.* ***1990***, *29*, 609; Marvell, E.N.; Whalley, W., in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 2, Wiley, NY, ***1971***, pp. 738–743.

[600]For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1306–1307.

[601]Evans, D.A.; Nelson, J.V. *J. Am. Chem. Soc.* ***1980***, *102*, 774; Miyashi, T.; Hazato, A.; Mukai, T. *J. Am. Chem. Soc.* ***1978***, *100*, 1008; Paquette, L.A.; Pegg, N.A.; Toops, D.; Maynard, G.D.; Rogers, R.D. *J. Am. Chem. Soc.* ***1990***, *112*, 277; Gajewski, J.J.; Gee, K.R. *J. Am. Chem. Soc.* ***1991***, *113*, 967. See also, Wender, P.A.; Ternansky, R.J.; Sieburth, S.M. *Tetrahedron Lett.* ***1985***, *26*, 4319. For a study of isomerization of the parent substrate in the gas phase, see Schulze, S.M.; Santella, N.; Grabowski, J.J.; Lee, J.K. *J. Org. Chem.* ***2001***, *66*, 7247.

[602]Mamdani, H.T.; Hartley, R.C. *Tetrahedron Lett.* ***2000***, *41*, 747.

[603]For a review, see Schneider, C. *Synlett* ***2001***, 1079.

[604]Braisted, A.C.; Schultz, P.G. *J. Am. Chem. Soc.* ***1994***, *116*, 2211.

[605]Black, K.A.; Leach, A.G.; Kalani, Y.S.; Houk, K.N. *J. Am. Chem. Soc.* ***2004***, *126*, 9695.

[606]Paquette, L.A.; Reddy, Y.R.; Vayner, G.; Houk, K.N. *J. Am. Chem. Soc.* ***2000***, *122*, 10788.

[607]See Rychnovsky, S.D.; Marumoto, S.; Jaber, J.J. *Org. Lett.* ***2001***, *3*, 3815.

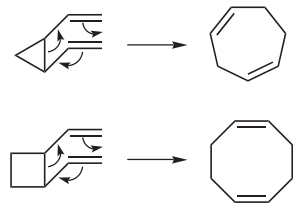
[608]Beholz, L.G.; Stille, J.R. *J. Org. Chem.* ***1993***, *58*, 5095; Sprules, T.J.; Galpin, J.D.; Macdonald, D. *Tetrahedron Lett.* ***1993***, *34*, 247; Cook, G.R.; Barta, N.S.; Stille, J.R. *J. Org. Chem.* ***1992***, *57*, 461. See Yadav, J.S.; Reddy, B.V.S.; Rasheed, M.A.; Kumar, H.M.S. *Synlett* ***2000***, 487.

[609]Dobson, H.K.; LeBlanc, R.; Perrier, H.; Stephenson, C.; Welch, T.R.; Macdonald, D. *Tetrahedron Lett.* ***1999***, *40*, 3119.

[610]Allin, S.M.; Button, M.A.C. *Tetrahedron Lett.* ***1999***, *40*, 3801.

The 1,5-diene system may be inside a ring or part of an allenic system[611] (this example illustrates both of these situations):[612]

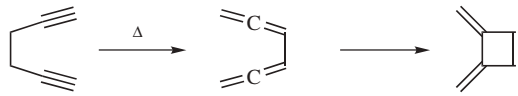
but the reaction does not take place when one of the double bonds is part of an aromatic system (e.g., 4-phenyl-1-butene).[613] When the two double bonds are in vinylic groups attached to adjacent ring positions, the product is a ring four carbons larger. This has been applied to divinylcyclopropanes and divinylcyclobutanes:[614]



Indeed, *cis*-1,2-divinylcyclopropanes give this rearrangement so rapidly that they generally cannot be isolated at room temperature,[615] though exceptions are known.[616] When heated, 1,5-diynes are converted to 3,4-dimethylenecyclobutenes **125**.[617] A rate-determining Cope rearrangement is followed by a very rapid electrocyclic (**18-27**) reaction. The interconversion of 1,3,5-trienes and cyclohexadienes

[611]Duncan, J.A.; Azar, J.K.; Beatle, J.C.; Kennedy, S.R.; Wulf, C.M. *J. Am. Chem. Soc.* ***1999***, *121*, 12029.
[612]Harris, Jr., J.F. *Tetrahedron Lett.* ***1965***, 1359.
[613]See, for example, Lambert, J.B.; Fabricius, D.M.; Hoard, J.A. *J. Org. Chem.* ***1979***, *44*, 1480; Marvell, E.N.; Almond, S.W. *Tetrahedron Lett.* ***1979***, 2777, 2779; Newcomb, M.; Vieta, R.S. *J. Org. Chem.* ***1980***, *45*, 4793. For exceptions in certain systems, see Doering, W. von E.; Bragole, R.A. *Tetrahedron* ***1966***, *22*, 385; Jung, M.E.; Hudspeth, J.P. *J. Am. Chem. Soc.* ***1978***, *100*, 4309; Yasuda, M.; Harano, K.; Kanematsu, K. *J. Org. Chem.* ***1980***, *45*, 2368.
[614]Vogel, E.; Ott, K.H.; Gajek, K. *Liebigs Ann. Chem.* ***1961***, *644*, 172. For reviews, see Wong, H.N.C.; Hon, M.; Tse, C.; Yip, Y.; Tanko, J.; Hudlicky, T. *Chem. Rev.* ***1989***, *89*, 165, see pp. 172–174; Mil'vitskaya, E.M; Tarakanova, A.V.; Plate, A.F. *Russ. Chem. Rev.* ***1976***, *45*, 469, see pp. 475–476.
[615]Unsubstituted *cis*-1,2-divinylcyclopropane is fairly stable at −20°C: Brown, J.M.; Golding, B.T.; Stofko, Jr., J.J. *J. Chem. Soc., Chem. Commun.* ***1973***, 319; Schneider, M.P.; Rebell, J. *J. Chem. Soc., Chem. Commun.* ***1975***, 283.
[616]See, for example, Brown, J.M. *Chem. Commun.* ***1965***, 226; Schönleber, D. *Chem. Ber.* ***1969***, *102*, 1789; Bolesov, I.G.; Ii-hsein, U.; Levina, R.Ya. *J. Org. Chem. USSR* ***1970***, *6*, 1791; Schneider, M.P.; Rau, A. *J. Am. Chem. Soc.* ***1979***, *101*, 4426.
[617]For reviews of Cope rearrangements involving triple bonds, see Viola, A.; Collins, J.J.; Filipp, N. *Tetrahedron* ***1981***, *37*, 3765; Théron F.; Verny, M.; Vessière, R., in Patai, S. *The Chemistry of the Carbon–Carbon Triple Bond*, pt. 1, Wiley, NY, ***1978***, pp. 381–445, pp. 428–430; Huntsman, W.D. *Intra-Sci. Chem. Rep.* ***1972***, *6*, 151.

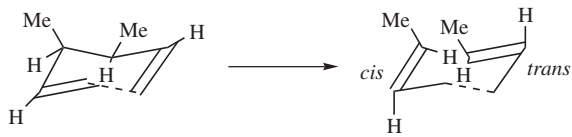
(in **18-27**) is very similar to the Cope rearrangement, but in **18-27**, the 3,4 bond goes from a double bond to a single bond rather than from a single bond to no bond.



125

Like [2 + 2]-cycloadditions (p. 1220), Cope rearrangements of simple 1,5-dienes can be catalyzed by certain transition-metal compounds. For example, the addition of $PdCl_2(PhCN)_2$ causes the reaction to take place at room temperature.[618] This can be quite useful synthetically, because of the high temperatures required in the uncatalyzed process.

As we have indicated with our arrows, the mechanism of the uncatalyzed Cope rearrangement is a simple six-centered pericyclic process.[619] Since the mechanism is so simple, it has been possible to study some rather subtle points, among them the question of whether the six-membered transition state is in the boat or the chair form.[620] For the case of 3,4-dimethyl-1,5-hexadiene, it was demonstrated conclusively that the transition state is in the chair form. This was shown by the stereospecific nature of the reaction: The meso isomer gave the cis–trans product, while the (±) diastereomer gave the trans–trans diene.[621] If the transition state is in the chair form (taking the meso isomer, e.g.), one methyl must be ''axial'' and the other ''equatorial'' and the product must be the cis–trans alkene:



[618]Overman, L.E.; Knoll, F.M. *J. Am. Chem. Soc.* ***1980***, *102*, 865; Hamilton, R.; Mitchell, T.R.B.; Rooney, J.J. *J. Chem. Soc., Chem. Commun.* ***1981***, 456. For reviews of catalysis of Cope and Claisen rearrangements, see Overman, L.E. *Angew. Chem. Int. Ed.* ***1984***, *23*, 579; Lutz, R.P. *Chem. Rev.* ***1984***, *84*, 205. For a study of the mechanism, see Overman, L.E.; Renaldo, A.F. *J. Am. Chem. Soc.* ***1990***, *112*, 3945.

[619]For a mechanistic discussion, see Poupko, R.; Zimmermann, H.; Müller, K.; Luz, Z. *J. Am. Chem. Soc.* ***1996***, *118*, 7995.

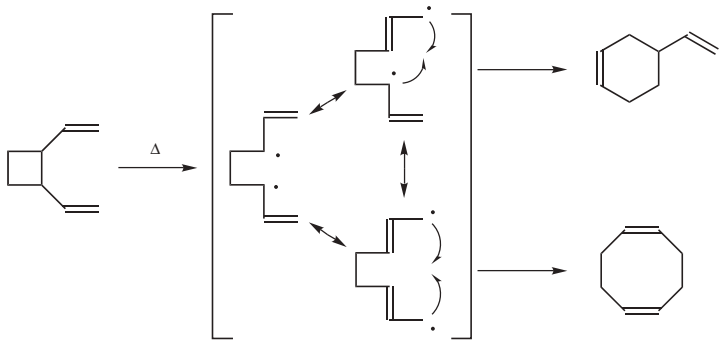
[620]For a discussion showing a preference for the chair conformation, see Shea, K.J.; Stoddard, G.J.; England, W.P.; Haffner, C.D. *J. Am. Chem. Soc*, ***1992***, *114*, 2635. See also, Tantillo, D.J.; Hoffmann, R. *J. Org. Chem.* ***2002***, *67*, 1419.

[621]Doering, W. von E.; Roth, W.R.*Tetrahedron* ***1962***, *18*, 67. See also, Hill, R.K.; Gilman, N.W. *Chem. Commun.* ***1967***, 619; Goldstein, M.J.; DeCamp, M.R. *J. Am. Chem. Soc.* ***1974***, *96*, 7356; Hansen, H.; Schmid, H. *Tetrahedron* ***1974***, *30*, 1959; Gajewski, J.J.; Benner, C.W.; Hawkins, C.M. *J. Org. Chem.* ***1987***, *52*, 5198; Paquette, L.A.; DeRussy, D.T.; Cottrell, C.E. *J. Am. Chem. Soc.* ***1988***, *110*, 890.

There are two possible boat forms for the transition state of the meso isomer. One leads to a trans–trans product;

the other to a cis–cis alkene. For the (±) pair the predictions are just the opposite: There is just one boat form, and it leads to the cis–trans alkene, while one chair form (''diaxial'' methyls) leads to the cis–cis product and the other (''diequatorial'' methyls) predicts the trans–trans product. Thus the nature of the products obtained demonstrates that the transition state is a chair and not a boat.[622] While 3,4-dimethyl-1,5-hexadiene is free to assume either the chair or boat (it prefers the chair), other compounds are not so free. Thus 1,2-divinylcyclopropane (p. 1661) can react *only* in the boat form, demonstrating that such reactions are not impossible.[623]

Because of the nature of the transition state[624] in the pericyclic mechanism, optically active substrates with a stereogenic carbon at C-3 or C-4 transfer the chirality to the product (see p. 1673 for an example in the mechanistically similar Claisen rearrangement).[625] There are many examples of asymmetric [3,3]-sigmatropic rearrangements.[626]



[622]Preference for the chair transition state is a consequence of orbital-symmetry relationships: Hoffmann, R.; Woodward, R.B. *J. Am. Chem. Soc.* ***1965***, *87*, 4389; Fukui, K.; Fujimoto, H. *Tetrahedron Lett.* ***1966***, 251.

[623]For other examples of Cope rearrangements in the boat form, see Goldstein, M.J.; Benzon, M.S. *J. Am. Chem. Soc.* ***1972***, *94*, 7147; Shea, K.J.; Phillips, R.B. *J. Am. Chem. Soc.* ***1980***, *102*, 3156; Wiberg, K.B.; Matturro, M.; Adams, R. *J. Am. Chem. Soc.* ***1981***, *103*, 1600; Gajewski, J.J.; Jiminez, J.L. *J. Am. Chem. Soc.* ***1986***, *108*, 468.

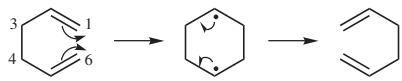
[624]See Jiao, H.; Schleyer, P.v.R. *Angew. Chem. Int. Ed.* ***1995***, *34*, 334; Özkan, I.; Zora, M. *J. Org. Chem.* ***2003***, *68*, 9635.

[625]For a review of Cope and Claisen reactions as enantioselective syntheses, see Hill, R.K., in Morrison, J.D. *Asymmetric Synthesis*, Vol. 3, Academic Press, NY, ***1984***, pp. 503–572, 503–545.

[626]For a review, see Nubbemeyer, U. *Synthesis* ***2003***, 961.

Not all Cope rearrangements proceed by the cyclic six-centered mechanism.[627] Thus *cis*-1,2-divinylcyclobutane (p. 1661) rearranges smoothly to 1,5-cyclooctadiene, since the geometry is favorable. The trans isomer also gives this product, but the main product is 4-vinylcyclohexene (resulting from **18-31**). This reaction can be rationalized as proceeding by a diradical mechanism,[628] although it is possible that at least part of the cyclooctadiene produced comes from a prior epimerization of the *trans*- to the *cis*-divinylcyclobutane followed by Cope rearrangement of the latter.[629]

It has been suggested that another type of diradical two-step mechanism may be preferred by some substrates.[630] Indeed, a nonconcerted Cope rearrangement has been reported.[631] In this pathway,[632] the 1,6 bond is formed before the 3,4 bond breaks:



This is related to the *Bergman cyclization* that was introduced in **18-27**.

It was pointed out earlier that a Cope rearrangement of the symmetrical 1,5-hexadiene gives 1,5-hexadiene. This is a *degenerate Cope rearrangement* (p. 1563). Another molecule that undergoes it is bicyclo[5.1.0]octadiene

126 **126**

[627]The diradical character of the Cope rearrangement transition state has been studied. See Staroverov, V.B.; Davidson, E.R. *J. Am. Chem. Soc.* ***2000***, *122*, 186; Navarro-Vázquez, A.; Prall, M.; Schreiner, P.R. *Org. Lett.* ***2004***, *6*, 2981.

[628]Hammond, G.S.; De Boer, C.D. *J. Am. Chem. Soc.* ***1964***, *86*, 899; Trecker, D.J.; Henry, J.P. *J. Am. Chem. Soc.* ***1964***, *86*, 902. Also see, Dolbier, Jr., W.R.; Mancini, G.J. *Tetrahedron Lett.* ***1975***, 2141; Kessler, H.; Ott, W. *J. Am. Chem. Soc.* ***1976***, *98*, 5014. For a discussion of diradical mechanisms in Cope rearrangements, see Berson, J.A., in de Mayo, P. *Rearrangements in Ground and Excited States*, Academic Press, NY, ***1980***, pp. 358–372.

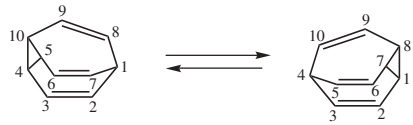
[629]See, for example, Berson, J.A.; Dervan, P.B. *J. Am. Chem. Soc.* ***1972***, *94*, 8949; Baldwin, J.E.; Gilbert, K.E. *J. Am. Chem. Soc.* ***1976***, *98*, 8283. For a similar result in the 1,2-divinylcyclopropane series, see Baldwin, J.E.; Ullenius, C. *J. Am. Chem. Soc.* ***1984***, *96*, 1542.

[630]Doering, W. von E.; Toscano, V.G.; Beasley, G.H. *Tetrahedron* ***1971***, *27*, 5299; Dewar, M.J.S.; Wade, Jr., L.E. *J. Am. Chem. Soc.* ***1977***, *99*, 4417; Padwa, A.; Blacklock, T.J. *J. Am. Chem. Soc.* ***1980***, *102*, 2797; Dollinger, M.; Henning, W.; Kirmse, W. *Chem. Ber.* ***1982***, *115*, 2309; Kaufmann, D.; de Meijere, A. *Chem. Ber.* ***1984***, *117*, 1128; Dewar, M.J.S.; Jie, C. *J. Am. Chem. Soc.* ***1987***, *109*, 5893; *J. Chem. Soc., Chem. Commun.* ***1989***, 98. For evidence against this view, see Gajewski, J.J. *Acc. Chem. Res.* ***1980***, *13*, 142; Morokuma, K.; Borden, W.T.; Hrovat, D.A. *J. Am. Chem. Soc.* ***1988***, *110*, 4474; Halevi, E.A.; Rom, R. *Isr. J. Chem.* ***1989***, *29*, 311; Owens, K.A.; Berson, J.A. *J. Am. Chem. Soc.* ***1990***, *112*, 5973.

[631]Roth, W.R.; Gleiter, R.; Paschmann, V.; Hackler, U.E.; Fritzsche, G.; Lange, H. *Eur. J. Org. Chem.* ***1998***, 961; Roth, W.R.; Schaffers, T.; Heiber, M. *Chem. Ber.* ***1992***, *125*, 739.

[632]For a report of still another mechanism, featuring a diionic variant of the diradical, see Gompper, R.; Ulrich, W. *Angew. Chem. Int. Ed.* ***1976***, *15*, 299.

(**126**).[633] At room temperature, the NMR spectrum of this compound is in accord with the structure shown on the left. At 180°C, it is converted by a Cope reaction to a compound equivalent to itself. The interesting thing is that at 180°C the NMR spectrum shows that what exists is an equilibrium mixture of the two structures. That is, at this temperature the molecule rapidly (faster than 10^3 times per second) changes back and forth between the two structures. This is called *valence tautomerism* and is quite distinct from resonance, even though only electrons shift.[634] The positions of the nuclei are not the same in the two structures. Molecules like **126** that exhibit valence tautomerism (in this case, at 180°C) are said to have *fluxional* structures. It may be recalled that *cis*-1,2- divinylcyclopropane does not exist at room temperature because it rapidly rearranges to 1,4-cycloheptadiene (p. 1661), but in **126** the *cis*-divinylcyclopropane structure is frozen into the molecule in both structures. Several other compounds with this structural feature are also known. Of these, *bullvalene* (**127**) is especially interesting.



127

The Cope rearrangement shown changes the position of the cyclopropane ring from 4,5,10 to 1,7,8. But the molecule could also have undergone rearrangements to put this ring at 1,2,8 or 1,2,7. Any of these could then undergo several Cope rearrangements. In all, there are $\frac{10!}{3}$ or >1.2 million tautomeric forms, and the cyclopropane ring can be at any three carbons that are adjacent. Since each of these tautomers is equivalent to all the others, this has been called an infinitely degenerate Cope rearrangement. Bullvalene has been synthesized and its ^{1}H NMR spectrum determined.[635] At −25°C, there are two peaks with an area ratio of 6:4. This is in accord with a single non-tautomeric structure. The six are the vinylic protons and the four are the allylic ones. But at 100°C the compound shows only one NMR peak, indicating that we have here a truly unusual situation where the compound rapidly interchanges its structure among 1.2 million equivalent forms.[636] The ^{13}C NMR spectrum of bullvalene also shows

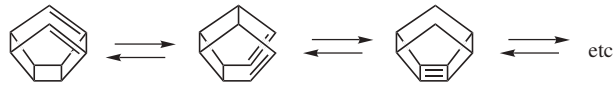
[633]Doering, W. von E.; Roth, W.R. *Tetrahedron* ***1963***, *19*, 715.

[634]For reviews of valence tautomerizations, see Decock-Le Révérend, B.; Goudmand, P. *Bull. Soc. Chim. Fr.* ***1973***, 389; Gajewski, J.J. *Mech. Mol. Migr.* ***1971***, *4*, 1, see pp. 32–49; Paquette, L.A. *Angew. Chem. Int. Ed.* ***1971***, *10*, 11; Domareva-Mandel'shtam, T.V.; D'yakonov, I.A. *Russ. Chem. Rev.* ***1966***, *35*, 559, 568; Schröder, G.; Oth, J.F.M.; Merényi, R. *Angew. Chem. Int. Ed.* ***1965***, *4*, 752.

[635]Schröder, G. *Chem. Ber.* ***1964***, *97*, 3140; Merényi, R.; Oth, J.F.M.; Schröder, G. *Chem. Ber.* ***1964***, *97*, 3150. For a review of bullvalenes, see Schröder, G.; Oth, J.F.M. *Angew. Chem. Int. Ed.* ***1967***, *6*, 414.

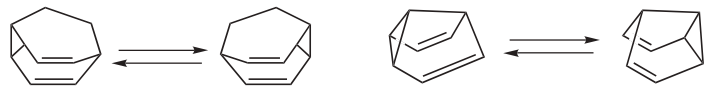
[636]A number of azabullvalenes (**127** containing heterocyclic nitrogen) have been synthesized. They also have fluxional structures when heated, though with fewer tautomeric forms than bullvalene itself: Paquette, L.A.; Malpass, J.R.; Krow, G.R.; Barton, T.J. *J. Am. Chem. Soc.* ***1969***, *91*, 5296.

only one peak at 100°C.[637]



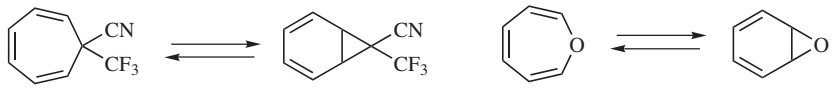
128

Another compound for which degenerate Cope rearrangements result in equivalence for all the carbons is *hypostrophene* (**128**).[638] In the case of the compound *barbaralane* (**129**)[639] (bullvalene in which one CH=CH has been replaced by a CH_2):



129 **130**

there are only 2 equivalent tautomers.[640] However, NMR spectra indicate that even at room temperature a rapid interchange of both tautomers is present, although by about −100°C this has slowed to the point where the spectrum is in accord with a single structure. In the case of *semibullvalene* (**130**) (barbaralane in which the CH_2 has been removed), not only is there a rapid interchange at room temperature, but even at −110°C.[641] Compound **130** has the lowest energy barrier of any known compound capable of undergoing the Cope rearrangement.[642]



131 **132** Oxepin Benzene oxide

[637]Oth, J.F.M.; Müllen, K.; Gilles, J.; Schröder, G. *Helv. Chim. Acta* ***1974***, *57*, 1415; Nakanishi, H.; Yamamoto, O. *Tetrahedron Lett.* ***1974***, 1803; Günther, H.; Ulmen, J. *Tetrahedron* ***1974***, *30*, 3781. For deuterium nmr spectra, see Poupko, R.; Zimmermann, H.; Luz, Z. *J. Am. Chem. Soc.* ***1984***, *106*, 5391. For a crystal structure study, see Luger, P.; Buschmann, J.; McMullan, R.K.; Ruble, J.R.; Matias, P.; Jeffrey, G.A. *J. Am. Chem. Soc.* ***1986***, *108*, 7825.

[638]McKennis, J.S.; Brener, L.; Ward, J.S.; Pettit, R. *J. Am. Chem. Soc.* ***1971***, *93*, 4957; Paquette, L.A.; Davis, R.F.; James, D.R. *Tetrahedron Lett.* ***1974***, 1615.

[639]For a study of sigmatropic shiftamers in extended barbaralanes, see Tantillo, D.J.; Hoffmann, R.; Houk, K.N.; Warner, P.M.; Brown, E.C.; Henze, D.K. *J. Am. Chem. Soc.* ***2004***, *126*, 4256.

[640]Barbaralane was synthesized by Biethan, U.; Klusacek, H.; Musso, H. *Angew. Chem. Int. Ed.* ***1967***, *6*, 176; by Tsuruta, H.; Kurabayashi, K.; Mukai, T. *Tetrahedron Lett.* ***1965***, 3775; by Doering, W. von E.; Ferrier, B.M.; Fossel, E.T.; Hartenstein, J.H.; Jones Jr., M.; Klumpp, G.W.; Rubin, R.M.; Saunders, M. *Tetrahedron* ***1967***, *23*, 3943; and by Henkel, J.G.; Hane, J.T. *J. Org. Chem.* ***1983***, *48*, 3858.

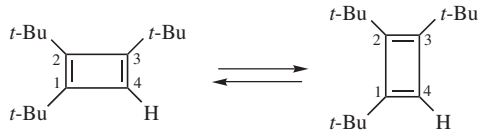
[641]Meinwald, J.; Schmidt, D. *J. Am. Chem. Soc.* ***1969***, *91*, 5877; Zimmerman, H.E.; Binkley, R.W.; Givens, R.S.; Grunewald, G.L.; Sherwin, M.A. *J. Am. Chem. Soc.* ***1969***, *91*, 3316.

[642]Cheng, A.K.; Anet, F.A.L.; Mioduski, J.; Meinwald, J. *J. Am. Chem. Soc.* ***1974***, *96*, 2887; Moskau, D.; Aydin, R.; Leber, W.; Günther, H.; Quast, H.; Martin, H.-D.; Hassenrück, K.; Miller, L.S.; Grohmann, K. *Chem. Ber.* ***1989***, *122*, 925. For a discussion concerning whether or not semibullvalenes are homoaromatic, see Williams, R.V.; Gadgil, V.R.; Chauhan, K.; Jackman, L.M.; Fernandes, E. *J. Org. Chem.* ***1998***, *63*, 3302.

The molecules taking part in a valence tautomerization need not be equivalent. Thus, NMR spectra indicate that a true valence tautomerization exists at room temperature between the cycloheptatriene **131** and the norcaradiene **132**.[643] In this case, one isomer (**132**) has the *cis*-1,2-divinylcyclopropane structure, while the other does not. In an analogous interconversion, benzene oxide[644] and oxepin exist in a tautomeric equilibrium at room temperature.[645]

Bullvalene and hypostrophene are members of a group of compounds all of whose formulas can be expressed by the symbol $(CH)_{10}$.[646] Many other members of this group are known. Similar groups of $(CH)_n$ compounds exist for other even-numbered values of "*n*".[646] For example, there are 20 possible $(CH)_8$[647] compounds,[648] and five possible $(CH)_6$ compounds,[649] all of which are known: benzene, prismane (p. 220), Dewar benzene (p. 1641), bicyclopropenyl,[650] and benzvalene.[651]

An interesting example of a valence tautomerism is the case of 1,2,3-tri-*tert*-butylcyclobutadiene (p. 74). There are two isomers, both rectangular, and ^{13}C NMR spectra show that they exist in a dynamic equilibrium, even at $-185°C$.[652]



[643]Ciganek, E. *J. Am. Chem. Soc.* ***1965***, *87*, 1149. For other examples of norcaradiene–cycloheptatriene valence tautomerizations, see Görlitz, M.; Günther, H. *Tetrahedron* ***1969***, *25*, 4467; Ciganek, E. *J. Am. Chem. Soc.* ***1965***, *93*, 2207; Dürr, H.; Kober, H. *Chem. Ber.* ***1973***, *106*, 1565; Betz, W.; Daub, J. *Chem. Ber.* ***1974***, *107*, 2095; Maas, G.; Regitz, M. *Chem. Ber.* ***1976***, *109*, 2039; Warner, P.M.; Lu, S. *J. Am. Chem. Soc.* ***1980***, *102*, 331; Neidlein, R.; Radke, C.M. *Helv. Chim. Acta* ***1983***, *66*, 2626; Takeuchi, K.; Kitagawa, T.; Ueda, A.; Senzaki, Y.; Okamoto, K. *Tetrahedron* ***1985***, *41*, 5455.

[644]For a review of arene oxides, see Shirwaiker, G.S.; Bhatt, M.V. *Adv. Heterocycl. Chem.* ***1984***, *37*, 67.

[645]For reviews, see Maier, G. *Angew. Chem. Int. Ed.* ***1967***, *6*, 402; Vogel, E.; Günther, H. *Angew. Chem. Int. Ed.* ***1967***, *6*, 385; Vogel, E. *Pure Appl. Chem.* ***1969***, *20*, 237. See also, Boyd, D.R.; Stubbs, M.E. *J. Am. Chem. Soc.* ***1983***, *105*, 2554.

[646]For reviews of rearrangements and interconversions of $(CH)_n$ compounds, see Balaban, A.T.; Banciu, M. *J. Chem. Educ.* ***1984***, *61*, 766; Greenberg, A.; Liebman, J.F. *Strained Organic Molecules*, Academic Press, NY, ***1978***, pp. 203–215; Scott, L.T.; Jones, Jr., M. *Chem. Rev.* ***1972***, *72*, 181. See also, Maier, G.; Wiegand, N.H.; Baum, S.; Wüllner, R. *Chem. Ber.* ***1989***, *122*, 781.

[647]For a review of strain in $(CH)_8$ compounds, see Hassenrück, K.; Martin, H.; Walsh, R. *Chem. Rev.* ***1989***, *89*, 1125.

[648]The structures of all possible $(CH)_n$ compounds, for $n = 4$, 6, 8, and 10, are shown in Balaban, A.T; Banziu, M. *J. Chem. Educ.* ***1984***, *61*, 766. For a review of $(CH)_{12}$ compounds, see Banciu, M.; Popa, C.; Balaban, A.T. *Chem. Scr.*, ***1984***, *24*, 28.

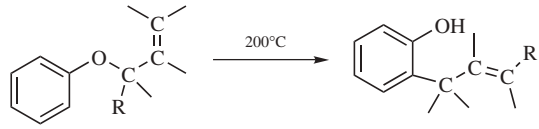
[649]For reviews of valence isomers of benzene and some related compounds, see Kobayashi, Y.; Kumadaki, I. *Top. Curr. Chem.* ***1984***, *123*, 103; Bickelhaupt, F.; de Wolf, W.H. *Recl. Trav. Chim. Pays-Bas* ***1988***, *107*, 459.

[650]For a study of how this compound isomerizes to benzene, see Davis, J.H.; Shea, K.J.; Bergman, R.G. *J. Am. Chem. Soc.* ***1977***, *99*, 1499.

[651]For reviews of benzvalenes, see Christl, M. *Angew. Chem. Int. Ed.* ***1981***, *20*, 529; Burger, U. *Chimia*, ***1979***, 147.

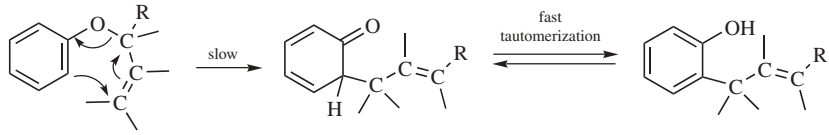
[652]Maier, G.; Kalinowski, H.; Euler, K. *Angew. Chem. Int. Ed.* ***1982***, *21*, 693.

18-33 The Claisen Rearrangement[653]



Allylic aryl ethers, when heated, rearrange to *o*-allylphenols in a reaction called the *Claisen rearrangement*.[654] If both ortho positions are filled, the allylic group migrates to the para position (this is often called the *para-Claisen rearrangement*).[655] There is no reaction when the para and both ortho positions are filled. Migration to the meta position has not been observed. In the ortho migration, the allylic group always undergoes an allylic shift. That is, as shown above, a substituent α to the oxygen is now γ to the ring (and vice versa). On the other hand, in the para migration there is never an allylic shift: The allylic group is found exactly as it was in the original ether. Compounds with propargylic groups (i.e., groups with a triple bond in the appropriate position) do not generally give the corresponding products.

The mechanism is a concerted pericyclic [3,3]-sigmatropic rearrangement[656] and accounts for all these facts. For the ortho rearrangement:



Evidence is the lack of a catalyst, the fact that the reaction is first order in the ether, the absence of crossover products when mixtures are heated, and the presence of the allylic shift, which is required by this mechanism. A *retro*-Claisen rearrangement is known and its mechanism has been examined.[657] The allylic

[653]For a reiview of the Claisen rearrangment since about 1910, see Castro, A.M.M. *Chem. Rev.* ***2004***, *104*, 2939.

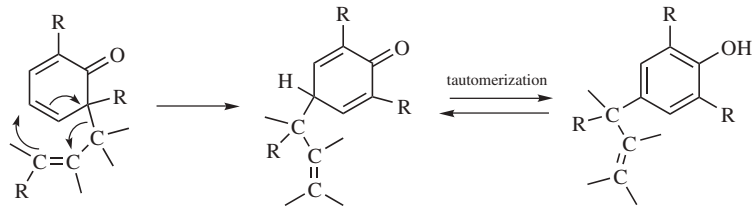
[654]For reviews, see Fleming, I. *Pericyclic Reactions*, Oxford University Press, Oxford, ***1999***, pp. 71–83; Moody, C.J. *Adv. Heterocycl. Chem.* ***1987***, *42*, 203; Bartlett, P.A. *Tetrahedron* ***1980***, *36*, 2, see pp. 28–39; Ziegler, F.E. *Acc. Chem. Res.* ***1977***, *10*, 227; Bennett, G.B. *Synthesis* ***1977***, 589; Rhoads, S.J.; Raulins, N.R. *Org. React.* ***1975***, *22*, 1; Shine, H.J. *Aromatic Rearrangements*; Elsevier, NY, ***1969***, pp. 89–120; Smith, G.G.; Kelly, F.W. *Prog. Phys. Org. Chem.* ***1971***, *8*, 75, 153–201; Hansen, H.; Schmid, H. *Chimia,* ***1970***, *24*, 89, *Chem. Br.* ***1969***, *5*, 111; Jefferson, A.; Scheinmann, F. *Q. Rev. Chem. Soc.* ***1968***, *22*, 391; Thyagarajan, B.S. *Adv. Heterocycl. Chem.* ***1967***, *8*, 143; Dalrymplem D.L.; Kruger, T.L.; White, W.N., in Patai *The Chemistry of the Ether Linkage*, Wiley, NY, ***1967***, pp. 635–660.

[655]For a discussion of regioselectivity, see Gozzo, F.C.; Fernandes, S.A.; Rodrigues, D.C.; Eberlin, M.N.; Marsaioli, A.J. *J. Org. Chem.* ***2003***, *68*, 5493.

[656]For isotope effect evidence regarding the nature of the concerted transition state, see McMichael, K.D.; Korver, G.L. *J. Am. Chem. Soc.* ***1979***, *101*, 2746; Gajewski, J.J.; Conrad, N.D. *J. Am. Chem. Soc.* ***1979***, *101*, 2747; Kupczyk-Subotkowska, L.; Saunders, Jr., W.H.; Shine, H.J. *J. Am. Chem. Soc.* ***1988***, *110*, 7153.

[657]Boeckman, Jr., R.K.; Shair, M.D.; Vargas, J.R.; Stolz, L.A. *J. Org. Chem.* ***1993***, *58*, 1295.

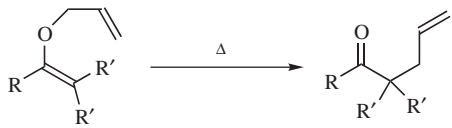
shift for the ortho rearrangement (and the absence of one for the para) has been demonstrated by ^{14}C labeling, even when no substituents are present. Studies of the transition-state geometry have shown that, like the Cope rearrangement, the Claisen rearrangement usually prefers a chair-like transition state.[658] When the ortho positions have no hydrogen, a second [3,3]-sigmatropic migration (a Cope reaction) follows:



133

and the migrating group is restored to its original structure. Intermediates of structure **133** have been trapped by means of a Diels–Alder reaction.[659] The rearrangement of aryl allyl ethers is facilitated by Ag–KI in hot acetic acid,[660] and by $AlMe_3$ in water.[661] A solid-phase reaction of polymer-bound substrate undergoes the Claisen rearrangement with microwave irradiation.[662]

Allylic ethers of enols (allylic vinylic ethers) also undergo the Claisen rearrangement;[663] in fact, it was discovered with these compounds first:[664]



In these cases of course, the final tautomerization does not take place even when R' = H, since there is no aromaticity to restore, and ketones are more stable than enols.[665] Catalytic Claisen rearrangements of allyl vinyl ethers are well known.[666]

[658]Wunderli, A.; Winkler, T.; Hansen, H. *Helv. Chim. Acta* ***1977***, *60*, 2436; Copley, S.D.; Knowles, J.R. *J. Am. Chem. Soc.* ***1985***, *107*, 5306. Also see, Yoo, H.Y.; Houk, K.N. *J. Am. Chem. Soc.* ***1994***, *116*, 12047; Kupczyk-Subotkowska, L.; Saunders, Jr., W.H.; Shine, H.J.; Subotkowski, W. *J. Am. Chem. Soc.* ***1993***, *115*, 5957; Kupczyk-Subotkowska, L.; Subotkowski, W.; Saunders, Jr., W.H.; Shine, H.J.; *J. Am. Chem. Soc.* ***1992***, *114*, 3441.

[659]Conroy, H.; Firestone, R.A. *J. Am. Chem. Soc.* ***1956***, *78*, 2290.

[660]Sharghi, H.; Aghapour, G. *J. Org. Chem.* ***2000***, *65*, 2813.

[661]Wipf, P.; Ribe, S. *Org. Lett.* ***2001***, *3*, 1503.

[662]Kumar, H.M.S.; Anjaneyulu, S.; Reddy, B.V.S.; Yadav, J.C. *Synlett* ***2000***, 1129.

[663]For a review, see Ziegler, F.E. *Chem. Rev.* ***1988***, *88*, 1423.

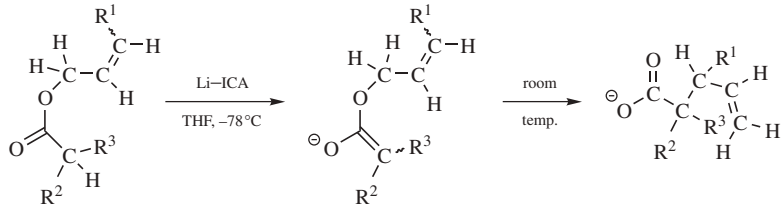
[664]Claisen, L. *Berchte.* ***1912***, *45*, 3157.

[665]However, it has proved possible to reverse the reaction, with a Lewis acid catalyst. See Boeckman Jr., R.K.; Flann, C.J.; Poss, K.M. *J. Am. Chem. Soc.* ***1985***, *107*, 4359.

[666]For a review, see Hiersemann, M.; Abraham, L. *Eur. J. Org. Chem.* ***2002***, 1461.

The use of water as solvent accelerates the reaction.[667] A microwave induced reaction on silica gel is known[668]. The mechanism is similar to that with allylic aryl ethers.[669] Allyl allene ethers undergo a Claisen rearrangement when heated in DMF to give the expected diene with a conjugated aldehyde unit.[670] Butenolides with a β-allylic ether unit undergo Claisen rearrangement–Conia reaction[671] cascade to give an oxaspiro heptane with β-keto lactone comprising the five-membered ring.[672] Allylic esters of β-keto acids undergo a Claisen rearrangement in what is known as the *Carroll rearrangement*[673] (also called the *Kimel–Cope rearrangement*[674]), and the reaction can be catalyzed by a ruthenium complex.[675]

It is possible to treat ketones with allyl alcohol and an acid catalyst to give γ,δ-unsaturated ketones directly, presumably by initial formation of the vinylic ethers, and then Claisen rearrangement.[676] In an analogous procedure, the enolates (**134**) of allylic esters [formed by treatment of the esters with lithium isopropylcyclohexylamide (LICA)] rearrange to γ,δ-unsaturated acids.[677] Allylic alcohols can be treated with a catalytic amount of mercuric acetate, and in the presence of an excess of allyl vinyl ethers give an alkene–aldehyde via a Claisen rearrangement.[678]



134

[667]Grieco, P.A.; Brandes, E.B.; McCann, S.; Clark, J.D. *J. Org. Chem.* ***1989***, *54*, 5849. The effect of water on the transition state has been examined; see Guest, J.M.; Craw, J.S.; Vincent, M.A.; Hillier, I.H. *J. Chem. Soc. Perkin Trans. 2* ***1997***, 71; Sehgal, A.; Shao, L.; Gao, J. *J. Am. Chem. Soc.* ***1995***, *117*, 11337.

[668]Kotha, S.; Mandal, K.; Deb, A.C.; Banerjee, S. *Tetrahedron Lett.* ***2004***, *45*, 9603.

[669]For discussions of the transition state, see Gajewski, J.J.; Jurayj, J.; Kimbrough, D.R.; Gande, M.E.; Ganem, B.; Carpenter, B.K. *J. Am. Chem. Soc.* ***1987***, *109*, 1170. For MO calculations, see Vance, R.L.; Rondan, N.G.; Houk, K.N.; Jensen, F.; Borden, W.T.; Komornicki, A.; Wimmer, E. *J. Am. Chem. Soc.* ***1988***, *110*, 2314; Dewar, M.J.S.; Jie, C. *J. Am. Chem. Soc.* ***1989***, *111*, 511.

[670]Parsons, P.J.; Thomson, P.; Taylor, A.; Sparks, T. *Org. Lett.* ***2000***, *2*, 571.

[671]For a review of the Conia-ene reaction, see Conia, J.M.; Le Perchec, P. *Synthesis* ***1975***, 1.

[672]Schobert, R.; Siegfried, S.; Gordon, G.; Nieuwenhuyzen, M.; Allenmark, S. *Eur. J. Org. Chem.* ***2001***, 1951.

[673]Carroll, M.F. *J. Chem. Soc.* ***1940***, 704, 1266; Carroll, M.F. *J. Chem. Soc.* ***1941***, 507; Ziegler, F.E. *Chem. Rev.* ***1988***, *88*, 1423.

[674]Kimel, W.; Cope, A.C. *J. Am. Chem. Soc.* ***1943***, *65*, 1992.

[675]Burger, E.C.; Tunge, J.A. *Org. Lett.* ***2004***, *6*, 2603.

[676]Lorette, N.B. *J. Org. Chem.* ***1961***, *26*, 4855. See also, Saucy, G.; Marbet, R. *Helv. Chim. Acta* ***1967***, *50*, 2091; Marbet, R.; Saucy, G. *Helv. Chim. Acta* ***1967***, *50*, 2095; Thomas, A.F. *J. Am. Chem. Soc.* ***1969***, *91*, 3281; Johnson, W.S.; Werthemann, L.; Bartlett, W.R.; Brocksom, T.J.; Li, T.; Faulkner, D.J.; Petersen, M.R. *J. Am. Chem. Soc.* ***1970***, *92*, 741; Pitteloud, R.; Petrzilka, M. *Helv. Chim. Acta* ***1979***, *62*, 1319; Daub, G.W.; Sanchez, M.G.; Cromer, R.A.; Gibson, L.L. *J. Org. Chem.* ***1982***, *47*, 743; Bartlett, P.A.; Tanzella, D.J.; Barstow, J.F. *J. Org. Chem.* ***1982***, *47*, 3941.

[677]Ireland, R.E.; Mueller, R.H.; Willard, A.K. *J. Am. Chem. Soc.* ***1976***, *98*, 2868; Gajewski, J.J.; Emrani, J. *J. Am. Chem. Soc.* ***1984***, *106*, 5733; Cameron A.G.; Knight, D.W. *J. Chem. Soc. Perkin Trans. 1* ***1986***, 161. See also, Wilcox, C.S.; Babston, R.E. *J. Am. Chem. Soc.* ***1986***, *108*, 6636.

[678]Tokuyama, H.; Makido, T.; Ueda, T.; Fukuyama, T. *Synth. Commun.* ***2002***, *32*, 869.

Alternatively, the silylketene acetal $R^3R^2C{=}C(OSiR_3)OCH_2CH{=}CHR^1$ is often used instead of **134**.[677,679] This rearrangement also proceeds at room temperature. By either procedure, the reaction is called the *Ireland–Claisen rearrangement*.[680] Note the presence of the negative charge in **134**. As with the oxy-Cope rearrangement (in **18-34**), negative charges generally accelerate the Claisen reaction,[681] although the extent of the acceleration can depend on the identity of the positive counterion.[682] The reaction proceeds with good syn selectivity in many cases.[683] The Ireland–Claisen rearrangement has been made enantioselective by converting **134** to an enol borinate in which the boron is attached to a chiral group.[684] The Ireland–Claisen rearrangement can be done with amide derivatives also.[685]

A number of expected analogs of the Claisen rearrangement are known, for example, rearrangement of $ArNHCH_2CH{=}CH_2$,[686] of *N*-allylic enamines ($R_2C{=}CRNRCR_2CR{=}CR_2$),[687] of allylic imino esters, $RC(OCH_2CH{=}CH_2){=}NR$[688] (these have often been rearranged with transition-metal catalysts[689]), and of $RCH{=}NRCHRCH_2CH{=}CH_2$. These rearrangements of nitrogen-containing compounds can be called *aza-Claisen rearrangements*,[690] but are often called

[679]Ireland, R.E.; Wipf, P.; Armstrong III, J.D. *J. Org. Chem.* ***1991***, *56*, 650.

[680]For a recent example, see Dell, C.P.; Khan, K.M.; Knight, D.W. *J. Chem. Soc. Perkin Trans. 1* ***1994***, 341. For a review, see Chai, Y.; Hong, S.-p.; Lindsay, H.A.; McFarland, C.; McIntosh, M.C. *Tetrahedron* ***2002***, *58*, 2905.

[681]See, for example, Denmark, S.E.; Harmata, M.A.; White, K.S. *J. Am. Chem. Soc.* ***1989***, *111*, 8878.

[682]Koreeda, M.; Luengo, J.I. *J. Am. Chem. Soc.* ***1985***, *107*, 5572; Kirchner, J.J.; Pratt, D.V.; Hopkins, P.B. *Tetrahedron Lett.* ***1988***, *29*, 4229.

[683]Mohamed, M.; Brook, M.A. *Tetrahedron Lett.* ***2001***, *42*, 191. For a discussion of boat or chair preferences, see Khaledy, M.M.; Kalani, M.Y.S.; Khuong, K.S.; Houk, K.N.; Aviyente, V.; Neier, R.; Soldermann, N.; Velker, J. *J. Org. Chem.* ***2003***, *68*, 572.

[684]Corey, E.J.; Lee, D. *J. Am. Chem. Soc.* ***1991***, *113*, 4026.

[685]Tsunoda, T.; Tatsuki, S.; Shiraishi, Y.; Akasaka, M.; Itô, S. *Tetrahedron Lett.* ***1993***, *34*, 3297. Also see, Walters, M.A.; Hoem, A.B.; Arcand, H.R.; Hegeman, A.D.; McDonough, C.S. *Tetrahedron Lett.* ***1993***, *34*, 1453.

[686]Marcinkiewicz, S.; Green, J.; Mamalis, P. *Tetrahedron* ***1961***, *14*, 208; Inada, S.; Ikado, S.; Okazaki, M. *Chem. Lett.* ***1973***, 1213; Schmid, M.; Hansen, H.; Schmid, H. *Helv. Chim. Acta* ***1973***, *56*, 105; Jolidon, S.; Hansen, H. *Helv. Chim. Acta* ***1977***, *60*, 978.

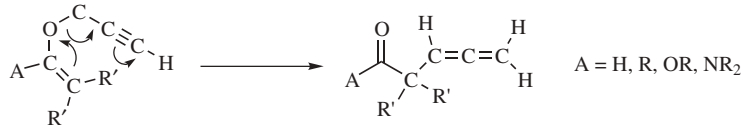
[687]Ficini, J.; Barbara, C. *Tetrahedron Lett.* ***1966***, 6425; Ireland, R.E.; Willard, A.K. *J. Org. Chem.* ***1974***, *39*, 421; Hill, R.K.; Khatri, H.N. *Tetrahedron Lett.* ***1978***, 4337; Anderson, J.C.; Flaherty, A.; Swarbrick, M.E. *J. Org. Chem.* ***2000***, *65*, 9152. For the reverse of this rearrangement, see Wu, P.; Fowler, F.W. *J. Org. Chem.* ***1988***, *53*, 5998.

[688]For examples, see Synerholm, M.E.; Gilman, N.W.; Morgan, J.W.; Hill, R.K. *J. Org. Chem.* ***1968***, *33*, 1111; Black, D.S.; Eastwood, F.W.; Okraglik, R.; Poynton, A.J.; Wade, A.M.; Welker, C.H. *Aust. J. Chem.* ***1972***, *25*, 1483; Overman, L.E. *J. Am. Chem. Soc.* ***1974***, *96*, 597; Metz, P.; Mues, C. *Tetrahedron* ***1988***, *44*, 6841. See Gradl, S.N.; Kennedy-Smith, J.J.; Kim, J.; Trauner, D. *Synlett* ***2002***, 411.

[689]See Schenck, T.G.; Bosnich, B. *J. Am. Chem. Soc.* ***1985***, *107*, 2058, and references cited therein. Palladium catalyzed: Jiang, Y.; Longmire, J.M.; Zhang, X. *Tetrahedron Lett.* ***1999***, *40*, 1449; Donde, Y.; Overman, L.E. *J. Am. Chem. Soc.* ***1999***, *121*, 2933; Anderson, C.E.; Overman, L.E. *J. Am. Chem. Soc.* ***2003***, *125*, 12412.

[690]See Majumdar, K.C.; Samanta, S.K. *Tetrahedron* ***2001***, *57*, 4955; Kirsch, S.F.; Overman, L.F.; Watson, M.P. *J. Org. Chem.* ***2004***, *69*, 8101.

aza-Cope rearrangements[691] as described in **18-34**. However, a palladium catalyzed aza-Claisen has been reported.[692] A so-called amine-Claisen rearrangement was reported for *N*-allyl indoles, when heated in the presence of BF_3•OEt_2.[693] An *azo-Cope* rearrangement: $CH_2{=}CHCR^1_2\ CR^2_2\ N{=}NAr \rightarrow R^1_2C{=}CHCH_2NArN{=}CR^2_2$ has been reported.[694] Propargylic vinylic compounds give allenic aldehydes, ketones, esters, or amides:[695]



The conversion of allylic aryl thioethers $ArSCH_2CH{=}CH_2$ to *o*-allylic thiophenols is not feasible, because the latter are not stable,[696] but react to give bicyclic compounds.[697] However, many allylic vinylic sulfides do give the rearrangement (the *thio-Claisen rearrangement*).[698] Allylic vinylic sulfones, for example, $H_2C{=}CRCH_2{-}SO_2{-}CH{=}CH_2$, rearrange, when heated in the presence of ethanol and pyridine, to unsaturated sulfonate salts $CH_2{=}CRCH_2CH_2CH_2SO_3^-$, produced by reaction of the reagents with the unstable sulfene intermediates $CH_2{=}CRCH_2CH_2CH{=}SO_2$.[699] Allylic vinylic sulfoxides rapidly rearrange at room temperature or below.[700]

As mentioned for the Ireland–Claisen rearrangement, asymmetric Claisen rearrangement reactions are well known.[701] Chiral Lewis acids have been designed for

[691]For a review, see Przheval'skii, N.M.; Grandberg, I.I. *Russ. Chem. Rev.* ***1987***, *56*, 477. For reviews of [3,3]-sigmatropic rearrangements with heteroatoms present, see Blechert, S. *Synthesis* ***1989***, 71; Winterfeldt, E. *Fortschr. Chem. Forsch.* ***1970***, *16*, 75. For a review of [3,3]-rearrangements of iminium salts, see Heimgartner, H.; Hansen, H.; Schmid, H. *Adv. Org. Chem.* ***1979***, *9*, pt. 2, 655.

[692]Uozumi, Y.; Kato, K.; Hayashi, T. *Tetrahedron Asymmetry*, ***1998***, *9*, 1065; Mehmandoust, M.; Petit, Y.; Larchevêque, M. *Tetrahedron Lett.* ***1992***, *33*, 4313. For a 3-aza-Claisen rearrangement, see Gilbert, J.C.; Cousins, K.R. *Tetrahedron* ***1994***, *50*, 10671.

[693]Anderson, W.K.; Lai, G. *Synthesis* ***1995***, 1287.

[694]Mitsuhashi, T. *J. Am. Chem. Soc.* ***1986***, *108*, 2400.

[695]For reviews of Claisen rearrangements involving triple bonds, see Schuster, H.F.; Coppola, G.M. *Allenes in Organic Synthesis*, Wiley, NY, ***1984***, pp. 337–343; Viola, A.; Collins, J.J.; Filipp, N. *Tetrahedron* ***1981***, *37*, 3765; Théron F.; Verny, M.; Vessière, R., in Patai, S. *The Chemistry of the Carbon–Carbon Triple Bond*, pt. 1, Wiley, NY, ***1978***, pp. 421–428. See also, Henderson, M.A.; Heathcock, C.H. *J. Org. Chem.* ***1988***, *53*, 4736.

[696]They have been trapped: See, for example, Mortensen, J.Z.; Hedegaard, B.; Lawesson, S. *Tetrahedron* ***1971***, *27*, 3831; Kwart, H.; Schwartz, J.L. *J. Org. Chem.* ***1974***, *39*, 1575.

[697]Meyers, C.Y.; Rinaldi, C.; Banoli, L. *J. Org. Chem.* ***1963***, *28*, 2440; Kwart, H.; Cohen, M.H. *J. Org. Chem.* ***1967***, *32*, 3135; *Chem. Commun.* ***1968***, 319; Makisumi, Y.; Murabayashi, A. *Tetrahedron Lett.* ***1969***, 1971, 2449.

[698]For a review, see Majumdar, K.C.; Ghosh, S.; Ghosh, M. *Tetrahedron* ***2003***, *59*, 7251.

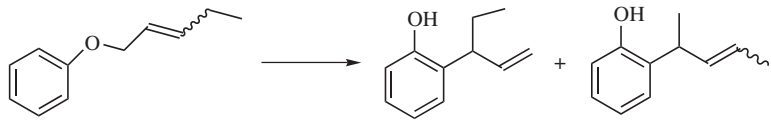
[699]King, J.F.; Harding, D.R.K. *J. Am. Chem. Soc.* ***1976***, *98*, 3312.

[700]Block, E.; Ahmad, S. *J. Am. Chem. Soc.* ***1985***, *107*, 6731.

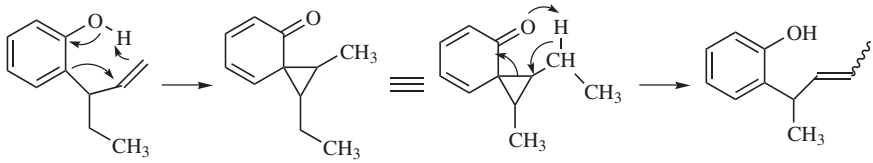
[701]For example, see Zumpe, F.L.; Kazmaier, U. *Synlett* ***1998***, 434; Ito, H.; Sato, A.; Taguchi, T. *Tetrahedron Lett.* ***1997***, *38*, 4815; Kazmaier, U.; Krebs, A. *Angew. Chem. Int. Ed.* ***1995***, *34*, 2012. For asymmetric induction in the thio-Claisen rearrangement, see Reddy, K.V.; Rajappa, S. *Tetrahedron Lett.* ***1992***, *33*, 7957.

this purpose.[702] In general, asymmetric [3,3]-sigmatropic rearrangements are well known.[703]

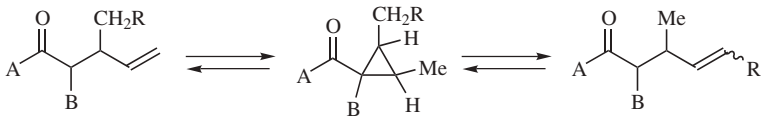
Ethers with an alkyl group in the γ position (ArO–C–C=C–R systems) sometimes give abnormal products, with the β carbon becoming attached to the ring:[704]



It has been established that these abnormal products do not arise directly from the starting ether, but are formed by a further rearrangement of the normal product:[705]



This rearrangement, which has been called an *enolene rearrangement*, a *homodienyl* [1,5]-*sigmatropic hydrogen shift* (see **18-29**), and a [1,5]-*homosigmatropic rearrangement*, involves a shift of three electron pairs over *seven* atoms. It has been found that this ''abnormal'' Claisen rearrangement is general and can interconvert the enol forms of systems of the types **135** and **136** through the cyclopropane intermediate **137**.[706]



135 **136** **137**

A = H, R, Ar, OR, and so on
B = H, R, Ar, COR, COAr, COOR, and so on

[702]Maruoka, K.; Saito, S.; Yamamoto, J. *J. Am. Chem. Soc.* ***1995***, *117*, 1165. See Sharma, G.V.M.; Ilangovan, A.; Sreevivas, P.; Mahalingam, A.K. *Synlett* ***2000***, 615. **Yb**: Hiersemann, M.; Abraham, L. *Org. Lett.* ***2001***, *3*, 49. **Rh**: Miller, S.P.; Morken, J.P. *Org. Lett.* ***2002***, *4*, 2743.

[703]For a review, see Enders, D.; Knopp, M.; Schiffers, R. *Tetrahedron Asymmetry*, ***1996***, *7*, 1847.

[704]For reviews of these abnormal Claisen rearrangements, see Hansen, H. *Mech. Mol. Migr.* ***1971***, *3*, 177; Marvell, E.N.; Whalley, W., in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 2, Wiley, NY, ***1971***, pp. 743–750.

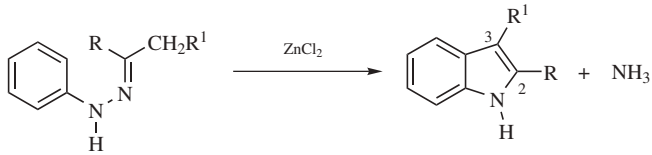
[705]Habich, A.; Barner, R.; Roberts, R.; Schmid, H. *Helv. Chim. Acta* ***1962***, *45*, 1943; Lauer, W.M.; Johnson, T.A. *J. Org. Chem.* ***1963***, *28*, 2913; Fráter, G.; Schmid, H. *Helv. Chim. Acta* ***1966***, *49*, 1957; Marvell, E.N.; Schatz, B. *Tetrahedron Lett.* ***1967***, 67.

[706]Watson, J.M.; Irvine, J.L.; Roberts, R.M. *J. Am. Chem. Soc.* ***1973***, *95*, 3348.

Since the Claisen rearrangement mechanism does not involve ions, it should not be greatly dependent on the presence or absence of substituent groups on the ring.[707] This is the case. Electron-donating groups increase the rate and electron-withdrawing groups decrease it, but the effect is small, with the *p*-amino compound reacting only ~10–20 times faster than the *p*-nitro compound.[708] However, solvent effects[709] are greater: Rates varied over a 300-fold range when the reaction was run in 17 different solvents.[710] An especially good solvent is trifluoroacetic acid, in which the reaction can be carried out at room temperature.[711] Most Claisen rearrangements are performed without a catalyst, but $AlCl_3$ or BF_3 are sometimes used.[712] In this case, it may become a Friedel–Crafts reaction, with the mechanism no longer cyclic,[713] and ortho, meta, and para products may be obtained.

OS **III**, 418; **V**, 25; **VI**, 298, 491, 507, 584, 606; **VII**, 177; **VIII**, 251, 536.

18-34 The Fischer Indole Synthesis



When arylhydrazones of aldehydes or ketones are treated with a catalyst, elimination of ammonia takes place and an indole is formed, in the *Fischer indole synthesis*.[714] Zinc chloride is the catalyst most frequently employed, but dozens of others, including other metal halides, proton and Lewis acids, and certain transition

[707]However, there are substituent effects, see Aviyente, V.; Yoo, H.Y.; Houk, K.N. *J. Org. Chem.* ***1997***, *62*, 6121.

[708]Goering, H.L.; Jacobson, R.R. *J. Am. Chem. Soc.* ***1958***, *80*, 3277; White, W.N.; Gwynn, D.; Schlitt, R.; Girard, C.; Fife, W.K. *J. Am. Chem. Soc.* ***1958***, *80*, 3271; White, W.N.; Slater, C.D. *J. Org. Chem.* ***1962***, *27*, 2908; Zahl, G.; Kosbahn, W.; Kresze, G. *Liebigs Ann. Chem.* ***1975***, 1733. See also, Desimoni, G.; Faita, G.; Gamba, A.; Righetti, P.P.; Tacconi, G.; Toma, L. *Tetrahedron* ***1990***, *46*, 2165; Gajewski, J.J.; Gee, K.R.; Jurayj, J. *J. Org. Chem.* ***1990***, *55*, 1813.

[709]For a discussion of the role played by solvent and substituents, see Gajewski, J.J. *Acc. Chem. Res.* ***1997***, *30*, 219. For solvent effects, see Davidson, M.M.; Hillier, I.H.; Hall, R.J.; Burton, N.A. *J. Am. Chem. Soc.* ***1994***, *116*, 9294.

[710]White, W.N.; Wolfarth, E.F. *J. Org. Chem.* ***1970***, *35*, 2196. See also Brandes, E.; Greico, P.A.; Gajewski, J.J. *J. Org. Chem.* ***1989***, *54*, 515.

[711]Svanholm, U.; Parker, V.D. *J. Chem. Soc. Perkin Trans. 2* ***1974***, 169.

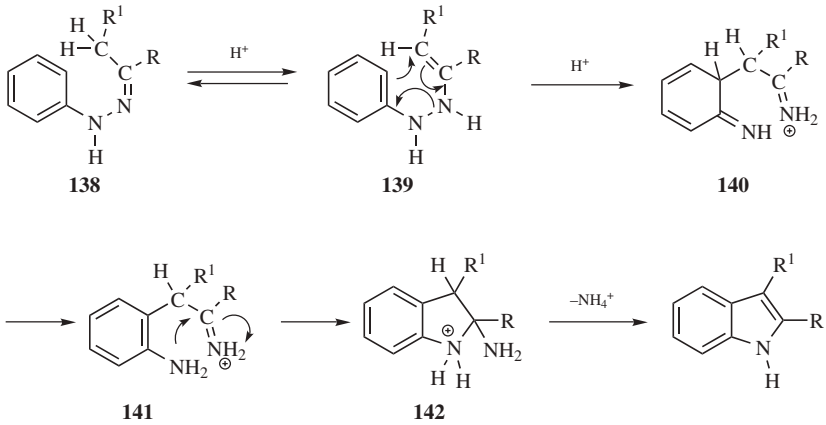
[712]For a review, see Lutz, R.P. *Chem. Rev.* ***1984***, *84*, 205.

[713]For example, crossover experiments have demonstrated that the $ZnCl_2$-catalyzed reaction is intermolecular: Yagodin, V.G.; Bunina-Krivorukova, L.I.; Bal'yan, Kh.V. *J. Org. Chem. USSR* ***1971***, *7*, 1491.

[714]For a monograph, see Robinson, B. *The Fischer Indole Synthesis*, Wiley, NY, ***1983***. For reviews, see Grandberg, I.I.; Sorokin, V.I. *Russ. Chem. Rev.* ***1974***, *43*, 115; Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1969***, pp. 190–207; Sundberg, R.J. *The Chemistry of Indoles*, Academic Press, NY, ***1970***, pp. 142–163; Robinson, B. *Chem. Rev.* ***1969***, *69*, 227. For reviews of some abnormal Fischer indole syntheses, see Ishii, H. *Acc. Chem. Res.* ***1981***, *14*, 275; Fusco, R.; Sannicolo, F. *Tetrahedron* ***1980***, *36*, 161.

metals have also been used. Microwave irradiation has been used to facilitate this reaction.[715] The reaction has been done using an $AlCl_3$ complex as an ionic liquid,[716] and solid-phase Fischer-indole syntheses are known.[717] Aniline derivatives react with α-diazoketones, in the presence of a rhodium catalyst, to give indoles as well.[718] Arylhydrazones are easily prepared by the treatment of aldehydes or ketones with phenylhydrazine (**16-2**) or by aliphatic diazonium coupling (**12-7**). However, it is not necessary to isolate the arylhydrazone. The aldehyde or ketone can be treated with a mixture of phenylhydrazine and the catalyst; this is now common practice. In order to obtain an indole, the aldehyde or ketone must be of the form $RCOCH_2R'$ (R = alkyl, aryl, or hydrogen). Vinyl ethers, such as dihydrofuran, serves as an aldehyde surrogate when treated with phenylhydrazine and a catalytic amount of aqueous sulfuric acid to give an 3-substituted indole.[719]

At first glance, the reaction does not seem to be a rearrangement. However, the key step of the mechanism[720] is a [3,3]-sigmatropic rearrangement:[721]



There is much evidence for this mechanism, for example, (*1*) the isolation of **142**,[722] (*2*) the detection of **141** by ^{13}C and ^{15}N NMR,[723] (*3*) the isolation of side products that could only have come from **140**,[724] and (*4*) ^{15}N labeling experiments that showed

[715]Abramovitch, R.A.; Bulman, A. *Synlett* ***1992***, 795; Lipińska, T.; Guibé-Jampel, E.; Petit, A.; Loupy, A. *Synth. Commun.* ***1999***, *29*, 1349.
[716]In $AlCl_3$–*N*-butylpyridinium: Rebeiro, G.LO.; Khadilkar, B.M. *Synthesis* ***2001***, 370.
[717]Rosenbaum, C.; Katzka, C.; Marzinzik, A.; Waldmann, H. *Chem. Commun.* ***2003***, 1822.
[718]Moody, C.J.; Swann, E. *Synlett* ***1998***, 135.
[719]Campos, K.R.; Woo, J.C.S.; Lee, S.; Tillyer, R.D. *Org. Lett.* ***2004***, *6*, 79.
[720]For a mechanistic study, see Hughes, D.L.; Zhao, D. *J. Org. Chem.* ***1993***, *58*, 228.
[721]This mechanism was proposed by Robinson, G.M.; Robinson, R. *J. Chem. Soc.* ***1918***, *113*, 639.
[722]Southwick, P.L.; Vida, J.A.; Fitzgerald, B.M.; Lee, S.K. *J. Org. Chem.* ***1968***, *33*, 2051; Forrest, T.P.; Chen, F.M.F. *J. Chem. Soc., Chem. Commun.* ***1972***, 1067.
[723]Douglas, A.W. *J. Am. Chem. Soc.* ***1978***, *100*, 6463; ***1979***, *101*, 5676.
[724]Bajwa, G.S.; Brown, R.K. *Can. J. Chem.* ***1969***, *47*, 785; ***1970***, *48*, 2293, and references cited therein.

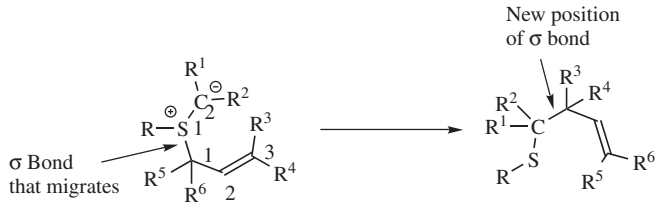
that it was the nitrogen farther from the ring that is eliminated as ammonia.[725] The main function of the catalyst seems to be to speed the conversion of **138** to **139**. The reaction can be performed without a catalyst.

There are alternative methods to produce indoles. Acetophenone reacts with 2-chloro nitrobenzene derivatives in the presence of a phenol and a palladium catalyst to give an indole.[726]

OS **III**, 725; **IV**, 884. Also see, OS **IV**, 657.

18-35 [2,3]-Sigmatropic Rearrangements

(2/*S*-3/) → (1/5/)-*sigma*-Migration



Sulfur ylids bearing an allylic group are converted on heating to unsaturated sulfides.[727] This is a concerted [2,3]-sigmatropic rearrangement[728] and has also been demonstrated for the analogous cases of nitrogen ylids[729] and the conjugate bases of allylic ethers (in the last case it is called the *[2,3]-Wittig rearrangement*).[730] It has been argued that the [2,3]-Wittig rearrangement demands severe deformation of the molecule in order to proceed.[731] The SmI_2 compound has been shown to induce

[725]Clausius, K.; Weisser, H.R. *Helv. Chim. Acta* ***1952***, *35*, 400.

[726]Rutherford, J.L.; Rainka, M.P.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2002***, *124*, 15168.

[727]For example, see Blackburn, G.M.; Ollis, W.D.; Plackett, J.D.; Smith, C.; Sutherland, I.O. *Chem. Commun.* ***1968***, 186; Trost, B.M.; LaRochelle, R. *Tetrahedron Lett.* ***1968***, 3327; Baldwin, J.E.; Hackler, R.E.; Kelly, D.P. *Chem. Commun.* ***1968***, 537, 538, 1083; Bates, R.B.; Feld, D. *Tetrahedron Lett.* ***1968***, 417; Kirmse, W.; Kapps, M. *Chem. Ber.* ***1968***, *101*, 994, 1004; Biellmann, J.F.; Ducep, J.B. *Tetrahedron Lett.* ***1971***, 33; Ceré, V.; Paolucci, C.; Pollicino, S.; Sandri, E.; Fava, A. *J. Org. Chem.* ***1981***, *46*, 3315; Kido, F.; Sinha, S.C.; Abiko, T.; Yoshikoshi, A. *Tetrahedron Lett.* ***1989***, *30*, 1575. For a review as applied to ring expansions, see Vedejs, E. *Acc. Chem. Res.* ***1984***, *17*, 358.

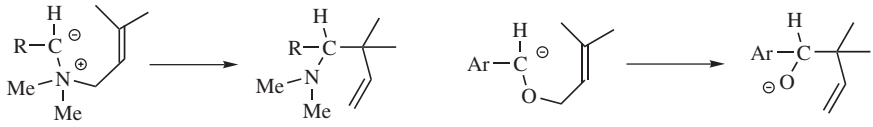
[728]For a review of the stereochemistry of these reactions, see Hoffmann, R.W. *Angew. Chem. Int. Ed.* ***1979***, *18*, 563.

[729]For example, see Jemison, R.W.; Ollis, W.D. *Chem. Commun.* ***1969***, 294; Rautenstrauch, V. *Helv. Chim. Acta* ***1972***, *55*, 2233; Mageswaran, S.; Ollis, W.D.; Sutherland, I.O.; Thebtaranonth, Y. *J. Chem. Soc., Chem. Commun.* ***1973***, 651; Ollis, W.D.; Sutherland, I.O.; Thebtaranonth, Y. *J. Chem. Soc., Chem. Commun.* ***1973***, 657; Mander, L.N.; Turner, J.V. *J. Org. Chem.* ***1973***, *38*, 2915; Stévenart-De Mesmaeker, N.; Merényi, R.; Viehe, H.G. *Tetrahedron Lett.* ***1987***, *28*, 2591; Honda, K.; Inoue, S.; Sato, K. *J. Am. Chem. Soc.* ***1990***, *112*, 1999.

[730]See, for example, Makisumi, Y.; Notzumoto, S. *Tetrahedron Lett.* ***1966***, 6393; Schöllkopf, U.; Fellenberger, K.; Rizk, M. *Liebigs Ann. Chem.* ***1970***, *734*, 106; Rautenstrauch, V. *Chem. Commun.* ***1970***, 4. For a review, see Nakai, T.; Mikami, K. *Chem. Rev.* ***1986***, *86*, 885. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1063–1067.

[731]You, Z.; Koreeda, M. *Tetrahedron Lett.* ***1993***, *34*, 2597.

a [2,3]-Wittig rearrangement.[732] The reaction has been extended to certain other systems,[733] even to an all-carbon system.[734]



Since the reactions involve migration of an allylic group from a sulfur, nitrogen, or oxygen atom to an adjacent negatively charged carbon atom, they are special cases of the Stevens or Wittig rearrangements (**18-21**, **18-22**). However, in this case the migrating group *must* be allylic (in **18-21** and **18-22** other groups can also migrate). Thus, when the migrating group is allylic, there are two possible pathways: (*1*) the radical-ion or ion-pair mechanisms (**18-21**, **18-22**) and (*2*) the concerted pericyclic [2,3]-sigmatropic rearrangement. These can easily be told apart, since the latter always involves an allylic shift (as in the Claisen rearrangement), while the former pathway does not.

Of these reactions, the [2,3]-Wittig rearrangement in particular has often been used as a means of transferring chirality. The product of this reaction has potential stereogenic centers at C-3 and C-4 (if $R^5 \neq R^6$), and if the starting ether is optically active because of a stereogenic center at C-1, the product may be optically active as well. Many examples are known in which an optically active ether was converted to a product that was optically active because of chirality at C-3, C-4, or both.[735] If a

[732]Kunishima, M.; Hioki, K.; Kono, K.; Kato, A.; Tani, S. *J. Org. Chem.* ***1997***, *62*, 7542. Also see, Hioki, K.; Kono, K.; Tani, S.; Kunishima, M. *Tetrahedron Lett.* ***1998***, *39*, 5229. For an enantioselective [2,3]-Wittig rearrangment, see Fujimoto, K.; Nakai, T. *Tetrahedron Lett.* ***1994***, *35*, 5019.

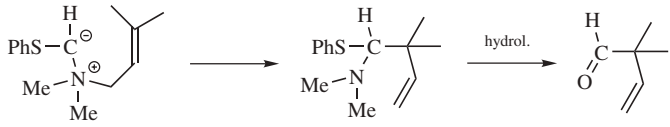
[733]See, for example, Baldwin, J.E.; Brown, J.E.; Höfle, G. *J. Am. Chem. Soc.* ***1971***, *93*, 788; Yamamoto, Y.; Oda, J.; Inouye, Y. *J. Chem. Soc., Chem. Commun.* ***1973***, 848; Ranganathan, S.; Ranganathan, D.; Sidhu, R.S.; Mehrotra, A.K. *Tetrahedron Lett.* ***1973***, 3577; Murata, Y.; Nakai, T. *Chem. Lett.* ***1990***, 2069. For reviews with respect to selenium compounds, see Reich, H.J., in Liotta, D.C. *Organoselenium Chemistry*, Wiley, NY, ***1987***, pp. 365–393; Reich, H.J., in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. C, Academic Press, NY, ***1978***, pp. 102–111.

[734]Baldwin, J.E.; Urban, F.J. *Chem. Commun.* ***1970***, 165.

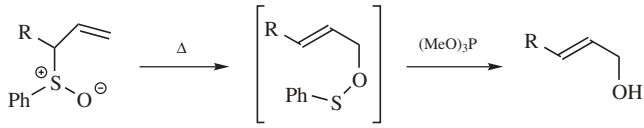
[735]For reviews of stereochemistry in this reaction, see Mikami, K.; Nakai, T. *Synthesis* ***1991***, 594; Nakai, T.; Mikami, K. *Chem. Rev.* ***1986***, *86*, 885, 888–895. See also, Nakai, T.; Nakai, E. *Tetrahedron Lett.* ***1988***, *29*, 4587; Balestra, M.; Kallmerten, J. *Tetrahedron Lett.* ***1988***, *29*, 6901; Brückner, R. *Chem. Ber.* ***1989***, *122*, 193, 703; Scheuplein, S.W.; Kusche, A.; Brückner, R.; Harms, K. *Chem. Ber.* ***1990***, *123*, 917; Wu, Y.; Houk, K.N.; Marshall, J.A. *J. Org. Chem.* ***1990***, *55*, 1421; Marshall, J.A.; Wang, X. *J. Org. Chem.* ***1990***, *55*, 2995.

suitable stereogenic center is present in R^1 (or if a functional group in R^1 can be so converted), then stereocontrol over three contiguous stereogenic centers can be achieved. Stereocontrol of the new double bond (*E* or *Z*) has also been accomplished.

If an OR or SR group is attached to the negative carbon, the reaction becomes a method for the preparation of β,γ-unsaturated aldehydes, because the product is easily hydrolyzed.[736]

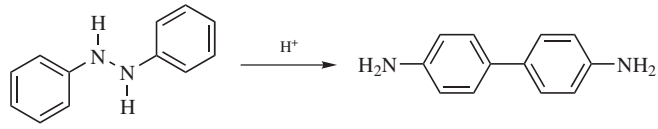


Another [2,3]-sigmatropic rearrangement converts allylic sulfoxides to allylically rearranged alcohols by treatment with a thiophilic reagent, such as trimethyl phosphite.[737] This is often called the *Mislow–Evans rearrangement*. In this case, the migration is from sulfur to oxygen. [2,3]-Oxygen-to-sulfur migrations are also known.[738] The Sommelet–Hauser rearrangement (**13-31**) is also a [2,3]-sigmatropic rearrangement.



OS **VIII**, 427.

18-36 The Benzidine Rearrangement



Hydrazobenzene **143**

[736]Huynh, C.; Julia, S.; Lorne, R.; Michelot, D. *Bull. Soc. Chim. Fr.* ***1972***, 4057.

[737]Tang, R.; Mislow, K. *J. Am. Chem. Soc.* ***1970***, *92*, 2100; Evans, D.A.; Andrews, G.C. *Acc. Chem. Res.* ***1974***, *7*, 147; Hoffmann, R.W. *Angew. Chemie. Int. Ed., Engl.*, ***1979***, *18*, 563; Sato, T.; Otera, J.; Nozaki, H. *J. Org. Chem.* ***1989***, *54*, 2779; Bickart, P.; Carson, F.W.; Jacobus, J.; Miller, E.G.; Mislow, K. *J. Am. Chem. Soc.* ***1968***, *90*, 4869.

[738]Braverman, S.; Mechoulam, H. *Isr. J. Chem.* ***1967***, *5*, 71, Braverman, S.; Stabinsky, Y. *Chem. Commun.* ***1967***, 270; Rautenstrauch, V. *Chem. Commun.* ***1970***, 526; Smith, G.; Stirling, C.J.M. *J. Chem. Soc. C* ***1971***, 1530; Tamaru, Y.; Nagao, K.; Bando, T.; Yoshida, Z. *J. Org. Chem.* ***1990***, *55*, 1823.

When hydrazobenzene is treated with acids, it rearranges to give ~70% 4,4′-diaminobiphenyl (**143**, benzidine) and ~30% 2,4′-diaminobiphenyl. This reaction is called the *benzidine rearrangement* and is general for *N,N′*-diarylhydrazines.[739] Usually, the major product is the 4,4′-diaminobiaryl, but four other products may also be produced. These are the 2,4′-diaminobiaryl, already referred to, the 2,2′-diaminobiaryl, and the *o*- and *p*-arylaminoanilines (called *semidines*). The 2,2′- and *p*-arylaminoaniline compounds are formed less often and in smaller amounts than the other two side products. Usually, the 4,4′-diaminobiaryl predominates, except when one or both para positions of the diarylhydrazine are occupied. However, the 4,4′-diamine may still be produced even if the para positions are occupied. If SO_3H, COOH, or Cl (but not R, Ar, or NR_2) is present in the para position, it may be ejected. With dinaphthylhydrazines, the major products are not the 4,4′-diaminobinaphthyls, but the 2,2′ isomers. Another side reaction is disproportionation to $ArNH_2$ and ArN=NAr. For example, *p,p′*-$PhC_6H_4NHNHC_6H_4Ph$ gives 88% disproportionation products at 25°C.[740]

The mechanism has been exhaustively studied and several mechanisms have been proposed.[741] At one time, it was believed that NHAr broke away from ArNHNHAr and became attached to the para position to give the semidine, which then went on to product. The fact that semidines could be isolated lent this argument support, as did the fact that this would be analogous to the rearrangements considered in Chapter 11 (**11-28**–**11-32**). However, this theory was killed when it was discovered that semidines could not be converted to benzidines under the reaction conditions. Cleavage into two independent pieces (either ions or radicals) has been ruled out by many types of crossover experiments, which always showed that the two rings of the starting material are in the product; that is, ArNHNHAr′ gives no molecules (of any of the five products) containing two Ar groups or two Ar′ groups, and mixtures of ArNHNHAr and Ar′NHNHAr′ give no molecules containing both Ar and Ar′. An important discovery was the fact that, although the reaction is always first order in substrate, it can be either

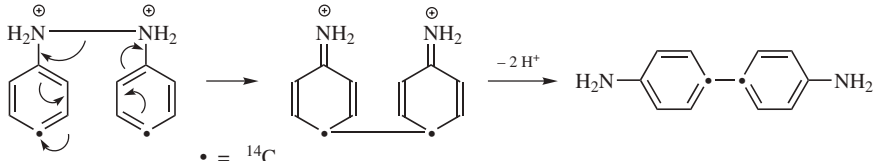
[739]For reviews, see, in Patai, S. *The Chemistry of the Hydrazo, Azo, and Azoxy Groups*, pt. 2, Wiley, NY, ***1975***, the reviews by Cox, R.A.; Buncel, E. pp. 775–807; Koga, G.; Koga, N.; Anselme, J. pp. 914–921; Williams, D.L.H., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9, Elsevier, NY, ***1973***, Vol. 13, 1972, pp. 437–448; Shine, H.J. *Mech. Mol. Migr.* ***1969***, *2*, 191; *Aromatic Rearrangements*, Elsevier, NY, ***1969***, pp. 126–179; Banthorpe, D.V. *Top. Carbocyclic Chem.* ***1969***, *1*, 1; Lukashevich, V.O. *Russ. Chem. Rev.* ***1967***, *36*, 895.

[740]Shine, H.J.; Stanley, J.P. *J. Org. Chem.* ***1967***, *32*, 905. For investigations of the mechanism of the disproportionation reactions, see Rhee, E.S.; Shine, H.J. *J. Am. Chem. Soc.* ***1986***, *108*, 1000; ***1987***, *109*, 5052.

[741]For a history of the mechanistic investigations and controversies, see Shine, H.J. *J. Phys. Org. Chem.* ***1989***, *2*, 491.

first[742] or second[743] order in [H^+]. With some substrates the reaction is entirely first order in [H^+], while with others it is entirely second order in [H^+], regardless of the acidity. With still other substrates, the reaction is first order in [H^+] at low acidities and second order at higher acidities. With the latter substrates fractional orders can often be observed,[744] because at intermediate acidities, both processes take place simultaneously. These kinetic results seem to indicate that the actual reacting species can be either the monoprotonated substrate $ArNHNH_2Ar$ or the diprotonated $ArNH_2NH_2Ar$.

Most of the proposed mechanisms[745] attempted to show how all five products could be produced by variations of a single process. An important breakthrough was the discovery that the two main products are formed in entirely different ways, as shown by isotope-effect studies.[746] When the reaction was run with hydrazobenzene labeled with ^{15}N at both nitrogen atoms, the isotope effect was 1.022 for formation of **143**, but 1.063 for formation of 2,4′-diaminobiphenyl. This showed that the N–N bond is broken in the rate-determining step in both cases, but the steps themselves are obviously different. When the reaction was run with hydrazobenzene labeled with ^{14}C at a para position, there was an isotope effect of 1.028 for formation of **143**, but essentially no isotope effect (1.001) for formation of 2,4′-diaminobiphenyl. This can only mean that for **143** formation of the new C–C bond *and* breaking of the N–N bond both take place in the rate-determining step; in other words, the mechanism is concerted. The following [5.5]-sigmatropic rearrangement accounts for this:[745,747]



144

[742]Banthorpe, D.V.; Hughes, E.D.; Ingold, C.K. *J. Chem. Soc.* ***1962***, 2386, 2402, 2407, 2413, 2418, 2429; Shine, H.J.; Chamness, J.T. *J. Org. Chem.* ***1963***, *28*, 1232; Banthorpe, D.V.; O'Sullivan, M. *J. Chem. Soc. B* ***1968***, 627.

[743]Hammond, G.S.; Shine, H.J. *J. Am. Chem. Soc.* ***1950***, *72*, 220; Banthorpe, D.V.; Cooper, A. *J. Chem. Soc. B* ***1968***, 618; Banthorpe, D.V.; Cooper, A.; O'Sullivan, M. *J. Chem. Soc. B* ***1971***, 2054.

[744]Carlin, R.B.; Odioso, R.C. *J. Am. Chem. Soc.* ***1954***, *76*, 100; Banthorpe, D.V.; Ingold, C.K.; Roy, J. *J. Chem. Soc. B* ***1968***, 64; Banthorpe, D.V.; Ingold, C.K.; O'Sullivan, M. *J. Chem. Soc. B* ***1968***, 624.

[745]For example, see the "polar-transition-state mechanism:" Banthorpe, D.V.; Hughes, E.D.; Ingold, C.K. *J. Chem. Soc.* ***1964***, 2864, and the "π-complex mechanism:" Dewar, M.J.S., in de Mayo, P. *Molecular Rearrangments*, Vol. 1, Wiley, NY, ***1963***, pp. 323–344.

[746]Shine, H.J.; Zmuda, H.; Park, K.H.; Kwart, H.; Horgan, A.J.; Collins, C.; Maxwell, B.E. *J. Am. Chem. Soc.* ***1981***, *103*, 955; Shine, H.J.; Zmuda, H.; Park, K.H.; Kwart, H.; Horgan, A.J.; Brechbiel, M. *J. Am. Chem. Soc.* ***1982***, *104*, 2501.

[747]This step was also part of the "polar-transition-state mechanism".

The diion **144** was obtained as a stable species in super acid solution at −78°C by treatment of hydrazobenzene with $FSO_3H–SO_2$ (SO_2ClF).[748] Though the results just given were obtained with hydrazobenzene, which reacts by the diprotonated pathway, monoprotonated substrates have been found to react by the same [5,5]-sigmatropic mechanism.[749] Some of the other rearrangements in this section are also sigmatropic. Thus, formation of the *p*-semidine takes place by a [1,5]-sigmatropic rearrangement,[750] and the conversion of 2,2′-hydrazonaphthalene to 2,2′-diamino-1,1′-binaphthyl by a [3,3]-sigmatropic rearrangement.[751]

2,4′-Diaminobiphenyl is formed by a completely different mechanism, though the details are not known. There is rate-determining breaking of the N–N bond, but the C–C bond is not formed during this step.[752] The formation of the *o*-semidine also takes place by a nonconcerted pathway.[753] Under certain conditions, benzidine rearrangements have been found to go through radical cations.[754]

C. Other Cyclic Rearrangements

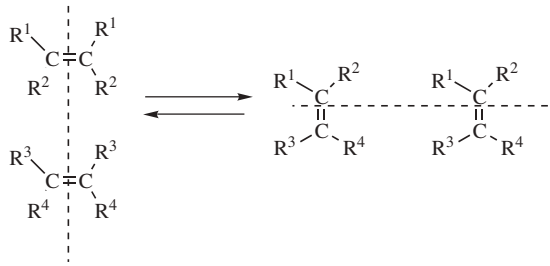
18-37 Metathesis of Alkenes (Alkene or Olefin Metathesis)[755]

Alkene metathesis

$$CH_3CH{=}CHCH_2CH_3 \xrightarrow[WCl_6\text{–}EtOH]{EtAlCl_2} CH_3CH{=}CHCH_3 + CH_3CH_2CH{=}CHCH_2CH_3$$

When alkenes are treated with certain catalysts they are converted to other alkenes in a reaction in which the alkylidene groups ($R^1R^2C{=}$) have become interchanged by a process schematically illustrated by the equation:

[748]Olah, G.A.; Dunne, K.; Kelly, D.P.; Mo, Y.K. *J. Am. Chem. Soc.* ***1972***, *94*, 7438.
[749]Shine, H.J.; Park, K.H.; Brownawell, M.L.; San Filippo, Jr., J. *J. Am. Chem. Soc.* ***1984***, *106*, 7077.
[750]Heesing, A.; Schinke, U. *Chem. Ber.* ***1977***, *110*, 3319; Shine, H.J.; Zmuda, H.; Kwart, H.; Horgan, A.G.; Brechbiel, M. *J. Am. Chem. Soc.* ***1982***, *104*, 5181.
[751]Shine, H.J.; Gruszecka, E.; Subotkowski, W.; Brownawell, M.; San Filippo, Jr., J. *J. Am. Chem. Soc.* ***1985***, *107*, 3218.
[752]See Rhee, E.S.; Shine, H.J. *J. Am. Chem. Soc.* ***1986***, *108*, 1000; ***1987***, *109*, 5052.
[753]Rhee, E.S.; Shine, H.J. *J. Org. Chem.* ***1987***, *52*, 5633.
[754]See, for example, Nojima, M.; Ando, T.; Tokura, N. *J. Chem. Soc. Perkin Trans. 1* ***1976***, 1504.
[755]For reviews, see Grubbs, R.H. *Tetrahedron* ***2004***, *60*, 7117; Wakamatsu, H.; Blechert, S. *Angew. Chem. Int. Ed.* ***2002***, *41*, 2403; Schrock, R.R.; Hoveyda, A.H. *Angew. Chem. Int. Ed.* ***2003***, *42*, 4592.



The reaction is called *metathesis* of alkenes or *alkene metathesis* (*olefin metathesis*).[756] In the example shown above, 2-pentene (either cis, trans, or a cis–trans mixture) is converted to a mixture of ~50% 2-pentene, 25% 2-butene, and 25% 3-hexene. The reaction is reversible[757] and the alkene starting material and products exist in an equilibrium, so the same mixture can be obtained by starting with equimolar quantities of 2-butene and 3-hexene.[758] In general, the reaction can be applied to a single unsymmetrical alkene, giving a mixture of itself and two other alkenes, or to a mixture of two alkenes, in which case the number of different molecules in the product depends on the symmetry of the reactants. As in the case above, a mixture of $R^1R^2C{=}CR^1R^2$ and $R^3R^4C{=}CR^3R^4$ gives rise to only one new alkene ($R^1R^2C{=}CR^3R^4$), while in the most general case, a mixture of $R^1R^2C{=}CR^3R^4$ and $R^5R^6C{=}CR^7R^8$ gives a mixture of 10 alkenes: the original $2 + 8$ new ones. In early work, tungsten, molybdenum,[759] or rhenium complexes were used, and with simple alkenes the proportions of products are generally statistical,[760] which limited the synthetic utility of the reaction

[756]For monographs, see Drăguţn, V.; Balaban, A.T.; Dimonie, M. *Olefin Metathesis and Ring-Opening Polymerization of Cyclo-Olefins*, Wiley, NY, ***1985***; Ivin, K.J. *Olefin Metathesis*, Academic Press, NY, ***1983***. For reviews, see Feast, W.J.; Gibson, V.C., in Hartley, F.R. *The Chemistry of the Metal-Carbon Bond*, Vol. 5, Wiley, NY, 1989, pp. 199–228; Streck, R. *CHEMTECH* ***1989*** , 498; Schrock, R.R. *J. Organomet. Chem.* ***1986***, *300*, 249; Grubbs, R.H., in Wilkinson, G. *Comprehensive Organometallic Chemistry*, Vol. 8, Pergamon, Elmsford, NY, ***1982***, pp. 499–551; Basset, J.M.; Leconte, M. *CHEMTECH* ***1980***, 762; Banks, R.L. *CHEMTECH* ***1979***, 494; *Fortschr. Chem. Forsch.* ***1972***, *25*, 39; Calderon N.; Lawrence, J.P.; Ofstead, E.A. *Adv. Organomet. Chem.* ***1979***, *17*, 449; Grubbs, R.H. *Prog. Inorg. Chem.* ***1978***, *24*, 1; Calderon N., in Patai, S. *The Chemistry of Functional Groups: Supplement A* pt. 2, Wiley, NY, ***1977***, pp. 913–964; *Acc. Chem. Res.* ***1972***, *5*, 127; Katz, T.J. *Adv. Organomet. Chem.* ***1977***, *16*, 283; Haines, R.J.; Leigh, G.J. *Chem. Soc. Rev.* ***1975***, *4*, 155; Hocks, L. *Bull. Soc. Chim. Fr.* ***1975***, 1893; Mol, J.C.; Moulijn, J.A. *Adv. Catal.* ***1974***, *24*, 131; Hughes, W.B. *Organomet. Chem. Synth.* ***1972***, *1*, 341; Khidekel', M.L.; Shebaldova, A.D.; Kalechits, I.V. *Russ. Chem. Rev.* ***1971***, *40*, 669; Bailey, G.C. *Catal. Rev.* ***1969***, *3*, 37.

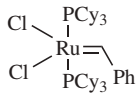
[757]Smith III, A.B.; Adams, C.M.; Kozmin, S.A. *J. Am. Chem. Soc.* ***2001***, *123*, 990.

[758]Calderon N.; Chen, H.Y.; Scott, K.W. *Tetrahedron Lett.* ***1967***, 3327; Wang, J.; Menapace, H.R. *J. Org. Chem.* ***1968***, *33*, 3794; Hughes, W.B. *J. Am. Chem. Soc.* ***1970***, *92*, 532.

[759]For an example, see Crowe, W.E.; Zhang, Z.J. *J. Am. Chem. Soc.* ***1993***, *115*, 10998.; Fu, G.C.; Grubbs, R.H. *J. Am. Chem. Soc.* ***1993***, *115*, 3800.

[760]Calderon N.; Ofstead, E.A.; Ward, J.P.; Judy, W.A.; Scott, K.W. *J. Am. Chem. Soc.* ***1968***, *90*, 4133.

since the yield of any one product is low. However, in some cases one alkene may be more or less thermodynamically stable than the rest, so that the proportions are not statistical. Furthermore, it may be possible to shift the equilibrium. For example, 2-methyl-1-butene gives rise to ethylene and 3,4-dimethyl-3-hexene. By allowing the gaseous ethylene to escape, the yield of 3,4-dimethyl-3-hexene can be raised to 95%.[761]



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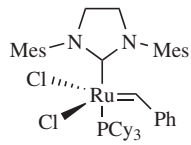

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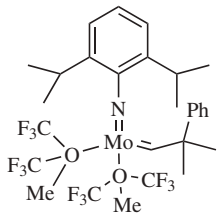


147

The development of new catalysts have revolutionized this reaction, making it one of the most important methods available for synthesis. Tailoring the substrate to include two terminal alkenes leads to ethylene as a product, whose escape from the reaction drives the equilibrium to product. Many catalysts, both homogeneous[762] and heterogeneous,[763] have been used for this reaction. Although there are several examples of the former, ruthenium complexes are the most important,[764] while among the latter are oxides of Mo, W, and Re deposited on alumina or silica gel.[765] The major breakthrough in these catalysts was the development of catalysts that are relatively air stable. The three most used catalysts are carbene complexes **145**[766] and **146**[767] (Grubbs catalysts I and II, respectively), and **147** (the Shrock catalyst).[768] Catalyst **146** can be generated *in situ* from air stable

[761]Knoche, H. Ger. Pat.(Offen.) 2024835, 1970 [*Chem. Abstr.*, ***1971***, *74*, 44118b]. See also Chevalier, P.; Sinou, D.; Descotes, G. *Bull. Soc. Chim. Fr.* ***1976***, 2254; Bespalova, N.B.; Babich, E.D.; Vdovin, V.M.; Nametkin, N.S. *Doklad. Chem.* ***1975***, *225*, 668; Ichikawa, K.; Fukuzumi, K. *J. Org. Chem.* ***1976***, *41*, 2633; Baker, R.; Crimmin, M.J. *Tetrahedron Lett.* ***1977***, 441.

[762]First reported by Calderon N.; Chen, H.Y.; Scott, K.W. *Tetrahedron Lett.* ***1967***, 3327. For a lengthy list, see Hughes, W.B. *Organomet. Chem. Synth.* ***1972***, *1*, 341, see pp. 362–368. For a homogeneous rhenium catalyst, see Toreki, R.; Schrock, R.R. *J. Am. Chem. Soc.* ***1990***, *112*, 2448.

[763]First reported by Banks, R.L.; Bailey, G.C. *Ind. Eng. Chem. Prod. Res. Dev.*, ***1964***, *3*, 170. See also, Banks, R.L. *CHEMTECH* ***1986***, 112.

[764]Gilbertson, S.R.; Hoge, G.S.; Genov, D.G. *J. Org. Chem.* ***1998***, *63*, 10077; Maier, M.E.; Bugl, M. *Synlett* ***1998***, 1390; Stefinovic, M.; Snieckus, V. *J. Org. Chem.* ***1998***, *63*, 2808.

[765]For a list of heterogeneous catalysts, see Banks, R.L. *Fortschr. Chem. Forsch.* ***1972***, *25*, 39, 41–46.

[766]Schwab, P.; Grubbs, R.H.; Ziller, J.W. *J. Am. Chem. Soc.* ***1996***, *118*, 100.

[767]Scholl, M.; Ding, S.; Lee, C.W.; Grubbs, R.H. *Org. Lett.* ***1999***, *1*, 953.

[768]Bazan, G.C.; Oskam, J.H.; Cho, H.-N.; Park, L.Y.; Schrock, R.R. *J. Am. Chem. Soc.* ***1991***, *113*, 6899, and references cited therein.

precursors. [769] Recyclable catalyst have been developed,[770] and the reaction has been done in ionic liquids,[771] as well as supercritical CO_2[772] (p. 414). Microwave-induced ring-closing metathesis reactions are known.[773] Polymer-bound ruthenium catalysts[774] and molybdenum catalysts[775] have been used, and the **146** has been immobilized on polyethylene glycol, PEG).[776] Efficient methods have been developed for the removal of ruthenium by-products from metathesis reactions.[777] By choice of the proper catalyst, the reaction has been applied to terminal and internal alkenes, straight chain or branched. The effect of substitution on the ease of reaction is $CH_2{=}{>}RCH_2CH{=}{>}R_2CHCH{=}{>}R_2C{=}$.[778] Note that isomerization of the C=C unit can occur after metathesis.[779] Cross-metathesis[780,781] (or symmetrical homo-metathesis[782]) of alkenes to give new alkenes

[769]Louie, J.; Grubbs, R.H. *Angew. Chem. Int. Ed.* ***2001***, *40*, 247.

[770]Kingsbury, J.S.; Harrity, J.P.A.; Bonitatebus Jr., P.J.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***1999***, *121*, 791.

[771]In bmim PF_6, 1-butyl-3-methylimidazolium hexafluorophosphate: Buijsman, R.C.; van Vuuren, E.; Sterrenburg, J.G. *Org. Lett.* ***2001***, *3*, 3785. See Clavier, H.; Audic, N.; Mauduit, M.; Guillemin, J.-C. *Chem. Commun.* ***2004***, 2282.

[772]Fürstner, A.; Ackerman, L.; Beck, K.; Hori, H.; Koch, D.; Langemann, K.; Liebl, M.; Six, C.; Leitner, W. *J. Am. Chem. Soc.* ***2001***, *123*, 9000.

[773]Grabacia, S.; Desai, B.; Lavastre, O.; Kappe, C.O. *J. Org. Chem.* ***2003***, *68*, 9136; Mayo, K.G.; Nearhoof, E.H.; Kiddle, J.J. *Org. Lett.* ***2002***, *4*, 1567; Balan, D.; Adolfsson, H. *Tetrahedron Lett.* ***2004***, *45*, 3089. For a solvent-free microwave-induced reaction, see Thanh, G.V.; Loupy, A. *Tetrahedron Lett.* ***2003***, *44*, 9091.

[774]Yao, Q. *Angew. Chem. Int. Ed.* ***2000***, *39*, 3896; Schürer, S.C.; Gessler, S.; Buschmann, N.; Blechert, S. *Angew. Chem. Int. Ed.* ***2000***, *39*, 3898.

[775]Hultzsch, K.C.; Jernelius, J.A.; Hoveyda, A.H.; Schrock, R.R. *Angew. Chem. Int. Ed.* ***2002***, *41*, 589.

[776]A recyclable catalyst, see Yao, Q.; Motta, A.R. *Tetrahedron Lett.* ***2004***, *45*, 2447.

[777]Ahn, Y.M.; Yang, K.; Georg, G.I. *Org. Lett.* ***2001***, *3*, 1411; Cho, J.H.; Kim, B.M. *Org. Lett.* ***2003***, *5*, 531. A scavenger resin has been developed, see Westhus, M.; Gonthier, E.; Brohm, D.; Breinbauer, R. *Tetrahedron Lett.* ***2004***, *45*, 3141.

[778]For an explanation for this order, see McGinnis, J.; Katz, T.J.; Hurwitz, S. *J. Am. Chem. Soc.* ***1976***, *98*, 605; Casey, C.J.; Tuinstra, H.E.; Saeman, M.C. *J. Am. Chem. Soc.* ***1976***, *98*, 608. A model for selectivity has been proposed, see Chatterjee, A.K.; Choi, T.-L.; Sanders, D.P.; Grubbs, R.H. *J. Am. Chem. Soc.* ***2003,*** *125*, 11360.

[779]For example, see Schmidt, B. *J. Org. Chem.* ***2004***, *69*, 7672; Sutton, A.E.; Seigal, B.A.; Finnegan, D.F.; Snapper, M.L. *J. Am. Chem. Soc.* ***2002***, *124*, 13390.

[780]See La, D.S.; Sattely, E.S.; Ford, J.G.; Schrock, R.R.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***2001***, *123*, 7767.

[781]Chatterjee, A.K.; Grubbs, R.H. *Org. Lett*. ***1999***, *1*, 1751; Chatterjee, A.K.; Morgan, J.P.; Scholl, M.; Grubbs, R.H. *J. Am. Chem. Soc*. ***2000***, *122*, 3783; Fassina, V.; Ramminger, C.; Seferin, M.; Monteiro, A.L. *Tetrahedron* ***2000***, *56*, 7403; Randl, S.; Buschmann, N.; Connon, S.J.; Blechert, S. *Synlett* ***2001***, 1547; Grela, K.; Bieniek, M. *Tetrahedron Lett*. ***2001***, *42,* 6425; Choi, T.-L.; Chatterjee, A.K.; Grubbs, R.H. *Angew. Chem. Int. Ed*. ***2001***, *40*, 1277; Arjona, O.; Csákÿ, A.G.; Medel, R.; Plumet, J. *J. Org. Chem*. ***2002***, *67*, 1380; Chatterjee, A.K.; Sanders, D.P.; Grubbs, R.H. *Org. Lett*. ***2002***, *4*, 1939; Hansen, E.C.; Lee, D. *Org. Lett*. ***2004***, *6*, 2035; BouzBouz, S.; Simmons, R.; Cossy, J. *Org. Lett*. ***2004,*** *6*, 3465.

[782]Blanco, O.M.; Castedo, L. *Synlett* ***1999***, 557.

can be accomplished with the modern metathesis catalysts. Monosubstiuted alkenes react faster than disubstituted alkenes.[783] A double metathesis reaction of a diene (also called domino metathesis[784] or tandem metathesis[785]) with conjugated aldehydes has been reported,[786] and a triple-metathesis was reported to for a dihydropyran with two dihydropyran substituents.[787] Cross-metathesis of a terminal alkyne and a terminal alkenes (en-ynes)[788] to give a diene has also been reported.[789] Cross-metathesis of vinylcyclopropanes leads to an alkene with two cyclopropyl substituents.[790] Vinylcyclopropane-alkyne metathesis reactions have been reported.[791]Cyclic alkenes can be opened, usually with polymerization using metathesis catalysts. Ring-opening metathesis generates dienes from cyclic alkenes.[792] Allenes undergo a metathesis reaction to give symmetrical allenes.[793] The Grubbs catalyst is compatible with forming cyclic alkenes by ring-closing metathesis followed by treatment with hydrogen to give the saturated cyclic compound.[794] An interesting variation reacts an α,ω-diene with a cyclic alkene. The combination of ring-opening metathesis and ring-closing cross-metathesis leads to ring expansion to give a macrocyclic nonconjugated diene.[795]

Dienes can react intermolecularly or intramolecularly.[796] Intramolecular reactions generate rings, usually alkenes or dienes. Alkene metathesis can be

[783]For an example with a styrene derivative versus a terminal alkene in the same molecule, see Lautens, M.; Maddess, M.L. *Org. Lett.* ***2004***, *6*, 1883.

[784]Rückert, A.; Eisele, D.; Blechert, S. *Tetrahedron Lett.* ***2001***, *42*, 5245.

[785]Choi, T.-L.; Grubbs, R.H. *Chem. Commun.* ***2001***, *26* 48.

[786]BouzBouz, S.; Cossy, J. *Org. Lett.* ***2001***, *3*, 1451; van Otterlo, W.A.L.; Ngidi, E.L.; de Koning, C.D.; Fernandes, M.A. *Tetrahedron Lett.* ***2004***, *45*, 659.

[787]Sundararajan, G.; Prabagaran, N.; Varghese, B. *Org. Lett.* ***2001***, *3*, 1973.

[788]For a discussion of (*Z*/*E*) selectivity and substituent effects, see Kang, B.; Lee, J.M.; Kwak, J.; Lee, Y.S.; Chang, S. *J. Org. Chem.* ***2004***, *69*, 7661. For a review, see Diver, S.T.; Giessert, A.J. *Chem. Rev.* ***2004***, *104*, 1317.

[789]For a review, see Poulsen, C.S.; Madsen, R. *Synthesis* ***2003***, 1. See Stragies, R.; Voigtmann, U.; Blechert, S. *Tetrahedron Lett.* ***2000***, *41*, 5465; Yao, Q. *Org. Lett.* ***2001***, *3*, 2069; Lee, H.-Y.; Kim, B.G.; Snapper, M.L. *Org. Lett.* ***2003***, *5*, 1855; Giessert, A.J.; Brazis, N.J.; Diver, S.T. *Org. Lett.* ***2003***, *5*, 3819; Kim, M.; Park, S.; Maifeld, S.V.; Lee, D. *J. Am. Chem. Soc.* ***2004***, *126*, 10242; Tonogaki, K.; Mori, M. *Tetrahedron Lett.* ***2002***, *43*, 2235. See also, Kang, B.; Kim, D.-h.; Do, Y.; Chang, S. *Org. Lett.* ***2003***, *5*, 3041.

[790]Verbicky, C.A.; Zercher, C.K. *Tetrahedron Lett.* ***2000***, *41*, 8723.

[791]López, F.; Delgado, A.; Rodríguez, J.R.; Castedo, L.; Mascareñas, J.L. *J. Am. Chem. Soc.* ***2004***, *126*, 10262.

[792]See La, D.S.; Ford, J.G.; Sattely, E.S.; Bonitatebus, P.J.; Schrock, R.R.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***1999***, *121*, 11603; Wright, D.L.; Usher, L.C.; Estrella-Jimenez, M. *Org. Lett.* ***2001***, *3*, 4275; Randl, S.; Connon, S.J.; Blechert, S. *Chem. Commun.* ***2001***, 1796; Morgan, J.P.; Morrill, C.; Grubbs, R.H. *Org. Lett.* ***2002***, *4*, 67.

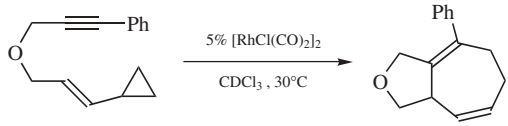
[793]Ahmed, M.; Arnauld, T.; Barrett, A.G.M.; Braddock, D.C.; Flack, K.; Procopiou, P.A. *Org. Lett.* ***2000***, *2*, 551.

[794]Louie, J.; Bielawski, C.W.; Grubbs, R.H. *J. Am. Chem. Soc.* ***2001***, *123*, 11312.

[795]Lee, C.W.; Choi, T.-L.; Grubbs, R.H. *J. Am. Chem. Soc.* ***2002***, *124*, 3224.

[796]Kroll, W.R.; Doyle, G. *Chem. Commun.* ***1971***, 839. For a review see Grubbs, R.H.; Miller, S.J.; Fu, G.C. *Acc. Chem. Res.* ***1995***, *28*, 446.

used to form very large rings, including 21-membered lactone rings.[797] Diynes can also react intramolecularly to give large-ring alkynes.[798] Metathesis with vinyl-cyclopropyl-alkynes is also known, producing a ring expanded product (see **148**).[799]



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The synthetic importance of ring-closing and ring-opening metathesis reactions has led to the development of several new catalysts.[800] Catalysts have been developed that are compatible with both water and methanol.[801] The reaction is compatible with the presence of other functional groups,[802] such as other alkene units,[803] carbonyl units,[804] the alkene unit of conjugated esters,[805] butenolides[806] and other lactones,[807] amines,[808] amides,[809] sulfones,[810] phosphine oxides,[811] sulfonate esters,[812] and sulfonamides[813]

[797]Fürstner, A.; Langemann, K. *J. Org. Chem.* ***1996***, *61*, 3942. Also see, Goldring, W.P.D.; Hodder, A.S.; Weiler, L. *Tetrahedron Lett.* ***1998***, *39*, 4955; Ghosh, A.K.; Hussain, K.A. *Tetrahedron Lett.* ***1998***, *39*, 1881.

[798]Chen, F.-E.; Kuang, Y.-Y.; Dai, H.-F.; Lu, L.; Huo, M. *Synthesis* ***2003***, 2629.

[799]Wender, P.A.; Sperandio, D. *J. Org.Chem.* ***1998***, *63*, 4164.

[800]Schrock, R.R.; Hoveyda, A.H. *Angew. Chem. Int. Ed.* ***2003***. *42*, 4592; Garber, S.B.; Kingsbury, J.S.; Gray, B.L.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***2000***, *122*, 8168; Grela, K.; Kim, M. *Eur. J. Org. Chem.* ***2003***, 963; Conon, S.J.; Dunne, A.M.; Blechert, S. *Angew. Chem. Int. Ed.* ***2002***, *41*, 3835; Zhang, W.; Kraft, S.; Moore, J.S. *J. Am. Chem. Soc.* ***2004***, *126*, 329; Aggarwal, V.K.; Alonso, E.; Fang, G.; Ferrara, M.; Hynd, G.; Porcelloni, M. *Angew. Chem. Int. Ed.* ***2001***, *40*, 1433. Also see, references cited therein.

[801]Kirkland, T.A.; Lynn, D.M.; Grubbs, R.H. *J. Org. Chem.* ***1998***, *63*, 9904.

[802]Oxygen and nitrogen-containing heterocycles can be prepared. For a review, see Deiter, S.A.; Martin, S.F. *Chem. Rev.* ***2004***, *104*, 2199.

[803]Takahashi, T.; Kotora, M.; Kasai, K. *J. Chem. Soc., Chem. Commun.* ***1994***, 2693.

[804]Schneider, M.F.; Junga, H.; Blechert, S. *Tetrahedron* ***1995***, *51*, 13003; Junga, H.; Blechert, S. *Tetrahedron Lett.* ***1993***, *34*, 3731; Llebaria, A.; Camps, F.; Moretó, J.M. *Tetrahedron Lett.* ***1992***, *33*, 3683.

[805]Lee, C.W.; Grubbs, R.H. *J. Org. Chem.* ***2001***, *66*, 7155.

[806]Paquette, L.A.; Méndez-Andino, J. *Tetrahedron Lett.* ***1999***, *40*, 4301.

[807]Brimble, M.A.; Trzoss, M. *Tetrahedron* ***2004***, *60*, 5613.

[808]Wright, D.L.; Schulte II, J.P.; Page, M.A. *Org. Lett.* ***2000***, *2*, 1847; Dolman, S.J.; Sattely, E.S.; Hoveyda, A.H.; Schrock, R.R. *J. Am. Chem. Soc.* ***2002***, *124*, 6991.

[809]Vo-Thanh, G.; Boucard, V.; Sauriat-Dorizon, H.; Guibé, F. *Synlett* ***2001***, 37; Ma, S.; Ni, B.; Liang, Z. *J. Org. Chem.* ***2004***, *69*, 6305.

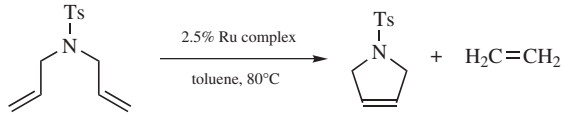
[810]Yao, Q. *Org. Lett.* ***2002***, *4*, 427.

[811]Demchuk, O.M.; Pietrusiewicz, K.M.; Michrowska, A.; Grela, K. *Org. Lett.* ***2003***, *5*, 3217.

[812]LeFlohic, A. ;Meyer, C.; Cossy, J.; Desmurs, J.-R.; Galland, J.-C. *Synlett* ***2003***, 667.

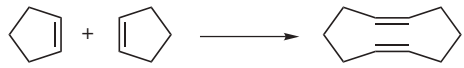
[813]Hanson, P.R.; Probst, D.A.; Robinson, R.E.; Yau, M. *Tetrahedron Lett.* ***1999***, *40*, 4761; Kinderman, S.S.; Van Maarseveen, J.H.; Schoemaker, H.E.; Hiemstra, H.; Rutjes, F.P.J.T. *Org. Lett.* ***2001***, *3*, 2045.

(see **149**).[814] Ether groups,[815] including vinyl ethers,[816] vinyl halides,[817] vinyl silanes,[818] vinyl sulfones,[819] allylic ethers,[820] and thioethers[821] are also compatible. Asymmetric ring-closing metathesis reactions have been reported.[822] Asymmetric ring-opening metathesis has also been reported.[823]



149

Two cyclic alkenes react to give dimeric dienes,[824] for example,



However, the products can then react with additional monomers and with each other, so that polymers are generally produced, and the cyclic dienes are obtained only in low yield. The reaction between a cyclic and a linear alkene can give an ring-opened diene:[825]

[814]Fürstner, A.; Picquet, M.; Bruneau, C.; Dixneuf, P.H. *Chem. Commun.* ***1998***, 1315; Maier, M.E.; Lapeva, T. *Synlett* ***1998***, 891; Mori, M.; Sakakibara, N.; Kinoshita, A. *J. Org. Chem.* ***1998***, *63*, 6082; O'Mahony, D.J.R.; Belanger, D.B.; Livinghouse, T. *Synlett* ***1998***, 443; Visser, M.S.; Heron N.M.; Didiuk, M.T.; Sagal, J.F.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***1996***, *118*, 4291.

[815]Edwards, S.D.; Lewis, T.; Taylor, R.J.K. *Tetrahedron Lett.* ***1999***, *40*, 4267.

[816]Sturino, C.F.; Wong, J.C.Y. *Tetrahedron Lett.* ***1998***, *39*, 9623; Rainier, J.D.; Cox, J.M.; Allwein, S.P. *Tetrahedron Lett.* ***2001***, *42*, 179.

[817]Chao, W.; Weinreb, S.M. *Org. Lett.* ***2003***, *5*, 2505.

[818]Schuman, M.; Gouverneur, V. *Tetrahedron Lett.* ***2002***, *43*, 3513.

[819]Kim, S.; Lim, C.J. *Angew. Chem. Int. Ed.* ***2002***, *41*, 3265.

[820]Delgado, M.; Martín, J.D. *Tetrahedron Lett.* ***1997***, *38*, 6299; Miller, S.J.; Kim, S.-H.; Chen, Z.-R.; Grubbs, R.H. *J. Am. Chem. Soc.* ***1995***, *117*, 2108.

[821]Leconte, M.; Pagano, S.; Mutch, A.; Lefebvre, F.; Basset, J.M. *Bull. Soc. Chim. Fr.* ***1995***, *132*, 1069.

[822]Cefalo, D.R.; Kiely, A.F.; Wuchrer, M.; Jamieson, J.Y. ; Schrock, R.R.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***2001***, *123*, 3139.

[823]Gillingham, D.G.; Kataoka, O.; Garber, S.B.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***2004***, *126*, 12288.

[824]Calderon N.; Ofstead, E.A.; Judy, W.A. *J. Polym. Sci. Part A-1* ***1967***, *5*, 2209; Wasserman, E.; Ben-Efraim, D.A.; Wolovsky, R. *J. Am. Chem. Soc.* ***1968***, *90*, 3286; Wolovsky, R.; Nir, Z. *Synthesis* ***1972***, 134.

[825]Wasserman, E.; Ben-Efraim, D.A.; Wolovsky, R. *J. Am. Chem. Soc.* ***1968***, *90*, 3286; Ray, G.C.; Crain, D.L. Fr. Pat. 1511381, 1968 [*Chem. Abstr.*, ***1969***, *70*, 114580q]; Mango, F.D. U.S. Pat. 3424811, 1969 [*Chem. Abstr.*, ***1969***, *70*, 106042a]; Rossi, R.; Diversi, P.; Lucherini, A.; Porri, L. *Tetrahedron Lett.* ***1974***, 879; Lal, J.; Smith, R.R. *J. Org. Chem.* ***1975***, *40*, 775.

Alkenes containing functional groups[826] do not give the reaction with most of the common catalysts, but some success has been reported with WCl_6–$SnMe_4$[827] and with certain other catalysts.

The reaction has also been applied to internal triple bonds:[828]

$$2\,RC{\equiv}CR' \rightleftharpoons RC{\equiv}CR + R'C{\equiv}CR'$$

but it has not been successful for terminal triple bonds,[829] although as noted above, molecules with a terminal alkene and a terminal alkyne react quite well. Ring-closing metathesis of alkene–alkynes leads to a cyclic alkene with a pendant vinyl unit (a diene).[830] Intramolecular reactions of a double bond with a triple bond are known[831] and a tetracyclic tetraene has been prepared from a poly-yne-diene.[832]

The generally accepted mechanism is a chain mechanism,[833] involving the intervention of a metal–carbene complex (**150** and **151**)[834] and a four-membered ring

[826]For a review, see Mol, J.C. *CHEMTECH* ***1983***, 250. See also, Bosma, R.H.A.; van den Aardweg, G.C.N.; Mol, J.C. *J. Organomet. Chem.* ***1983***, *255*, 159; ***1985***, *280*, 115; Xiaoding, X.; Mol, J.C. *J. Chem. Soc., Chem. Commun.* ***1985***, 631; Crisp, C.T.; Collis, M.P. *Aust. J. Chem.* ***1988***, *41*, 935.

[827]First shown by van Dam, P.B.; Mittelmeijer, M.C.; Boelhouwer, C. *J. Chem. Soc., Chem. Commun.* ***1972***, 1221.

[828]Pennella, F.; Banks, R.L.; Bailey, G.C. *Chem. Commun.* ***1968***, 1548; Villemin, D.; Cadiot, P. *Tetrahedron Lett.* ***1982***, *23*, 5139; McCullough, L.G.; Schrock, R.R. *J. Am. Chem. Soc.* ***1984***, *106*, 4067; Fürstner, A.; Mathes, C. *Org. Lett.* ***2001***, *3*, 221; Fürstner, A.; Mathes, C.; Lehmann, C.W. *J. Am. Chem. Soc.* ***1999***, *121*, 9453; Fürstner, A.; Guth, O.; Rumbo, A.; Seidel, G. *J. Am. Chem. Soc.* ***1999***, *121*, 11108; Brizius, G.; Bunz, U.H.F. *Org. Lett.* ***2002***, *4*, 2829; Grela, K.; Ignatonska, J. *Org. Lett.* ***2002***, *4*, 3747. For a review, see Tamao, K.; Kobayashi, K.; Ito, Y. *Synlett* ***1992***, 539.

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[830]Mori, M.; Kitamura, T.; Sakakibara, N.; Sato, Y. *Org. Lett.* ***2000***, *2*, 543; Kitamura, T.; Mori, M. *Org. Lett.* ***2001***, *3*, 1161.

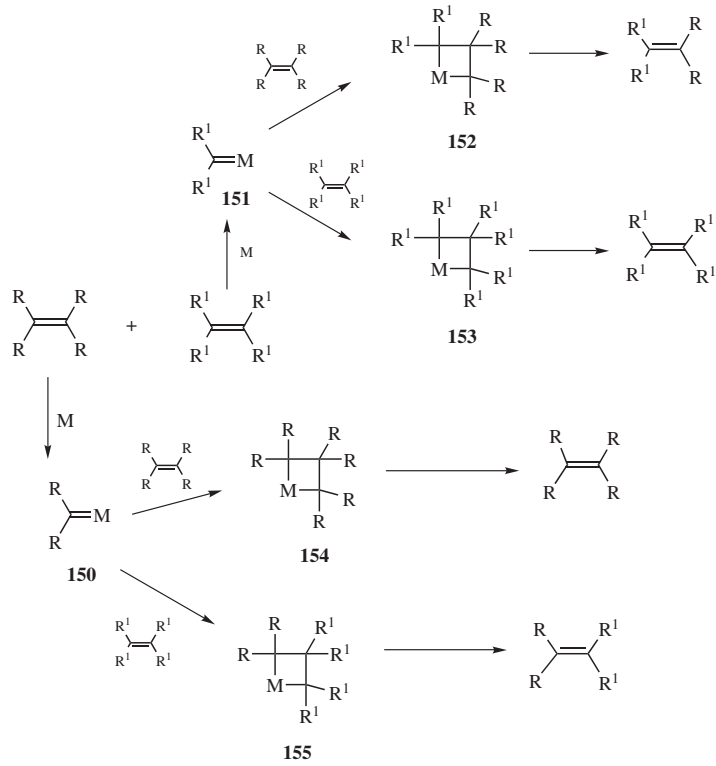
[831]Trost, B.M.; Trost, M.K. *J. Am. Chem. Soc.* ***1991***, *113*, 1850; Gilbertson, S.R.; Hoge, G.S. *Tetrahedron Lett.* ***1998***, *39*, 2075.

[832]Zuercher, W.J.; Scholl, M.; Grubbs, R.H. *J. Org. Chem.* ***1998***, *63*, 4291.

[833]For a discussion of the mechanism of ring-closing meththesis, see Sanford, M.S.; Ulman, M.; Grubbs, R.H. *J. Am. Chem. Soc.* ***2001***, *123*, 749; Sanford, M.S.; Love, J.A.; Grubbs, R.H. *J. Am. Chem. Soc.* ***2001***, *123*, 6543; Cavallo, L. *J. Am. Chem. Soc.* ***2002***, *124*, 8965; Adlhart, C.; Chen, P. *J. Am. Chem. Soc.* ***2004***, *126*, 3496.

[834]For a review of these complexes and their role in this reaction, see Crabtree, R.H. *The Organometallic Chemistry of the Transition Metals*, Wiley, NY, ***1988***, pp. 244–267.

containing a metal[835] (**152–155**).[836] In the cross-metathesis reaction shown as an example, $R_2C{=}CR_2$ reacts with $R^1{}_2C{=}CR^1{}_2$ in the presence of a metal catalyst, M. Initial reaction with the catalyst leads to the two expected metal carbenes, **150** and **151**. Metal carbene **151** can react with both alkenes to form metallocyclobutanes **152** and **153**. Each of these intermediates loses the metal to form the alkenes, the product of metathesis $R_2C{=}CR^1{}_2$ and the one of the original alkenes. In a likewise manner, **150** reacts with each alkene to form metallocyclobutanes **154** and **155**, which decomposes to $R_2C{=}CR_2$ and the metathesis product.

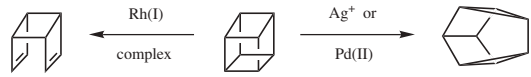


[835]For reviews of metallocycles, see Collman, J.C.; Hegedus, L.S.; Norton, J.R.; Finke, R.G. *Principles and Applications of Organotransition Metal Chemistry*, 2nd ed., University Science Books, Mill Valley, CA; ***1987***, pp. 459–520; Lindner, E. *Adv. Heterocycl. Chem.* ***1986***, *39*, 237.

[836]For reviews of the mechanism, see Grubbs, R.H. *Prog. Inorg. Chem.* ***1978***, *24*, 1; Katz, T.J. *Adv. Organomet. Chem.* ***1977***, *16*, 283; Calderon N.; Ofstead, E.A.; Judy, W.A. *Angew. Chem. Int. Ed.* ***1976***, *15*, 401. See also McLain, S.J.; Wood, C.D.; Schrock, R.R. *J. Am. Chem. Soc.* ***1977***, *99*, 3519; Casey, C.P.; Polichnowski, S.W. *J. Am. Chem. Soc.* ***1977***, *99*, 6097; Mango, F.D. *J. Am. Chem. Soc.* ***1977***, *99*, 6117; Stevens, A.E.; Beauchamp, J.L. *J. Am. Chem. Soc.* ***1979***, *101*, 6449; Lee, J.B.; Ott, K.C.; Grubbs, R.H. *J. Am. Chem. Soc.* ***1982***, *104*, 7491; Levisalles, J.; Rudler, H.; Villemin, D. *J. Organomet. Chem.* ***1980***, *193*, 235; Iwasawa, Y.; Hamamura, H. *J. Chem. Soc., Chem. Commun.* ***1983***, 130; Rappé, A.K.; Upton, T.H. *Organometallics*, ***1984***, *3*, 1440; Kress, J.; Osborn, J.A.; Greene, R.M.E.; Ivin, K.J.; Rooney, J.J. *J. Am. Chem. Soc.* ***1987***, *109*, 899; Feldman, J.; Davis, W.M.; Schrock, R.R. *Organometallics*, ***1989***, *8*, 2266.

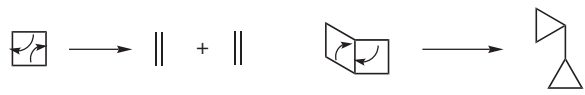
OS **80**, 85; **81**, 1.

18-38 Metal-Ion-Catalyzed σ-Bond Rearrangements



156 Cubane Cuneane

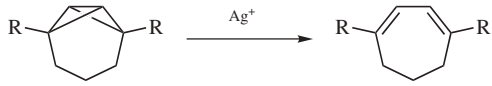
Many highly strained cage molecules undergo rearrangement when treated with metallic ions, such as Ag^+, Rh(I), or Pd(II).[837] The bond rearrangements observed can be formally classified into two main types: (*1*) [2+2]-ring



Type 1 Type 2

openings of cyclobutanes and (*2*) conversion of a bicyclo[2.2.0] system to a bicyclopropyl system. The molecule cubane supplies an example of each type (see above). Treatment with Rh(I) complexes converts cubane to tricyclo[4.2.0.0^{2,5}]octa-3,7-diene (**156**),[838] an example of type 1, while Ag^+ or Pd(II) causes the second type of reaction, producing cuneane.[839] Other examples are

Type 1



157 **158**

Ref. [840]

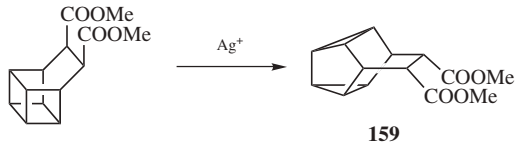
[837]For reviews, see Halpern, J., in Wender, I.; Pino, P. *Organic Syntheses via Metal Carbonyls*, Vol. 2, Wiley, NY, ***1977***, pp. 705–721; Bishop III, K.C. *Chem. Rev.* ***1976***, *76*, 461; Cardin, D.J.; Cetinkaya, B.; Doyle, M.J.; Lappert, M.F. *Chem. Soc. Rev.* ***1973***, *2*, 99, 132–139; Paquette, L.A. *Synthesis* ***1975***, 347; *Acc. Chem. Res.* ***1971***, *4*, 280.

[838]Eaton, P.E.; Chakraborty, U.R. *J. Am. Chem. Soc.* ***1978***, *100*, 3634.

[839]Cassar, L.; Eaton, P.E.; Halpern, J. *J. Am. Chem. Soc.* ***1970***, *92*, 6336.

[840]Gassman, P.G.; Atkins, T.J. *J. Am. Chem. Soc.* ***1971***, *93*, 4579; ***1972***, *94*, 7748; Sakai, M.; Westberg, H.H.; Yamaguchi, H.; Masamune, S. *J. Am. Chem. Soc.* ***1972***, *93*, 4611; Paquette, L.A.; Wilson, S.E.; Henzel, R.P. *J. Am. Chem. Soc.* ***1972***, *94*, 7771.

Type 2 [841]

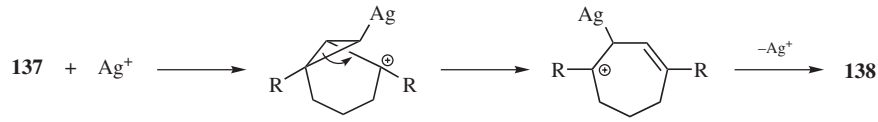


159

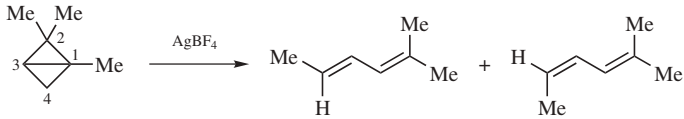
Ref. [842]

159 is the 9,10-dicarbomethyoxy derivative of *snoutane* (pentacyclo[3.3.2.0^{2,4}.0^{3,7}.0^{6,8}] decane).

The mechanisms of these reactions are not completely understood, although relief of strain undoubtedly supplies the driving force. The reactions are thermally forbidden by the orbital-symmetry rules, and the role of the catalyst is to provide low-energy pathways so that the reactions can take place. The type 1 reactions are the reverse of the catalyzed [2 + 2] ring closures discussed at **15-63**. The following mechanism, in which Ag^+ attacks one of the edge bonds, has been suggested for the conversion of **157** to **158**.[843]



Simpler bicyclobutanes can also be converted to dienes, but in this case the products usually result from cleavage of the central bond and one of the edge bonds.[844] For example, treatment of **160** with $AgBF_4$,[845]



160

[841]The starting compound here is a derivative of basketane, or 1,8-bishomocubane. For a review of homo-, bishomo-, and trishomocubanes, see Marchand, A.P. *Chem. Rev.* ***1989***, *89*, 1011.

[842]See, for example, Furstoss, R.; Lehn, J.M. *Bull. Soc. Chim. Fr.* ***1966***, 2497; Dauben, W.G.; Kielbania Jr., A.J. *J. Am. Chem. Soc.* ***1971***, *93*, 7345; Paquette, L.A.; Beckley, R.S.; Farnham, W.B. *J. Am. Chem. Soc.* ***1975***, *97*, 1089.

[843]Gassman, P.G.; Atkins, T.J. *J. Am. Chem. Soc.* ***1971***, *93*, 4579; Sakai, M.; Westberg, H.H.; Yamaguchi, H.; Masamune, S. *J. Am. Chem. Soc.* ***1972***, *93*, 4611.

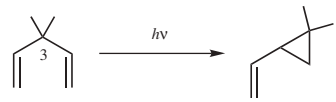
[844]Compound **157** can also be cleaved in this manner, giving a 3-methylenecyclohexene. See, for example, Dauben, W.G.; Kielbania Jr., A.J. *J. Am. Chem. Soc.* ***1972***, *94*, 3669; Gassman, P.G.; Reitz, R.R. *J. Am. Chem. Soc.* ***1973***, *95*, 3057; Paquette, L.A.; Zon, G. *J. Am. Chem. Soc.* ***1974***, *96*, 203, 224.

[845]Paquette, L.A.; Henzel, R.P.; Wilson, S.E. *J. Am. Chem. Soc.* ***1971***, *93*, 2335.

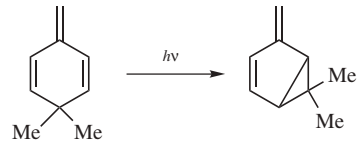
or $[(\pi\text{-allyl})PdCl]_2$[846] gives a mixture of the two dienes shown, resulting from a formal cleavage of the C_1–C_3 and C_1–C_2 bonds (note that a hydride shift has taken place). Dienes can also be converted to bicyclobutanes under photochemical conditions.[847]

18-39 The Di-π-methane and Related Rearrangements

Di-π-methane rearrangement



1,4-Dienes carrying alkyl or aryl substituents on C-3[848] can be photochemically rearranged to vinylcyclopropanes in a reaction called the *di-π-methane rearrangement*.[849] An example is conversion of **161** to **162**.[850] For most



161 **162**

1,4-dienes it is only the singlet excited states that give the reaction; triplet states generally take other pathways.[851] For unsymmetrical dienes, the reaction is regioselective. For example, **163** gave **164**, not **165**:[852]

[846]Gassman, P.G.; Meyer, R.G.; Williams, F.J. *Chem. Commun.* ***1971***, 842.

[847]Garavelli, M.; Frabboni, B.; Fato, M.; Celani, P.; Bernardi, F.; Robb, M.A.; Olivucci, M. *J. Am. Chem. Soc.* ***1999***, *121*, 1537.

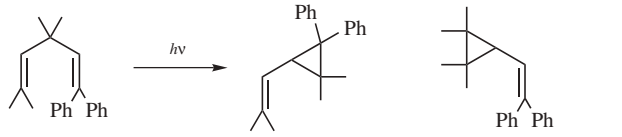
[848]Zimmerman, H.E.; Pincock, J.A. *J. Am. Chem. Soc.* ***1973***, *95*, 2957.

[849]For reviews, see Zimmerman, H.E. *Org. Photochem.* ***1991***, *11*, 1; Zimmerman, H.E., in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 3, Academic Press, NY, ***1980***, pp. 131–166; Hixson, S.S.; Mariano, P.S.; Zimmerman, H.E. *Chem. Rev.* ***1973***, *73*, 531. See also: Roth, W.R.; WIldt, H.; Schlemenat, A. *Eur. J. Org. Chem.* **2001**, 4081.

[850]Zimmerman, H.E.; Hackett, P.; Juers, D.F.; McCall, J.M.; Schröder, B. *J. Am. Chem. Soc.* ***1971***, *93*, 3653.

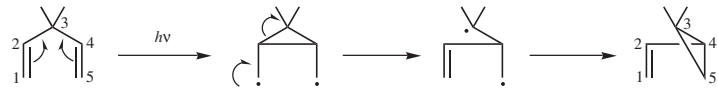
[851]However, some substrates, generally rigid bicyclic molecules, (e.g., barrelene, p. 152, which is converted to semi-bullvalene) give the di-π-methane rearrangement only from triplet states.

[852]Zimmerman, H.E.; Baum, A.A. *J. Am. Chem. Soc.* ***1971***, *93*, 3646. See also, Zimmerman, H.E.; Welter, T.R. *J. Am. Chem. Soc.* ***1978***, *100*, 4131; Alexander, D.W.; Pratt, A.C.; Rowley, D.H.; Tipping, A.E. *J. Chem. Soc., Chem. Commun.* ***1978***, 101; Paquette, L.A.; Bay, E.; Ku, A.Y.; Rondan, N.G.; Houk, K.N. *J. Org. Chem.* ***1982***, *47*, 422.

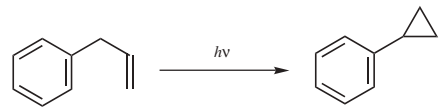


163 **164** **165** Not formed

The mechanism can be described by the diradical pathway given[853] (the C-3 substituents act to stabilize the radical), though the species shown are not necessarily intermediates, but may be transition states. It has been shown, for the case of certain substituted substrates, that configuration is retained at C-1 and C-5 and inverted at C-3.[854]



The reaction has been extended to allylic benzenes[855] (in this case C-3 substituents are not required), to β,γ-unsaturated ketones[856] (the latter reaction, which is called the *oxa-di-π-methane rearrangement*,[857] generally occurs only from the triplet state), to β,γ-unsaturated imines,[858] and to triple-bond systems.[859]



[853]See Zimmerman, H.E.; Little, R.D. *J. Am. Chem. Soc.* ***1974***, *96*, 5143; Zimmerman, H.E.; Boettcher, R.J.; Buehler, N.E.; Keck, G.E. *J. Am. Chem. Soc.* ***1975***, *97*, 5635. For an argument against the intermediacy of the $\bullet CH_2$–cyclopropyl–$CH_2\bullet$ intermediate, see Adam, W.; De Lucchi, O.; Dörr, M. *J. Am. Chem. Soc.* ***1989***, *111*, 5209.

[854]Zimmerman, H.E.; Robbins, J.D.; McKelvey, R.D.; Samuel, C.J.; Sousa, L.R. *J. Am. Chem. Soc.* ***1989***, *111*, 5209.

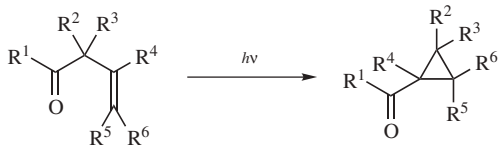
[855]For example, see Griffin, G.W.; Covell, J.; Petterson, R.C.; Dodson, R.M.; Klose, G. *J. Am. Chem. Soc.* ***1965***, *87*, 1410; Hixson, S.S. *J. Am. Chem. Soc.* ***1972***, *94*, 2507; Cookson, R.C.; Ferreira, A.B.; Salisbury, K. *J. Chem. Soc., Chem. Commun.* ***1974***, 665; Fasel, J.; Hansen, H. *Chimia*, ***1982***, *36*, 193; Paquette, L.A.; Bay, E. *J. Am. Chem. Soc.* ***1984***, *106*, 6693; Zimmerman, H.E.; Swafford, R.L. *J. Org. Chem.* ***1984***, *49*, 3069.

[856]For reviews of photochemical rearrangements of unsaturated ketones, see Schuster, D.I., in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 3, Academic Press, NY, ***1980***, pp. 167–279; Houk, K.N. *Chem. Rev.* ***1976***, *76*, 1; Schaffner, K. *Tetrahedron* ***1976***, *32*, 641; Dauben, W.G.; Lodder, G.; Ipaktschi, J. *Top. Curr. Chem.* ***1975***, *54*, 73.

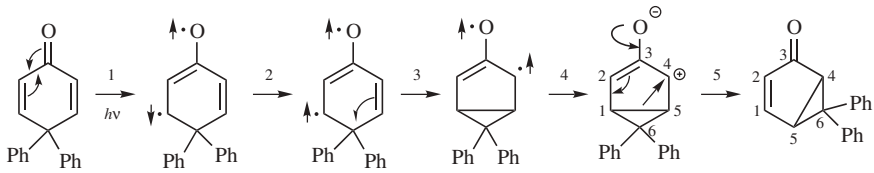
[857]For a review, see Demuth, M. *Org. Photochem.* ***1991***, *11*, 37.

[858]See Armesto, D.; Horspool, W.M.; Langa, F.; Ramos, A. *J. Chem. Soc. Perkin Trans. 1* ***1991***, 223.

[859]See Griffin, G.W.; Chihal, D.M.; Perreten, J.; Bhacca, N.S. *J. Org. Chem.* ***1976***, *41*, 3931.



When photolyzed, 2,5-cyclohexadienones can undergo a number of different reactions, one of which is formally the same as the di-π-methane rearrangement.[860] In this reaction, photolysis of the substrate **166** gives the bicyclo[3.1.0]hexenone (**171**). Although the reaction is formally the same (note the conversion of **161** to **162**



166 **167** **168** **169** **170** **171**

Singlet Triplet Triplet

above), the mechanism is different from that of the di-π-methane rearrangement, because irradiation of a ketone can cause an $n \rightarrow \pi^*$ transition, which is of course not possible for a diene lacking a carbonyl group. The mechanism[861] in this case has been formulated as proceeding through the excited triplet states **168** and **169**. In step 1, the molecule undergoes an $n \rightarrow \pi^*$ excitation to the singlet species **167**, which cross to the triplet **168**. Step 3 is a rearrangement from one excited state to another. Step 4 is a $\pi^* \rightarrow n$ electron demotion (an intersystem crossing from $T_1 \rightarrow S_0$, see p. 339). The conversion of **170** to **171** consists of two 1,2 alkyl migrations (a one-step process would be a 1,3-migration of alkyl to a carbocation center, see p. $$$): The old C_6–C_5 bond becomes the new C_6–C_4 bond and the old C_6–C_1 bond becomes the new C_6–C_5 bond.[862]

2,4-Cyclohexadienones also undergo photochemical rearrangements, but the products are different, generally involving ring opening.[863]

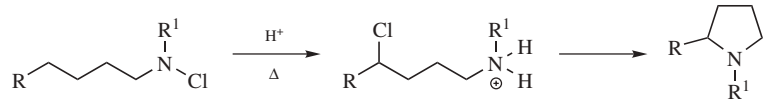
[860]For reviews of the photochemistry of 2,5-cyclohexadienones and related compounds, see Schaffner, K.; Demuth, M., in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 3, Academic Press, NY, ***1980***, pp. 281–348; Zimmerman, H.E. *Angew. Chem. Int. Ed.* ***1969***, *8*, 1; Kropp, P.J. *Org. Photochem.* ***1967***, *1*, 1; Schaffner, K. *Adv. Photochem.* ***1966***, *4*, 81. For synthetic use, see Schultz, A.G.; Lavieri, F.P.; Macielag, M.; Plummer, M. *J. Am. Chem. Soc.* ***1987***, *109*, 3991, and references cited therein.

[861]Schuster, D.I. *Acc. Chem. Res.* ***1978***, *11*, 65; Zimmerman, H.E.; Pasteris, R.J. *J. Org. Chem.* ***1980***, *45*, 4864, 4876; Schuster, D.I.; Liu, K. *Tetrahedron* ***1981***, *37*, 3329.

[862]Zimmerman, H.E.; Crumine, D.S.; Döpp, D.; Huyffer, P.S. *J. Am. Chem. Soc.* ***1969***, *91*, 434.

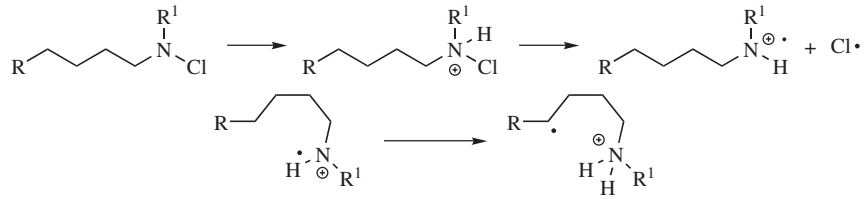
[863]For reviews, see Schaffner, K.; Demuth, M., in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 3, Academic Press, NY, ***1980***, p. 281; Quinkert, G. *Angew. Chem. Int. Ed.* ***1972***, *11*, 1072; Kropp, P.J. *Org. Photochem.* ***1967***, *1*, 1.

18-40 The Hofmann–Löffler and Related Reactions

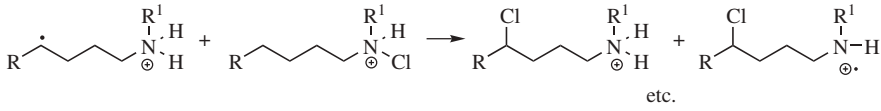


A common feature of the reactions in this section[864] is that they serve to introduce functionality at a position remote from functional groups already present. As such, they have proved very useful in synthesizing many compounds, especially in the steroid field (see also, **19-2** and **19-17**). When *N*-haloamines in which one alkyl group has a hydrogen in the 4 or 5 position are heated with sulfuric acid, pyrrolidines, or piperidines are formed, in a reaction known as the *Hofmann–Löffler reaction* (also called the *Hofmann–Löffler–Freytag reaction*).[865] The R′ group is normally alkyl, but the reaction has been extended to R′ = H by the use of concentrated sulfuric acid solution and ferrous salts.[866] The first step of the reaction is a rearrangement, with the halogen migrating from the nitrogen to the 4 or 5 position of the alkyl group. It is possible to isolate the resulting haloamine salt, but usually this is not done, and the second step, the ring closure (**10-31**), takes place. Though the reaction is most often induced by heat, this is not necessary, and irradiation and chemical initiators (e.g., peroxides) have been used instead. The mechanism is of a free-radical type, with the main step involving an internal hydrogen abstraction.[867]

Initiation



Propagation



A similar reaction has been carried out on *N*-halo amides, which give γ-lactones:[868]

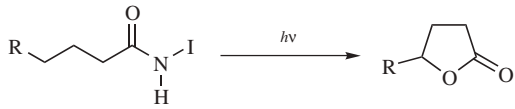
[864]For a review of the reactions in this section, see Carruthers, W. *Some Modern Methods of Organic Synthesis* 3rd ed.; Cambridge University Press: Cambridge, ***1986***, pp. 263–279.

[865]For reviews, see Stella, L. *Angew. Chem. Int. Ed.* ***1983***, *22*, 337; Sosnovsky, G.; Rawlinson, D.J. *Adv. Free-Radical Chem.* ***1972***, *4*, 203, see pp. 249–259; Deno, N.C. *Methods Free-Radical Chem.* ***1972***, *3*, 135, see pp. 136–143.

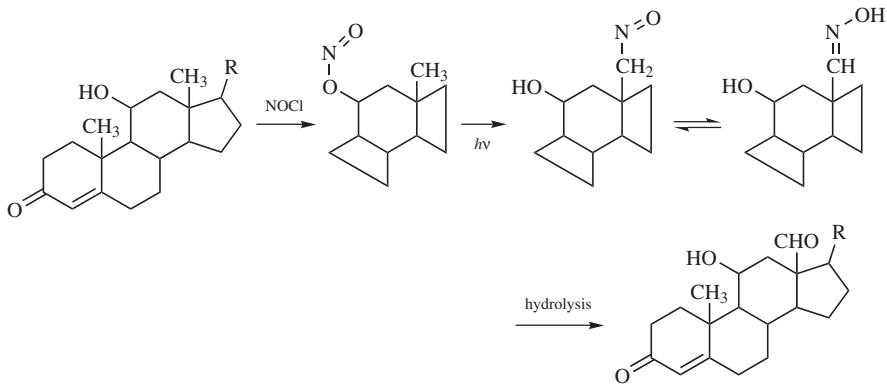
[866]Schmitz, E.; Murawski, D. *Chem. Ber.* ***1966***, *99*, 1493.

[867]Wawzonek, S.; Thelan, P.J. *J. Am. Chem. Soc.* ***1950***, *72*, 2118.

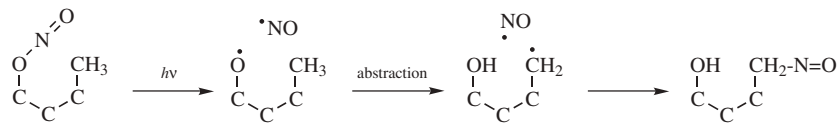
[868]Barton, D.H.R.; Beckwith, A.L.J.; Goosen, A. *J. Chem. Soc.* ***1965***, 181; Petterson, R.C.; Wambsgans, A. *J. Am. Chem. Soc.* ***1964***, *86*, 1648; Neale, R.S.; Marcus, N.L.; Schepers, R.G. *J. Am. Chem. Soc.* ***1966***, *88*, 3051. For a review of *N*-halo amide rearrangements, see Neale, R.S. *Synthesis* ***1971***, 1.



Another related reaction is the *Barton reaction*,[869] by which a methyl group in the ∂ position to an OH group can be oxidized to a CHO group. The alcohol is first converted to the nitrite ester. Photolysis of the nitrite results in conversion of the nitrite group to the OH group and nitrosation of the methyl group. Hydrolysis of the oxime tautomer gives the aldehyde, for example,[870]



This reaction takes place only when the methyl group is in a favorable steric position.[871] The mechanism is similar to that of the Hofmann–Löffler reaction.[872]



[869]For reviews, see Hesse, R.H. *Adv. Free-Radical Chem.* ***1969***, *3*, 83; Barton, D.H.R. *Pure Appl. Chem.* ***1968***, *16*, 1.

[870]Barton, D.H.R.; Beaton, J.M. *J. Am. Chem. Soc.* ***1961***, *83*, 4083. Also see, Barton, D.H.R.; Beaton, J.M.; Geller, L.E.; Pechet, M.M. *J. Am. Chem. Soc.* ***1960***, *82*, 2640.

[871]For a discussion of which positions are favorable, see Burke, S.D.; Silks III, L.A.; Strickland, S.M.S. *Tetrahedron Lett.* ***1988***, *29*, 2761.

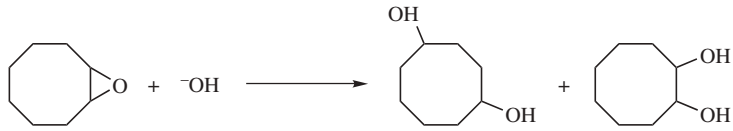
[872]Kabasakalian, P.; Townley, E.R. *J. Am. Chem. Soc.* ***1962***, *84*, 2711; Akhtar, M.; Barton, D.H.R.; Sammes, P.G. *J. Am. Chem. Soc.* ***1965***, *87*, 4601. See also, Nickon, A.; Ferguson, R.; Bosch, A.; Iwadare, T. *J. Am. Chem. Soc.* ***1977***, *99*, 4518; Barton, D.H.R.; Hesse, R.H.; Pechet, M.M.; Smith, L.C. *J. Chem. Soc. Perkin Trans. 1* ***1979***, 1159; Green, M.M.; Boyle, B.A.; Vairamani, M.; Mukhopadhyay, T.; Saunders, Jr., W.H.; Bowen, P.; Allinger, N.L. *J. Am. Chem. Soc.* ***1986***, *108*, 2381.

This is one of the few known methods for effecting substitution at an angular methyl group. Not only CH_3 groups, but also alkyl groups of the form RCH_2 and R_2CH can give the Barton reaction if the geometry of the system is favorable. An RCH_2 group is converted to the oxime R(C=NOH) (which is hydrolyzable to a ketone) or to a nitroso dimer, while an R_2CH group gives a nitroso compound $R_2C(NO)$. With very few exceptions, the only carbons that become nitrosated are those in the position δ to the original OH group, indicating that a six-membered transition state is necessary for the hydrogen abstraction.[873]

OS **III**, 159.

D. Noncyclic Rearrangements

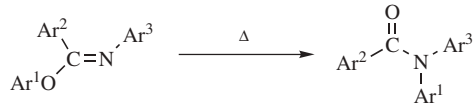
18-41 Hydride Shifts



The above is a typical example of a transannular hydride shift. The 1,2-diol is formed by a normal epoxide hydrolysis reaction (**10-7**). For a discussion of 1,3 and longer hydride shifts (see p. 1572).

18-42 The Chapman Rearrangement

1/*O* → 3/*N*-Aryl-migration

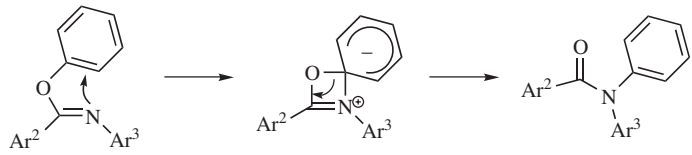


In the *Chapman rearrangement*, *N,N*-diaryl amides are formed when aryl imino esters are heated.[874] Best yields are obtained in refluxing tetraethylene glycol dimethyl ether (tetraglyme),[875] although the reaction can also be carried out without any solvent at all. Many groups may be present in the rings, for example, alkyl, halo, OR, CN, and COOR. Aryl migrates best when it contains electron-withdrawing groups. On the other hand, electron-withdrawing groups in Ar^2 or Ar^3 decrease the reactivity. The products can be hydrolyzed to diarylamines, and

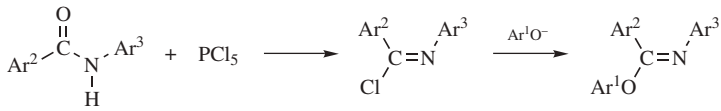
[873]For a discussion, see Nickon, A.; Ferguson, R.; Bosch, A.; Iwadare, T. *J. Am. Chem. Soc.* ***1977***, *99*, 4518.

[874]For reviews, see Schulenberg, J.W.; Archer, S. *Org. React.* ***1965***, *14*, 1; McCarty, C.G., in Patai, S. *The Chemistry of the Carbon-Nitrogen Double Bond*, Wiley, NY, ***1970***, pp. 439–447; McCarty, C.G.; Garner, L.A., in Patai, S. *The Chemistry of Amidines and Imidates*, Wiley, NY, ***1975***, pp. 189–240. For a review of 1,3 migrations of R in general, see Landis, P.S. *Mech. Mol. Migr.* ***1969***, *2*, 43.

[875]Wheeler, O.H.; Roman, F.; Santiago, M.V.; Quiles, F. *Can. J. Chem.* ***1969***, *47*, 503.

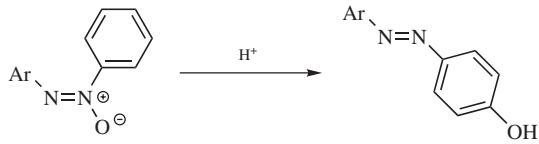


this is a method for preparing these compounds. The mechanism probably involves an intramolecular[876] aromatic nucleophilic substitution, resulting in a 1,3 oxygen-to-nitrogen shift. Aryl imino esters can be prepared from *N*-aryl amides by reaction with PCl_5, followed by treatment of the resulting imino chloride with an aroxide ion.[877]



Imino esters with any or all of the three groups being alkyl also rearrange, but they require catalysis by H_2SO_4 or a trace of methyl iodide or methyl sulfate.[878] The mechanism is different, involving an intermolecular process.[879] This is also true for derivatives for formamide ($Ar^2 = H$).

18-43 The Wallach Rearrangement



172 **173**

The conversion of azoxy compounds, on acid treatment, to *p*-hydroxy azo compounds (or sometimes the *o*-hydroxy isomers[880]) is called the *Wallach rearrangement*.[881] When both para positions are occupied, the *o*-hydroxy product may be

[876]For evidence for the intramolecular character of the reaction, see Wiberg, K.B.; Rowland, B.I. *J. Am. Chem. Soc.* ***1955***, *77*, 2205; Wheeler, O.H.; Roman, F.; Rosado, O. *J. Org. Chem.* ***1969***, *34*, 966; Kimura, M. *J. Chem. Soc. Perkin Trans. 2* ***1987***, 205.

[877]For a review of the formation and reactions of imino chlorides, see Bonnett, R., in Patai, S. *The Chemistry of the Carbon–Nitrogen Double Bond*, Wiley, NY, ***1970***, pp. 597–662.

[878]Landis, P.S. *Mech. Mol. Migr.* ***1969***, *2*, 43.

[879]See Challis, B.C.; Frenkel, A.D. *J. Chem. Soc. Perkin Trans. 2* ***1978***, 192.

[880]For example, see Dolenko, A.; Buncel, E. *Can. J. Chem.* ***1974***, *52*, 623; Yamamoto, J.; Nishigaki, Y.; Umezu, M.; Matsuura, T. *Tetrahedron* ***1980***, *36*, 3177.

[881]For reviews, see Buncel, E. *Mech. Mol. Migr.* ***1968***, *1*, 61; Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1969***, pp. 272–284, 357–359; Cox, R.A.; Buncel, E., in Patai, S. *The Chemistry of the Hydrazo, Azo, and Azoxy Groups*, pt. 2, Wiley, NY, ***1975***, pp. 808–837.

obtained, but ipso substitution at one of the para positions is also possible.[882] Although the mechanism[883] is not completely settled, the following facts are known: (*1*) The para rearrangement is intermolecular.[884] (*2*) When the reaction was carried out with an azoxy compound in which the N–O nitrogen was labeled with ^{15}N, *both* nitrogens of the product carried the label equally,[885] demonstrating that the oxygen did not have a preference for migration to either the near or the far ring. This shows that there is a symmetrical intermediate. (*3*) Kinetic studies show that two protons are normally required for the reaction.[886] The following mechanism,[887] involving the symmetrical intermediate **175**, has been proposed to explain the facts.[888]

It has proved possible to obtain **174** and **175** as stable species in super acid solutions.[748] Another mechanism, involving an intermediate with only one positive charge, has been proposed for certain substrates at low acidities.[889]

A photochemical Wallach rearrangement[890] is also known: The product is the *o*-hydroxy azo compound, the OH group is found in the farther ring, and the rearrangement is intramolecular.[891]

[882]See, for example, Shimao, I.; Oae, S. *Bull. Chem. Soc. Jpn.* ***1983***, *56*, 643.

[883]For reviews, see Furin, G.G. *Russ. Chem. Rev.* ***1987***, *56*, 532; Williams, D.L.H.; Buncel, E. *Isot. Org. Chem.* ***1980***, *5*, 184; Buncel, E. *Acc. Chem. Res.* ***1975***, *8*, 132.

[884]See, for example, Oae, S.; Fukumoto, T.; Yamagami, M. *Bull. Chem. Soc. Jpn.* ***1963***, *36*, 601.

[885]Shemyakin, M.M.; Maimind, V.I.; Vaichunaite, B.K. *Chem. Ind.* (*London*) ***1958***, 755; *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1960***, 808. Also see Behr, L.C.; Hendley, E.C. *J. Org. Chem.* ***1966***, *31*, 2715.

[886]Buncel, E.; Lawton, B.T. *Chem. Ind. (London)* ***1963***, 1835; Hahn, C.S.; Lee, K.W.; Jaffé, H.H. *J. Am. Chem. Soc.* ***1967***, *89*, 4975; Cox, R.A. *J. Am. Chem. Soc.* ***1974***, *96*, 1059.

[887]Buncel, E.; Strachan, W.M.J. *Can. J. Chem.* ***1970***, *48*, 377; Cox, R.A. *J. Am. Chem. Soc.* ***1974***, *96*, 1059; Buncel, E.; Keum, S. *J. Chem. Soc., Chem. Commun.* ***1983***, 578.

[888]For other proposed mechanisms, see Shemyakin, M.M.; Agadzhanyan, Ts.E.; Maimind, V.I.; Kudryavtsev, R.V. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1963***, 1216; Hahn, C.S.; Lee, K.W.; Jaffé, H.H. *J. Am. Chem. Soc.* ***1967***, *89*, 4975; Hendley, E.C.; Duffey, D. *J. Org. Chem.* ***1970***, *35*, 3579.

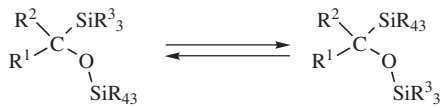
[889]Cox, R.A.; Dolenko, A.; Buncel, E. *J. Chem. Soc. Perkin Trans. 2* ***1975***, 471; Cox, R.A.; Buncel, E. *J. Am. Chem. Soc.* ***1975***, *97*, 1871.

[890]For a thermal rearrangement (no catalyst), see Shimao, I.; Hashidzume, H. *Bull. Chem. Soc. Jpn.* ***1976***, *49*, 754.

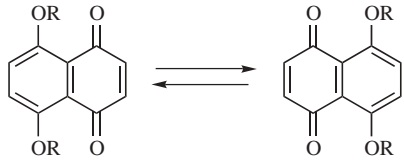
[891]For discussions of the mechanism of the photochemical reaction, see Goon, D.J.W.; Murray, N.G.; Schoch, J.; Bunce, N.J. *Can. J. Chem.* ***1973***, *51*, 3827; Squire, R.H.; Jaffé, H.H. *J. Am. Chem. Soc.* ***1973***, *95*, 8188; Shine, H.J.; Subotkowski, W.; Gruszecka, E. *Can. J. Chem.* ***1986***, *64*, 1108.

18-44 Dyotropic Rearrangements

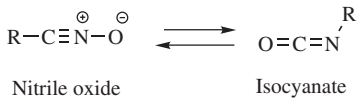
1/*C*-Trialkylsilyl,2/*O*-trialkylsilyl-interchange



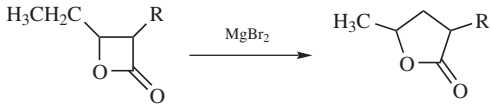
A *dyotropic rearrangement*[892] is an uncatalyzed process in which two σ bonds simultaneously migrate intramolecularly.[893] There are two types. The above is an example of type 1, which consists of reactions in which the two σ bonds interchange positions. In type 2, the two σ bonds do not interchange positions. An example is

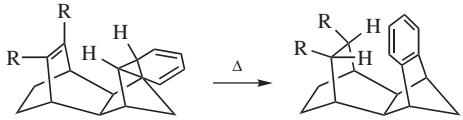


Some other examples are

Type 1  Ref. [894]

Nitrile oxide Isocyanate

Type 1  Ref. [895]

Type 2  Ref. [896]

A useful type 1 example is the *Brook rearrangement*,[897] a stereospecific intramolecular migration of silicon from carbon to oxygen that occurs for

[892]Reetz, M.T. *Angew. Chem. Int. Ed.* ***1972***, *11*, 129, 130.

[893]For reviews, see Minkin, V.I.; Olekhnovich, L.P.; Zhdanov, Yu.A. *Molecular Design of Tautomeric Compounds*, D. Reidel Publishing Co., Dordrecht, ***1988***, pp. 221–246; Minkin, V.I. *Sov. Sci. Rev. Sect. B* ***1985***, *7*, 51; Reetz, M.T. *Adv. Organomet. Chem.* ***1977***, *16*, 33. Also see Mackenzie, K.; Gravaatt, E.C.; Gregory, R.J.; Howard, J.A.K.; Maher, J.P. *Tetrahedron Lett.* ***1992***, *33*, 5629.

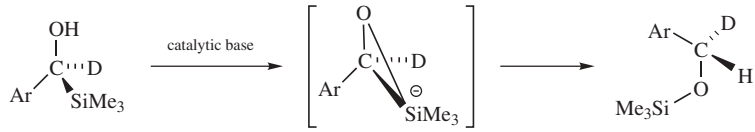
[894]See, for example, Taylor, G.A. *J. Chem. Soc. Perkin Trans. 1* ***1985***, 1181.

[895]See Black, T.H.; Hall, J.A.; Sheu, R.G. *J. Org. Chem.* ***1988***, *53*, 2371; Black, T.H.; Fields, J.D. *Synth. Commun.* ***1988***, *18*, 125.

[896]See Mackenzie, K.; Proctor, G.; Woodnutt, D.J. *Tetrahedron* ***1987***, *43*, 5981, and references cited therein.

[897]For a review, see Moser, W.H. *Tetrahedron* ***2001***, *57*, 2065.

(α-hydroxybenzyl)trialkylsilanes (**176**) in the presence of a catalytic amount of base.[898] Formation of a Si–O bond rather than the Si–C bond drives the rearrangement, which is believed to proceed via formation of **177**, and does proceed with inversion of configuration at carbon and retention of configuration at silicon.[899] A reverse Brook rearrangement is also known.[900] The reaction has been extended to other systems. A homo-Brook rearrangement has also been reported.[901] Another variation is the aza-Brook rearrangement of α-silylallyl)amines.[902] The Brook rearrangement has been used in synthesis involving silyl dithianes.[903] A Brook rearrangement mediated [6 + 2]-annulation has been used for the construction of eight-membered carbocycles.[904]



176 **177**

The Brook rearrangement has been used in two important synthetic applications, a multicomponent coupling protocol initiated by a Brook rearrangement involving silyl dithianes as mentioned, and anion relay chemistry (ARC) involving a Brook rearrangement. An example of the former is the conversion of the 2-silyl dithiane **178** to the anion with *tert*-butyllithium followed by ring opening of an epoxide to give **179**.[905] Treatment with HMPA triggers a solvent-controlled Brook rearrangement that gives a new dithiane anion (**180**), which then reacts with a different epoxide to give the final product, **181**. An example of the anion relay chemistry treats dithiane (**182**) with *n*-butyllithium, and then **183** to give **184**.[906] Subsequent treatment with a variety of electrophiles, such as allyl bromide, in HMPA, leads to **185** via a Brook rearrangement, and then alkylation of the resultant dithian anion. This reaction can be initiated by nucleophiles other

[898]Brook, A.G. *Acc. Chem. Res.* ***1974***, *7*, 77; Brook, A.G.; Bassendale, A.R., in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 2, Academic Press, NY, ***1980***, pp. 149–227.

[899]Brook, A. G.; Pascoe, J. D. *J. Am. Chem. Soc.* ***1971*** *93*, 6224.

[900]Wright, A.: West, R. *J. Am. Chem. Soc.* ***1974***, *96*,3214; Wright, A.; West, R. *J. Am. Chem. Soc.* ***1974***, *96*, 3227; Linderman, J.J.; Ghannam, A. *J. Am. Chem. Soc.* ***1990***, *112*, 2392.

[901]Wilson, S.R.; Georgiadis, G.M. *J. Org. Chem.* ***1983***, *48*, 4143.

[902]Honda, T.; Mori, M. *J. Org. Chem.* ***1996***, *61*, 1196.

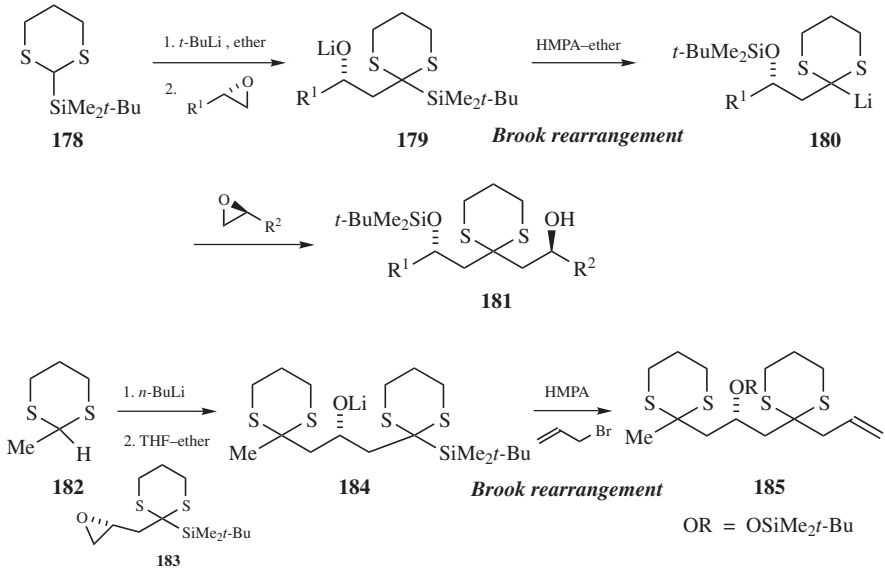
[903]For examples, see Smith III, A.B.; Adams, C. M. *Acc. Chem. Res.* ***2004***, *37*, 365; Smith III, A.B.; Kim, D.-S. *Org. Lett.* ***2005***, *7*, 3247.

[904]Takeda, K.; Haraguchi, H.; Okamoto, Y. *Org. Lett.* ***2003***, *5*, 3705; Sawada, Y.; Sasaki, M.; Takeda, K. *Org. Lett.* ***2004***, *6*, 2277.

[905]Smith III, A.B.; Boldi, A.M. *J. Am. Chem. Soc.* ***1997***, *119*, 6925; Smith III, A.B.; Pitram, S.M. ; Boldi, A.M.; Gaunt, M.J.; Sfouggatakis, C.; Moser, W.H. *J. Am. Chem. Soc.* ***2003***, *125*, 14435.

[906]Smith III, A.B.; Xian, M. *J. Am. Chem. Soc.* ***2006***, *128*, 66.

than dithiane anion. Organocuprates can be used, and the anion stabilizing group can be a nitrile.[907]



178 **179** **180** **181** **182** **183** **184** **185**

[907]Private communication, Professor Amos B. Smith III, University Pennsylvania.