# 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. 979), there is never any doubt about the *orientation* of unsymmetrical addition to these bonds. Nucleophilic attacking species always go to the carbon and electrophilic ones 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 Ph₂C=S, when treated with phenyllithium gives, after hydrolysis, benzhydryl phenyl sulfide Ph₂CHSPh.[4] The *stereochemistry* of addition is not generally a factor because it is not normally possible to determine whether the addition is syn or anti. In addition of YH to a ketone, e.g.,

$$R-\underset{\underset{O}{\parallel}}{C}-R' \xrightarrow{YH} R-\underset{\underset{OH}{\mid}}{\overset{\overset{Y}{\mid}}{C}}-R'$$
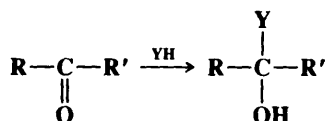
the product has a chiral carbon, but unless there is chirality in R or R' or YH is optically active, the product must be a racemic mixture and there is no way to tell from its steric nature whether the addition of Y and H was syn or anti. The same holds true for C=N and C=S bonds, since in none of these cases can chirality be present at the hetero atom. 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. 127), but these reactions are not very important. Of course, if R or R' *is* chiral, a racemic mixture will not always arise

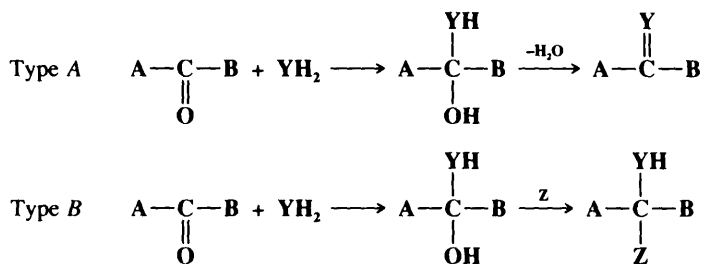[1] For a discussion, see Jencks *Prog. Phys. Org. Chem.* **1964**, *2*, 63-118.

[2] For reviews of thioketones and other compounds with C=S bonds, see Schaumann, in Patai *Supplement A: The Chemistry of Double-bonded Functional Groups*, vol. 2, pt. 2; Wiley: New York, 1989, pp. 1269-1367; Ohno, in Oae *Organic Chemistry of Sulfur*; Plenum: New York, 1977, pp. 189-229; Mayer, in Janssen *Organosulfur Chemistry*; Wiley: New York, 1967, pp. 219-240; Campaigne, in Patai *The Chemistry of the Carbonyl Group*, pt. 1; Wiley: New York, 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; Paterson, in Hartley; Patai *The Chemistry of the Metal–Carbon Bond*, vol. 2; Wiley: New York, 1985, pp. 219-338, pp. 261-267.

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

and the stereochemistry of addition can be studied in such cases. Cram's rule (p. 117) 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.

On p. 754 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:

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]

The mechanistic picture is further simplified by the fact that free-radical additions to carbon-hetero double bonds are rare.[7] The principal question remaining is which attacks first, the nucleophile or electrophile. In most cases it is the nucleophile, 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 attacking atom is either hydrogen or carbon. It may be noted that step 1 is exactly the same as step 1 of the tetrahedral mechanism of nucleophilic substitution at a carbonyl carbon (p. 331), and it might be expected that substitution would compete with addition. However, this is seldom the case. When A and B are H, R, or Ar, the substrate is an aldehyde or ketone and these almost never undergo substitution, owing to the extremely poor nature of H, R, and Ar as leaving groups. For carboxylic acids and their

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[5]For a discussion of such rules, see Eliel *The Stereochemistry of Carbon Compounds*; McGraw-Hill: New York, 1962, pp. 68-74. For reviews of the stereochemistry of addition to carbonyl compounds, see Bartlett *Tetrahedron* **1980**, *36*, 2-72, pp. 22-28; Ashby; Laemmle *Chem. Rev.* **1975**, *75*, 521-546; Goller *J. Chem. Educ.* **1974**, *51*, 182-185; Toromanoff *Top. Stereochem.* **1967**, *2*, 157-198.

[6]Cheung; Tseng; Lin; Srivastava; le Noble *J. Am. Chem. Soc.* **1986**, *108*, 1598; Laube; Stilz *J. Am. Chem. Soc.* **1987**, *109*, 5876.

[7]An example is found in **6-35**. For other examples, see Kaplan *J. Am. Chem. Soc.* **1966**, *88*, 1833; Drew; Kerr *Int. J. Chem. Kinet.* **1983**, *15*, 281; Fraser-Reid; Vite; Yeung; Tsang *Tetrahedron Lett.* **1988**, *29*, 1645; Beckwith; Hay *J. Am. Chem. Soc.* **1989**, *111*, 2674; Clerici; Porta *J. Org. Chem.* **1989**, *54*, 3872; Cossy; Pete; Portella *Tetrahedron Lett.* **1989**, *30*, 7361.

derivatives (B = OH, OR, NH_2, etc.) addition is seldom found, because these are much better leaving groups. It is thus the nature of A and B that determines whether a nucleophilic attack at a carbon-hetero multiple bond will lead to substitution or addition.

As is the case in the tetrahedral mechanism, it is also possible for the electrophilic species to attack first, in which case it goes to the hetero atom. This species is most often a proton and the mechanism is

Step 1
$$A—\overset{\displaystyle \|}{\underset{\displaystyle |\underset{..}{O}|}{C}}—B \ + \ H^+ \ \xrightarrow{\text{fast}} \ A—\overset{\displaystyle \oplus}{\underset{\displaystyle OH}{C}}—B$$

1

Step 2
$$A—\overset{\displaystyle \oplus}{\underset{\displaystyle OH}{C}}—B \ + \ \overline{Y} \ \xrightarrow{\text{slow}} \ A—\overset{\displaystyle Y}{\underset{\displaystyle OH}{C}}—B$$

No matter which species attacks first, 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.[8] Bases catalyze the reaction by converting a reagent of the form YH to the more powerful nucleophile Y^- (see p. 348). Acids catalyze it by converting the substrate to an ion (e.g., **1**) in which the positive charge on the carbon is greatly increased, thus making it more attractive to nucleophilic attack. Similar catalysis can also be found with metallic ions, such as Ag^+, which act here as Lewis acids.[9] We have mentioned before (p. 170) that ions of type **1** are comparatively stable carbocations because the positive charge is spread by resonance.

Reactivity factors in additions to carbon-hetero multiple bonds are similar to those for the tetrahedral mechanism of nucleophilic substitution.[10] 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-hetero multiple bond also lower addition rates, for similar reasons but, more important, may provide competition from 1,4 addition (p. 742). 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.

[8]For a discussion of acid and base catalysis in these reactions, see Jencks; Gilbert *Pure Appl. Chem.* **1977**, *49*, 1021-1027.

[9]Toromanoff *Bull. Soc. Chim. Fr.* **1962**, 1190.

[10]For a review of the reactivity of nitriles, see Schaefer, in Rappoport *The Chemistry of the Cyano Group*; Wiley: New York, 1970, pp. 239-305.

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 shall meet a number of such reactions, but most are of two types:

$$
\text{Type } A \qquad
\underset{\overset{\|}{O}}{A-C-B} + YH_2 \longrightarrow
\underset{\overset{|}{OH}}{\overset{YH}{A-C-B}} \xrightarrow{-H_2O}
\overset{Y}{\overset{\|}{A-C-B}}
$$

$$
\text{Type } B \qquad
\underset{\overset{\|}{O}}{A-C-B} + YH_2 \longrightarrow
\underset{\overset{|}{OH}}{\overset{YH}{A-C-B}} \xrightarrow{z}
\underset{\overset{|}{Z}}{\overset{YH}{A-C-B}}
$$

In type A, the 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 SN1 reactions occur very well on this type of compound (see p. 342), even when the leaving group is as poor as OH or NH_2. In this chapter we shall 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 shall 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., **6-2** and **6-14.** For reactions that are reversible, the principle of microscopic reversibility (p. 215) applies.

We shall discuss first reactions in which hydrogen or a metallic ion (or in one case phosphorus or sulfur) adds to the hetero atom and then reactions in which carbon adds to the hetero atom. Within each group, the reactions are classified by the nature of the nucleophile. Additions to isocyanides, which are different in character, are treated at the end.

Reactions in Which Hydrogen or a Metallic Ion Adds to the Hetero Atom

A. Attack by OH (Addition of H₂O)

6-1 The Addition of Water to Aldehydes and Ketones. Formation of Hydrates
    O-Hydro-*C*-hydroxy-addition

$$
\underset{\overset{\|}{O}}{-C-} + H_2O \underset{\overset{\longrightarrow}{OH^-}}{\overset{H^+ \text{ or}}{\rightleftharpoons}}
\underset{\overset{|}{OH}}{\overset{OH}{-C-}}
$$
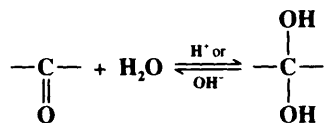
The adduct formed upon addition of water to an aldehyde or ketone is called a hydrate or *gem*-diol.[11] These compounds are usually stable only in water solution and decompose on distillation; i.e., the equilibrium shifts back toward the carbonyl compound. The position of the equilibrium is greatly 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.[12] 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.[13] 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[14] 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[15] polychlorinated and

chloral hydrate   hydrate of cyclopropanone
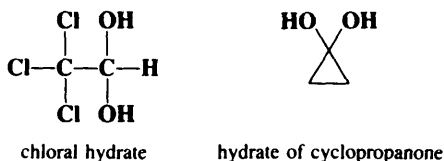
polyfluorinated aldehydes and ketones[16] and α-keto aldehydes also form stable hydrates, as do cyclopropanones.[17] In the last case[18] formation of the hydrate relieves some of the *I* strain (p. 276) of the parent ketone.

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:[19]
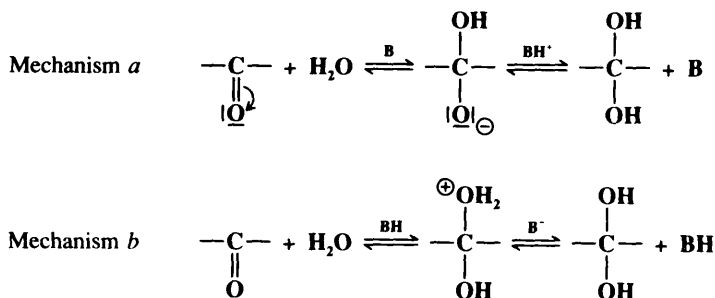
[11]For reviews, see Bell *The Proton in Chemistry*, 2nd ed.; Cornell University Press: Ithaca, NY, 1973, pp. 183-187, *Adv. Phys. Org. Chem.* **1966**, *4*, 1-29; Le Hénaff *Bull. Soc. Chim. Fr.* **1968**, 4687-4700.

[12]Bell; Clunie *Trans. Faraday Soc.* **1952**, *48*, 439. See also Bell; McDougall *Trans. Faraday Soc.* **1960**, *56*, 1281.

[13]Cohn; Urey *J. Am. Chem. Soc.* **1938**, *60*, 679.

[14]For a review of chloral, see Luknitskii *Chem. Rev.* **1975**, *75*, 259-289.

[15]For a discussion, see Schulman; Bonner; Schulman; Laskovics *J. Am. Chem. Soc.* **1976**, *98*, 3793.

[16]For a review of addition to fluorinated ketones, see Gambaryan; Rokhlin; Zeifman; Ching-Yun; Knunyants *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 947-956 [*Angew. Chem. 78*, 1008-1017].

[17]For other examples, see Krois; Langer; Lehner *Tetrahedron* **1980**, *36*, 1345; Krois; Lehner *Monatsh. Chem.* **1982**, *113*, 1019.

[18]Turro; Hammond *J. Am. Chem. Soc.* **1967**, *89*, 1028; Schaafsma; Steinberg; de Boer *Recl. Trav. Chim. Pays-Bas* **1967**, *86*, 651. For a review of cyclopropanone chemistry, see Wasserman; Clark; Turley *Top. Curr. Chem.* **1974**, *47*, 73-156.

[19]Bell; Rand; Wynne-Jones *Trans. Faraday Soc.* **1956**, *52*, 1093; Pocker *Proc. Chem. Soc.* **1960**, 17; Funderburk; Aldwin; Jencks *J. Am. Chem. Soc.* **1978**, *100*, 5444; Sørensen; Jencks *J. Am. Chem. Soc.* **1987**, *109*, 4675. For a comprehensive treatment, see Lowry; Richardson *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper and Row: New York, 1987, pp. 662-680.

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.[20] 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 **7-49**.

There are no OS references, but see OS **66,** 142, for the reverse reaction.

6-2 Hydrolysis of the Carbon–Nitrogen Double Bond
Oxo-de-alkylimino-bisubstitution, etc.

$$\underset{\underset{N-W}{\|}}{-C-} \xrightarrow{H_2O} \underset{\underset{O}{\|}}{-C-} + W-NH_2$$
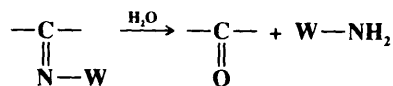
Compounds containing carbon–nitrogen double bonds can be hydrolyzed to the corresponding aldehydes or ketones. For imines (W = R or H) the hydrolysis is easy and can be carried out with water. When W = H, the imine is seldom stable enough for isolation, and hydrolysis usually occurs in situ, without isolation. The hydrolysis of Schiff bases (W = Ar) is more difficult and requires acid or basic 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[21] have been used to cleave C=N bonds, especially those not easily hydrolyzable with acidic or basic catalysts or which contain other functional groups that are attacked under these conditions. In particular, oximes have been converted to the corresponding aldehyde or ketone by treatment with, among other reagents, thallium(III) nitrate,[22] aqueous $TiCl_3$ and acetic acid,[23] aqueous $NaHSO_3$,[24] benzeneseleninic anhydride $(PhSeO)_2O$,[25] N_2O_4,[26] $Me_3SiCl–NaNO_2$,[27] $LiAlH_4$–HMPA,[28] Amberlyst 15 and acetone,[29] pyridinium dichromate–*t*-BuOOH,[30] alkaline H_2O_2,[31] and by treatment of the O-acetate of the oxime with chromium(II) acetate.[32] Tosylhydrazones can be hydrolyzed to the corresponding ketones with $NaOCl$,[33] aqueous acetone and BF_3–etherate,[34] $CuSO_4 \cdot 5H_2O$,[35] so-

[20]Jencks *Acc. Chem. Res.* **1976,** *9*, 425-432.
[21]For a list of many of these reagents, with references,see Ranu; Sarkar *J. Org. Chem.* **1988,** *53*, 878.
[22]McKillop; Hunt; Naylor; Taylor *J. Am. Chem. Soc.* **1971,** *93*, 4918.
[23]Timms; Wildsmith *Tetrahedron Lett.* **1971,** 195. See also McMurry; Silvestri *J. Org. Chem.* **1975,** *40*, 1502; Balicki; Kaczmarek; Malinowski *Liebigs Ann. Chem.* **1989,** 1139.
[24]Pine; Chemerda; Kozlowski *J. Org. Chem.* **1966,** *31*, 3446.
[25]Barton; Lester; Ley *J. Chem. Soc., Perkin Trans. 1* **1980,** 1212.
[26]Shim; Kim; Kim *Tetrahedron Lett.* **1987,** *28*, 645.
[27]Lee; Kwak; Hwang *Tetrahedron Lett.* **1990,** *31*, 6677.
[28]Wang; Sukenik *J. Org. Chem.* **1985,** *50*, 5448.
[29]Ballini; Petrini *J. Chem. Soc., Perkin Trans. 1* **1988,** 2563.
[30]Chidambaram; Satyanarayana; Chandrasekaran *Synth. Commun.* **1989,** *19*, 1727.
[31]Ho *Synth. Commun.* **1980,** *10*, 465.
[32]Corey; Richman *J. Am. Chem. Soc.* **1970,** *92*, 5276.
[33]Ho; Wong *J. Org. Chem.* **1974,** *39*, 3453.
[34]Sacks; Fuchs *Synthesis* **1976,** 456.
[35]Attanasi; Gasperoni *Gazz. Chim. Ital.* **1978,** *108*, 137.

dium peroxide,[36] as well as with other reagents.[37] Among other reagents that have been used to cleave C=N bonds are nitrous acid (as well as nitrosonium salts such as NO$^+$ BF$_4^-$)[38] and ozone[39] (see **9-9**).

The hydrolysis of carbon–nitrogen double bonds involves initial addition of water and elimination of a nitrogen moiety:
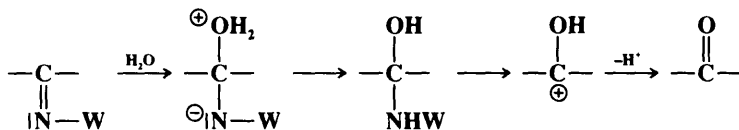
It is thus an example of reaction type A (p. 882). The sequence shown is generalized.[40] In specific cases there are variations in the sequence of the steps, depending on acid or basic catalysis or other conditions.[41] Which step is rate-determining also depends on acidity and on the nature of W and of the groups connected to the carbonyl.[42] Iminium ions (**2**)[43] would
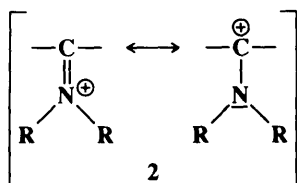
be expected to undergo hydrolysis quite readily, since there is a contributing form with a positive charge on the carbon. Indeed, they react with water at room temperature.[44] Acid-catalyzed hydrolysis of enamines (the last step of the Stork reaction, **2-19**) involves conversion to iminium ions:[45]
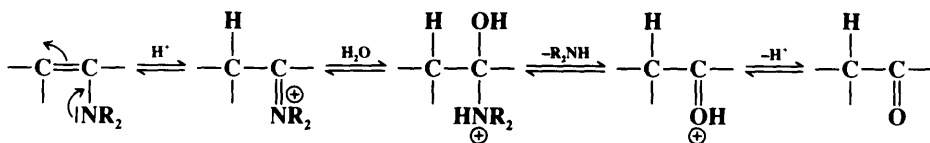
The mechanism of enamine hydrolysis is thus similar to that of vinyl ether hydrolysis (**0-6**).

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.

[36]Ho; Olah *Synthesis* **1976**, 611.

[37]For references, see Jiricny; Orere; Reese *Synthesis* **1970**, 919.

[38]Doyle; Wierenga; Zaleta *J. Org. Chem.* **1972**, *37*, 1597; Doyle; Zaleta; DeBoer; Wierenga *J. Org. Chem.* **1973**, *38*, 1663; Olah; Ho *Synthesis* **1976**, 610.

[39]For example, see Erickson; Andrulis; Collins; Lungle; Mercer *J. Org. Chem.* **1969**, *34*, 2961.

[40]For reviews of the mechanism, see Bruylants; Feytmants-de Medicis, in Patai *The Chemistry of the Carbon–Nitrogen Double Bond*; Wiley: New York, 1970, pp. 465-504; Salomaa, in Patai, Ref. 2, pt. 1, pp. 199-205.

[41]For example, see Reeves *J. Am. Chem. Soc.* **1962**, *82*, 3332; Sayer; Conlon *J. Am. Chem Soc.* **1980**, *102*, 3592.

[42]Cordes; Jencks *J. Am. Chem. Soc.* **1963**, *85*, 2843.

[43]For a review of iminium ions, see Böhme; Haake *Adv. Org. Chem.* **1976**, *9*, pt. 1, 107-223.

[44]Hauser; Lednicer *J. Org. Chem.* **1959**, *24*, 46. For a study of the mechanism, see Gopalakrishnan; Hogg *J. Org. Chem.* **1989**, *54*, 768.

[45]Stamhuis; Maas *J. Org. Chem.* **1965**, *30*, 2156; Maas; Janssen; Stamhuis; Wynberg *J. Org. Chem.* **1967**, *32*, 1111; Sollenberger; Martin *J. Am. Chem. Soc.* **1970**, *92*, 4261. For a review of enamine hydrolysis, see Stamhuis; Cook, in Cook *Enamines*, 2nd ed.; Marcel Dekker: New York, 1988, pp. 165-180.

6-3 Hydrolysis of Isocyanates and Isothiocyanates
Oxo-de-alkylimino-bisubstitution

$$R-N=C=O + H_2O \xrightarrow{OH^- \ or \ H^+} R-NH_2 + CO_2$$
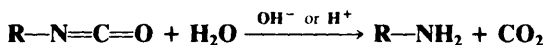
A common method for the preparation of primary amines involves the hydrolysis of iso-cyanates or isothiocyanates.[46] The latter react more slowly and more vigorous conditions are required. The reaction is catalyzed by acids or bases. In this case simple addition of water to the carbon–nitrogen double bond would give an N-substituted carbamic acid (**3**). Such compounds are unstable and break down to carbon dioxide (or COS in the case of isothiocyanates) and the amine:

$$R-\underset{\underset{H}{|}}{N}-\underset{\underset{OH}{|}}{C}=O \longrightarrow RNH_2 + CO_2$$

3
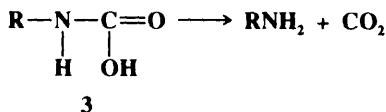
OS **II**, 24; **IV**, 819; **V**, 273; **VI**, 910.

6-4 Hydrolysis of Aliphatic Nitro Compounds
Oxo-de-hydro,nitro-bisubstitution
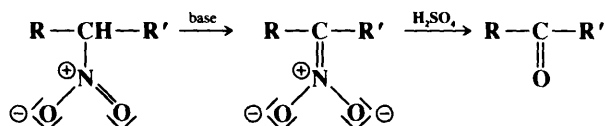
Primary or secondary aliphatic nitro compounds can be hydrolyzed, respectively, to alde-hydes or ketones, by treatment of their conjugate bases with sulfuric acid. This is called the *Nef reaction*.[47] Tertiary aliphatic nitro compounds do not give the reaction because they cannot be converted to their conjugate bases. Like **6-2**, this reaction involves hydrolysis of a C=N double bond. A possible mechanism is[48]

Aci form of the
nitro compound

4
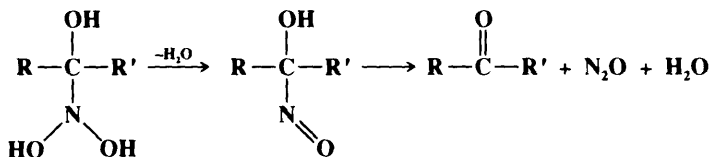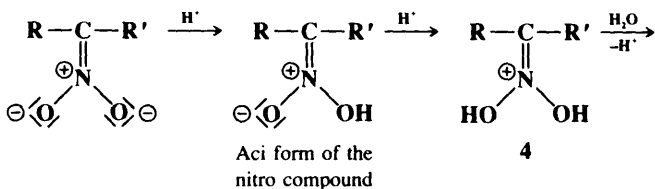
Intermediates of type **4** have been isolated in some cases.[49]

[46]For a study of the mechanism, see Castro; Moodie; Sansom *J. Chem. Soc., Perkin Trans. 2* **1985**, 737. For a review of the mechanisms of reactions of isocyanates with various nucleophiles, see Satchell; Satchell *Chem. Soc. Rev.* **1975**, *4*, 231-250.

[47]For reviews, see Pinnick *Org. React.* **1990**, *38*, 655-792; Haines *Methods for the Oxidation of Organic Compounds*; Academic Press: New York, 1988, pp. 220-231, 416-419.

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

[49]Feuer; Spinicelli *J. Org. Chem.* **1977**, *42*, 2091.

   The conversion of nitro compounds to aldehydes or ketones has been carried out with better yields and fewer side reactions by several alternative methods. Among these are treatment of the nitro compound with aqueous $TiCl_3$,[50] cetyltrimethylammonium permanganate,[51] tin complexes and $NaHSO_3$,[52] activated dry silica gel,[53] or 30% H_2O_2–K_2CO_3,[54] and treatment of the conjugate base[55] of the nitro compound with $KMnO_4$,[56] *t*-BuOOH and a catalyst,[57] ceric ammonium nitrate (CAN),[58] MoO_5–pyridine–HMPA,[59] or ozone.[60]

   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.[61] Both the Nef reaction and the hydroxamic acid process involve the aci form; the difference in products arises from higher acidity, e.g., a difference in sulfuric acid concentration from 2 M to 15.5 M changes the product from the aldehyde to the hydroxamic acid.[62] 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.

6-5   Hydrolysis of Nitriles

$$R—C{\equiv}N + H_2O \xrightarrow{\text{H}^+\text{ or OH}^-} R—\overset{\displaystyle O}{\underset{\displaystyle \|}{C}}—NH_2$$
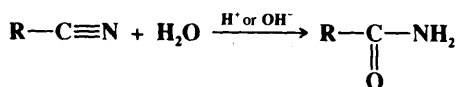
NN-Dihydro-C-oxo-biaddition

$$R—C{\equiv}N + H_2O \xrightarrow{\text{H}^+\text{ or OH}^-} R—\overset{\displaystyle O}{\underset{\displaystyle \|}{C}}—OH \text{ or } R—\overset{\displaystyle O}{\underset{\displaystyle \|}{C}}—O^-$$
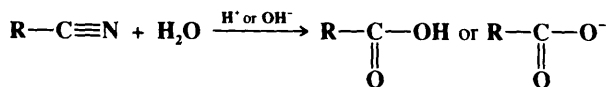
Hydroxy,oxo-de-nitrilo-tersubstitution

Nitriles can be hydrolyzed to give either amides or carboxylic acids.[63] The amide is formed initially, but since amides are also hydrolyzed with acid or basic treatment, the carboxylic acid is the more common product. When the acid is desired,[64] the reagent of choice is

   [50]McMurry; Melton *J. Org. Chem.* **1973**, *38*, 4367; McMurry *Acc. Chem. Res.* **1974**, *7*, 281-286, pp. 282-284. See also Kirchhoff *Tetrahedron Lett.* **1976**, 2533.
   [51]Vankar; Rathore; Chandrasekaran *Synth. Commun.* **1987**, *17*, 195.
   [52]Urpí; Vilarrasa *Tetrahedron Lett.* **1990**, *31*, 7499.
   [53]Keinan; Mazur *J. Am. Chem. Soc.* **1977**, *99*, 3861.
   [54]Olah; Arvanaghi; Vankar; Prakash *Synthesis* **1980**, 662.
   [55]For other methods, see Barton; Motherwell; Zard *Tetrahedron Lett.* **1983**, *24*, 5227; Yano; Ohshima; Sutoh *J. Chem. Soc., Chem. Commun.* **1984**, 695.
   [56]Shechter; Williams *J. Org. Chem.* **1962**, *27*, 3699; Freeman; Yeramyan *J. Org. Chem.* **1970**, *35*, 2061; Freeman; Lin *J. Org. Chem.* **1971**, *36*, 1335; Kornblum; Erickson; Kelly; Henggeler *J. Org. Chem.* **1982**, *47*, 4534; Steliou; Poupart *J. Org. Chem.* **1985**, *50*, 4971.
   [57]Bartlett; Green; Webb *Tetrahedron Lett.* **1977**, 331.
   [58]Olah; Gupta *Synthesis* **1980**, 44.
   [59]Galobardes; Pinnick *Tetrahedron Lett.* **1981**, *22*, 5235.
   [60]McMurry; Melton; Padgett *J. Org. Chem.* **1974**, *39*, 259. See Williams; Unger; Moore *J. Org. Chem.* **1978**, *43*, 1271, for the use of singlet oxygen instead of ozone.
   [61]Hydroxamic acids can also be prepared from primary nitro compounds with SeO_2 and Et_3N: Sosnovsky; Krogh *Synthesis* **1980**, 654.
   [62]Kornblum; Brown *J. Am. Chem. Soc.* **1965**, *87*, 1742. See also Cundall; Locke *J. Chem. Soc. B* **1968**, 98; Edward; Tremaine *Can. J. Chem.* **1971**, *49*, 3483, 3489, 3493.
   [63]For reviews, see Zil'berman *Russ. Chem. Rev.* **1984**, *53*, 900-912; Compagnon; Miocque *Ann. Chim. (Paris)* **1970**, [14] *5*, 11-22, 23-37.
   [64]For a list of reagents, with references, see Larock *Comprehensive Organic Transformations*; VCH: New York, 1989, p. 993.
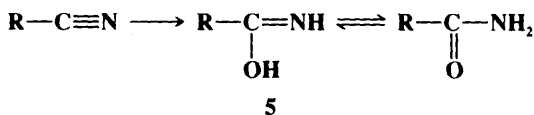
aqueous NaOH containing about 6 to 12% H_2O_2, though acid-catalyzed hydrolysis is also frequently carried out. However, there are a number of procedures for stopping at the amide stage,[65] among them the use of concentrated H_2SO_4; formic acid and HCl or HBr;[66] acetic acid and BF_3; H_2O_2 and OH^-;[67] 30% H_2O_2 in Me_2SO,[68] sodium percarbonate,[69] and dry HCl followed by H_2O. The same result can also be obtained by use of water and certain metal ions or complexes;[70] MnO_2 in methylene chloride[71] or on silica gel;[72] sodium perborate in aqueous MeOH;[73] $Hg(OAc)_2$ in HOAc;[74] 2-mercaptoethanol in a phosphate buffer;[75] $KF-Al_2O_3$;[76] or $TiCl_4$ and water.[77] Nitriles can be hydrolyzed to the carboxylic acids without disturbing carboxylic ester functions also present, by the use of tetrachloro- or tetrafluorophthalic acid.[78]

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. The sequences

$$\textbf{RX + NaCN} \longrightarrow \textbf{RCN} \longrightarrow \textbf{RCOOH} \qquad \textbf{(0-101)}$$

$$\textbf{RCHO + HCN} \longrightarrow \textbf{RCH(OH)CN} \longrightarrow \textbf{RCH(OH)COOH} \qquad \textbf{(6-49)}$$

$$\textbf{RCHO + NaCN + NH}_4\textbf{Cl} \longrightarrow \textbf{RCH(NH}_2\textbf{)CN} \longrightarrow \textbf{RCH(NH}_2\textbf{)COOH} \qquad \textbf{(6-50)}$$

are very common. The last two sequences are often carried out without isolation of the cyanide intermediates. Hydrolysis of cyanohydrins RCH(OH)CN is usually carried out under acidic conditions, because basic solutions cause competing reversion of the cyanohydrin to the aldehyde and CN^-. However, cyanohydrins have been hydrolyzed under basic conditions with borax or alkaline borates.[79]

The first addition product is **5**, which tautomerizes to the amide.

$$R-C{\equiv}N \longrightarrow \underset{\underset{\textstyle 5}{\textstyle OH}}{R-\overset{\textstyle |}{C}=NH} \rightleftharpoons R-\overset{\textstyle ||}{\underset{\textstyle O}{C}}-NH_2$$

Thiocyanates can be converted to thiocarbamates, in a similar reaction:[80] $R-S-C{\equiv}N$ + $H_2O \xrightarrow{H^+} R-S-CO-NH_2$. 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. Also see OS **III**, 609; **IV**, 359, 502; **66**, 142.

[65]For a discussion, see Beckwith, in Zabicky *The Chemistry of Amides*; Wiley: New York, 1970, pp. 119-125. For a list of reagents, with references, see Ref. 64, p. 994.
[66]Becke; Fleig; Pässler *Liebigs Ann. Chem.* **1971**, *749*, 198.
[67]For an example with phase transfer catalysis, see Cacchi; Misiti; La Torre *Synthesis* **1980**, 243.
[68]Katritzky; Pilarski; Urogdi *Synthesis* **1989**, 949.
[69]Kabalka; Deshpande; Wadgaonkar; Chatla *Synth. Commun.* **1990**, *20*, 1445.
[70]For example, see Watanabe *Bull. Chem. Soc. Jpn.* **1959**, *32*, 1280, **1964**, *37*, 1325; Bennett; Yoshida *J. Am. Chem. Soc.* **1973**, *95*, 3030; Paraskewas *Synthesis* **1974**, 574; McKenzie; Robson *J. Chem. Soc., Chem. Commun.* **1988**, 112.
[71]Cook; Forbes; Kahn *Chem. Commun.* **1966**, 121.
[72]Liu; Shih; Huang; Hu *Synthesis* **1988**, 715.
[73]McKillop; Kemp *Tetrahedron* **1989**, *45*, 3299; Reed; Gupton; Solarz *Synth. Commun.* **1990**, *20*, 563.
[74]Plummer; Menendez; Songster *J. Org. Chem.* **1989**, *54*, 718.
[75]Lee; Goo; Lee; Lee *Tetrahedron Lett.* **1989**, *30*, 7439.
[76]Rao *Synth. Commun.* **1982**, *12*, 177.
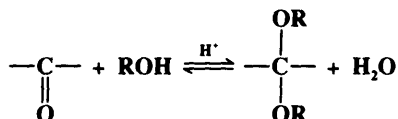[77]Mukaiyama; Kamio; Kobayashi; Takei *Chem. Lett.* **1973**, 357.
[78]Rounds; Eaton; Urbanowicz; Gribble *Tetrahedron Lett.* **1988**, *29*, 6557.
[79]Jammot; Pascal; Commeyras *Tetrahedron Lett.* **1989**, *30*, 563.
[80]Zil'berman; Lazaris *J. Gen. Chem. USSR* **1963**, *33*, 1012.

B.   Attack by OR (Addition of ROH)

6-6   The Addition of Alcohols to Aldehydes and Ketones
Dialkoxy-de-oxo-bisubstitution

$$—\overset{\parallel}{\underset{O}{C}}— \ + \ ROH \ \underset{}{\overset{H^\cdot}{\rightleftharpoons}} \ —\overset{OR}{\underset{OR}{C}}— \ + \ H_2O$$
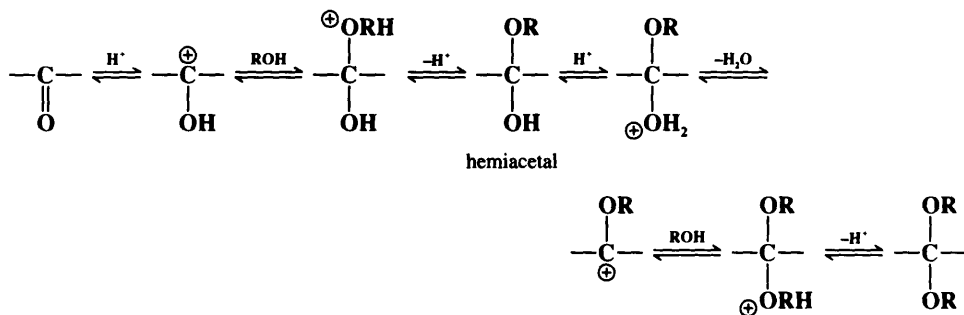
Acetals and ketals are formed by treatment of aldehydes and ketones, respectively, with alcohols in the presence of acid catalysts.[81] This reaction is reversible, and acetals and ketals can be hydrolyzed by treatment with acid (0-6). With small unbranched aldehydes the equilibrium lies to the right. If it is desired to prepare ketals, or acetals of larger molecules, 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.[82] The reaction in neither direction is catalyzed by bases, so most acetals and ketals are quite stable to bases, though they are easily hydrolyzed by acids. This makes this reaction 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.[83] 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.[84] Many functional groups may be present without being affected. 1,2-Glycols and 1,3-glycols form cyclic acetals and ketals, e.g.,

and these are often used to protect aldehydes and ketones.

The mechanism, which involves initial formation of a *hemiacetal*,[85] is the reverse of that given for acetal hydrolysis (0-6):

$$—\overset{\parallel}{\underset{O}{C}}— \ \overset{H^\cdot}{\rightleftharpoons} \ —\overset{\oplus}{\underset{OH}{C}}— \ \overset{ROH}{\rightleftharpoons} \ —\overset{\overset{\oplus}{ORH}}{\underset{OH}{C}}— \ \overset{-H^\cdot}{\rightleftharpoons} \ —\overset{OR}{\underset{OH}{C}}— \ \overset{H^\cdot}{\rightleftharpoons} \ —\overset{OR}{\underset{\oplus OH_2}{C}}— \ \overset{-H_2O}{\rightleftharpoons}$$

hemiacetal

$$—\overset{OR}{\underset{\oplus}{C}}— \ \overset{ROH}{\rightleftharpoons} \ —\overset{OR}{\underset{\oplus ORH}{C}}— \ \overset{-H^\cdot}{\rightleftharpoons} \ —\overset{OR}{\underset{OR}{C}}—$$

[81]For reviews, see Meskens *Synthesis* **1981**, 501-522; Schmitz; Eichhorn, in Patai *The Chemistry of the Ether Lingkage*; Wiley: New York, 1967, pp. 309-351.

[82]For many examples of each of these methods, see Meskens, Ref. 81, pp. 502-505.

[83]For other methods, see Caputo; Ferreri; Palumbo *Synthesis* **1987**, 386; Ott; Tombo; Schmid; Venanzi; Wang; Ward *Tetrahedron Lett.* **1989**, *30*, 6151, *New J. Chem.* **1990**, *14*, 495; Liao; Huang; Zhu *J. Chem. Soc., Chem. Commun.* **1990**, 493; Chan; Brook; Chaly *Synthesis* **1983**, 203.

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

[85]For a review of hemiacetals, see Hurd *J. Chem. Educ.* **1966**, *43*, 527-531.

In a study of the acid-catalyzed formation of the hemiacetal, Grunwald has shown[86] 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:[87]
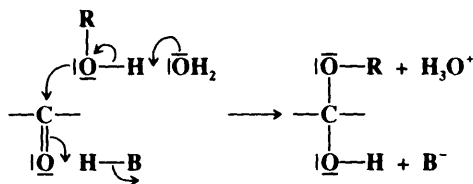

If the original aldehyde or ketone has an α hydrogen, it is possible for water to split out in that way and enol ethers can be prepared in this manner:
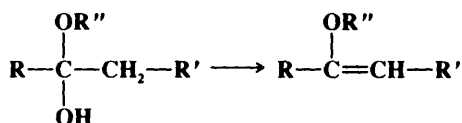
Similarly, treatment with an anhydride and a catalyst can give an enol ester.[88]

Hemiacetals themselves are no more stable than the corresponding hydrates (**6-1**). As with hydrates, hemiacetals of cyclopropanones[89] 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 **0-17**). 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,[90] in the presence of an acid catalyst (shown for an ortho ester):
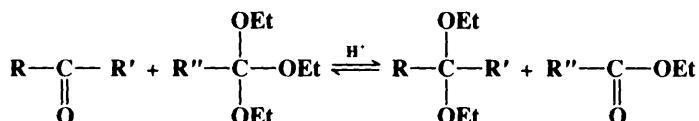
This method is especially useful for the conversion of ketones to ketals, since the direct reaction of a ketone with an alcohol often gives poor results. In another method, the substrate is treated with an alkoxysilane $ROSiMe_3$ in the presence of trimethylsilyl trifluoromethanesulfonate.[91]

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

[87]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 (**6-1**, mechanism *a*): Grunwald *J. Am. Chem. Soc.* **1985**, *107*, 4710. See also Sørensen; Pedersen; Pedersen; Kanagasabapathy; McClelland *J. Am. Chem. Soc.* **1988**, *110*, 5118; Leussing *J. Org. Chem.* **1990**, *55*, 666.

[88]For a list of catalysts, with references, see Ref. 64, p. 743.

[89]For a review, see Salaun *Chem. Rev.* **1983**, *83*, 619-632.

[90]For a review with respect to ortho esters, see DeWolfe *Carboxylic Ortho Ester Derivatives*; Academic Press: New York, 1970, pp. 154-164.

[91]Tsunoda; Suzuki; Noyori *Tetrahedron Lett.* **1980**, *21*, 1357; Kato; Iwasawa; Mukaiyama *Chem. Lett.* **1985**, 743. See also Torii; Takagishi; Inokuchi; Okumoto *Bull. Chem. Soc. Jpn.* **1987**, *60*, 775.

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:
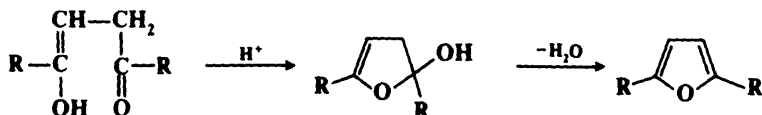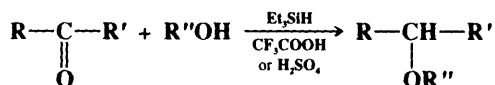

Similarly, 1,5-diketones give pyrans. Formic acid reacts with alcohols to give orthoformates.
   OS **I**, 1, 298, 364, 381; **II**, 137; **III**, 123, 387, 502, 536, 644, 731, 800; **IV**, 21, 479, 679; **V**, 5, 292, 303, 450, 539; **VI**, 567, 666, 954; **VII**, 59, 149, 168, 177, 241, 271, 297; **67**, 202. Also see OS **IV**, 558, 588; **V**, 25; **67**, 193.

6-7 Reductive Alkylation of Alcohols
    C-Hydro-O-alkyl-addition

$$R—\underset{\underset{O}{\|}}{C}—R' + R''OH \xrightarrow[\text{or } H_2SO_4]{\underset{CF_3COOH}{Et_3SiH}} R—\underset{\underset{OR''}{|}}{CH}—R'$$

Aldehydes and ketones can be converted to ethers by treatment with an alcohol and tri-ethylsilane in the presence of a strong acid[92] or by hydrogenation in alcoholic acid in the presence of platinum oxide.[93] The process can formally be regarded as addition of ROH to give a hemiacetal RR'C(OH)OR'', followed by reduction of the OH. In this respect it is similar to **6-15**. In a similar reaction, ketones can be converted to carboxylic esters (reductive acylation of ketones) by treatment with an acyl chloride and triphenyltin hydride.[94]

$$R—\underset{\underset{O}{\|}}{C}—R' + R''COCl \xrightarrow{Ph_3SnH} R—\underset{\underset{OCOR''}{|}}{CH}—R'$$
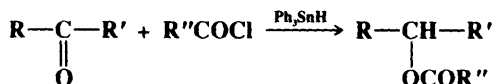
Ethers have also been prepared by the reductive dimerization of two molecules of an aldehyde or ketone (e.g., cyclohexanone → dicyclohexyl ether). This was accomplished by treatment of the substrate with a trialkylsilane and a catalyst.[95]

6-8 The Addition of Alcohols to Isocyanates
    N-Hydro-C-alkoxy-addition

$$R—N{=}C{=}O + R'OH \longrightarrow R—NH—\underset{\underset{OR'}{|}}{C}{=}O$$
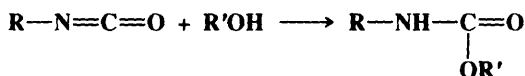
Carbamates (substituted urethans) are prepared when isocyanates are treated with alcohols. This is an excellent reaction, of wide scope, and gives good yields. Isocyanic acid HNCO gives unsubstituted carbamates. Addition of a second mole of HNCO gives *allophanates*.

$$HNCO + ROH \longrightarrow NH_2—\underset{\underset{OR}{|}}{C}{=}O \xrightarrow{HNCO} NH_2—\underset{\underset{O}{\|}}{C}—NH—\underset{\underset{OR}{|}}{C}{=}O$$

Allophanate
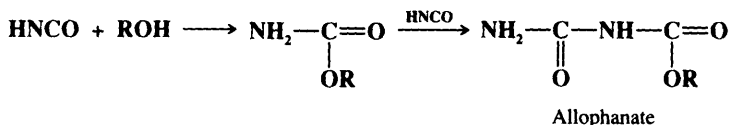
[92]Doyle; DeBruyn; Kooistra *J. Am. Chem. Soc.* **1972**, *94*, 3659.
    [93]Verzele; Acke; Anteunis *J. Chem. Soc.* **1963**, 5598. For still another method, see Loim; Parnes; Vasil'eva; Kursanov *J. Org. Chem. USSR* **1972**, *8*, 902.
    [94]Kaplan *J. Am. Chem. Soc.* **1966**, *88*, 4970.
    [95]Sassaman; Kotian; Prakash; Olah *J. Org. Chem.* **1987**, *52*, 4314. See also Kikugawa *Chem. Lett.* **1979**, 415.

Polyurethans are made by combining compounds with two NCO groups with compounds containing two OH groups. Isothiocyanates similarly give thiocarbamates[96] RNHCSOR', though they react slower than the corresponding isocyanates.

The details of the mechanism are poorly understood,[97] though the oxygen of the alcohol is certainly attacking the carbon of the isocyanate. Hydrogen bonding complicates the kinetic picture.[98] The addition of ROH to isocyanates can also be catalyzed by metallic compounds,[99] by light,[100] or, for tertiary ROH, by lithium alkoxides[101] or n-butyllithium.[102]

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

6-9 Alcoholysis of Nitriles
Alkoxy,oxo-de-nitrilo-tersubstitution

$$R—C≡N + R'OH \xrightarrow{\text{HCl}} R—\underset{\underset{OR'}{|}}{C}=NH_2^+ \quad Cl^- \xrightarrow[H^+]{H_2O} R—\underset{\underset{OR'}{|}}{C}=O$$
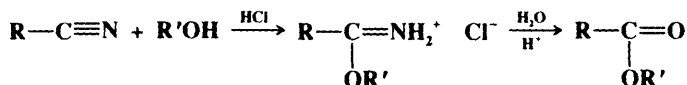
The addition of dry HCl to a mixture of a nitrile and an alcohol in the absence of water leads to the hydrochloride salt of an imino ester (imino esters are also called imidates and imino ethers). This reaction is called the *Pinner synthesis*.[103] The salt can be converted to the free imino ester by 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 aqueous HCl can be used and the need for gaseous HCl is eliminated. Imino esters can also be prepared from nitriles with basic catalysts.[104]

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 AlCl₃ to give carbamates:[105]

$$ClCN + 2ROH \xrightarrow[\text{or AlCl}_3]{\text{HCl}} ROCONH_2 + RCl$$
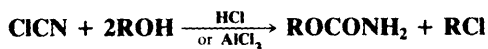
ROH can also be added to nitriles in another manner (**6-55**).
OS **I**, 5, 270; **II**, 284, 310; **IV**, 645; **VI**, 507; **67**, 193.

[96]For a review of thiocarbamates, see Walter; Bode *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 281-293 [*Angew. Chem.* *79*, 285-297].

[97]For reviews, see Satchell; Satchell, Ref. 46; Entelis; Nesterov *Russ. Chem. Rev.* **1966**, *35*, 917-930.

[98]See for example, Robertson; Stutchbury *J. Chem. Soc.* **1964**, 4000; Lammiman; Satchell *J. Chem. Soc., Perkin Trans. 2* **1972**, 2300, **1974**, 877; Donohoe; Satchell; Satchell *J. Chem. Soc., Perkin Trans. 2* **1990**, 1671. See also Sivakamasundari; Ganesan *J. Org. Chem.* **1984**, *49*, 720.

[99]For example, see Davies; Puddephatt *J. Chem. Soc. C* **1967**, 2663, **1968**, 1479; Hazzard; Lammiman; Poon; Satchell; Satchell *J. Chem. Soc., Perkin Trans. 2* **1985**, 1029; Duggan; Imagire *Synthesis* **1989**, 131.

[100]McManus; Bruner; Coble; Ortiz *J. Org. Chem.* **1977**, *42*, 1428.

[101]Bailey; Griffith *J. Org. Chem.* **1978**, *43*, 2690.

[102]Nikoforov; Jirovetz; Buchbauer *Liebigs Ann. Chem.* **1989**, 489.

[103]For a review, see Compagnon; Miocque *Ann. Chim. (Paris)* [14] *5*, 23-27, pp. 24-26. For a review of imino esters, see Neilson, in Patai *The Chemistry of Amidines and Imidates*; Wiley: New York, 1975, pp. 385-489.

[104]Schaefer; Peters *J. Org. Chem.* **1961**, *26*, 412.

[105]Bodrikov; Danova *J. Org. Chem. USSR* **1968**, *4*, 1611, **1969**, *5*, 1558; Fuks; Hartemink *Bull. Soc. Chim. Belg.* **1973**, *82*, 23.

6-10   The Formation of Xanthates
         S-Metallo-C-alkoxy-addition

$$S{=}C{=}S \ + \ ROH \xrightarrow{\text{NaOH}} RO{-}\underset{\underset{\displaystyle S}{\|}}{C}{-}S^{-} \ \ Na^{+}$$
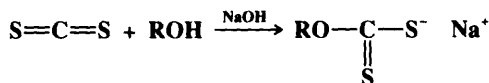
The addition of alcohols to carbon disulfide in the presence of a base produces xanthates.[106] The base is often OH⁻, but in some cases better results can be obtained by using methylsulfinyl carbanion $MeSOCH_2^-$.[107] If an alkyl halide RX is present, the xanthate ester ROCSSR' can be produced directly. In a similar manner, alkoxide ions add to CO_2 to give carbonate ester salts ROCOO⁻.

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

C.   Sulfur Nucleophiles

6-11   The Addition of H₂S and Thiols to Carbonyl Compounds
         O-Hydro-C-mercapto-addition[108]
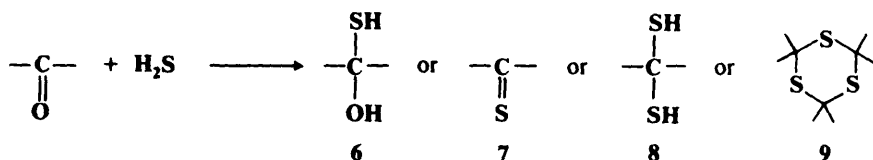
The addition of H_2S to an aldehyde or ketone can result in a variety of products. The most usual product is the trithiane **9.**[109] α-Hydroxy thiols (**6**) can be prepared from polychloro and polyfluoro aldehydes and ketones.[110] Apparently **6** are stable only when prepared from these compounds, and not even for all of them. Thioketones[2] (**7**) 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 tend to trimerize (to **9**) or to react with air. Thioaldehydes[111] are even less stable and simple ones[112] apparently have never been isolated, though t-BuCHS has been prepared in solution, where it exists for several hours at 20°C.[113] A high-yield synthesis of thioketones involves treatment of acyclic[114] ketones with 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide **10** (known as *Lawesson's*

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

[107]Meurling; Sjöberg; Sjöberg *Acta Chem. Scand.* **1972,** *26,* 279.

[108]This name applies to formation of **6.** Names for formation of **7, 8,** and **9,** are, respectively, **thioxo-de-oxo-bisubstitution, dimercapto-de-oxo-bisubstitution,** and **carbonyl-trithiane transformation.**

[109]Campaigne; Edwards *J. Org. Chem.* **1962,** *27,* 3760.

[110]Harris *J. Org. Chem.* **1960,** *25,* 2259.

[111]For a review of thioaldehydes, see Usov; Timokhina; Voronkov *Russ. Chem. Rev.* **1990,** *59,* 378-395.

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

[113]Vedejs; Perry *J. Am. Chem. Soc.* **1983,** *105,* 1683. See also Baldwin; Lopez *J. Chem. Soc., Chem. Commun.* **1982,** 1029.

[114]Cyclopentanone and cyclohexanone gave different products: Scheibye; Shabana; Lawesson; Rømming *Tetrahedron* **1982,** *38,* 993.
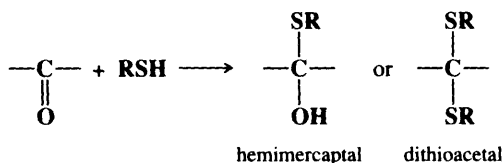
reagent[115]).[116] **10** also converts the C=O groups of amides and carboxylic esters[117] to C=S groups.[118] In similar reactions, bis(tricyclohexyltin)sulfide $(R_3Sn)_2S$ [R = cyclohexyl] and
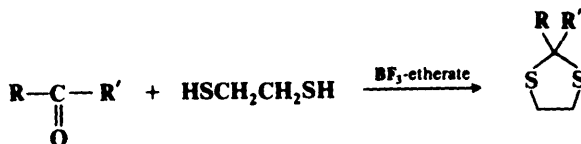
MeO—⟨○⟩—P—S—P—⟨○⟩—OMe

with S and S groups around the P atoms

10
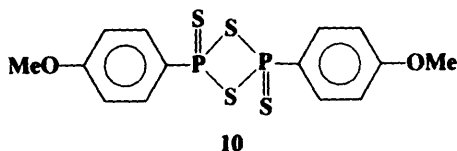
BCl_3 convert C=O groups of ketones, lactones, and lactams to C=S groups[119] and H_2S–Me_3SiCl–i-Pr_2NLi converts carboxylic esters to thiono esters.[120] Carboxylic acids RCOOH can be converted directly to dithiocarboxylic esters RCSSR',[120a] in moderate yield, with P_4S_{10} and a primary alcohol R'OH.[121] Thioketones can also be prepared by treatment of ketones with P_4S_{10},[122] and from oximes or various types of hydrazone (overall conversion C=N— → C=S).[123]

gem-Dithiols (**8**) are much more stable than the corresponding hydrates or α-hydroxy thiols.[124] They have been prepared by the treatment of ketones with H_2S under pressure[125] and under mild conditions with HCl as a catalyst.[126]

Thiols add to aldehydes and ketones to give hemimercaptals and dithioacetals. Hemimercaptals are ordinarily unstable,[127] though they are more stable than the corresponding

$$—\overset{|}{\underset{O}{C}}— + RSH \longrightarrow —\overset{SR}{\underset{OH}{C}}— \quad or \quad —\overset{SR}{\underset{SR}{C}}—$$

hemimercaptal   dithioacetal

hemiacetals and can be isolated in certain cases.[128] Dithioacetals, like acetals, are stable in the presence of bases, except that a strong base can remove the aldehyde proton, if there is one[129] (see **0-97**). A common method for the protection of ketones involves treatment

$$R—\overset{|}{\underset{O}{C}}—R' + HSCH_2CH_2SH \xrightarrow{BF_3\text{-etherate}} \overset{R\ R'}{\underset{}{\underset{S}{\diagdown}\underset{S}{\diagup}}}$$

[115]For reviews of this and related reagents, see Cava; Levinson *Tetrahedron* **1985**, *41*, 5061-5087; Cherkasov; Kutyrev; Pudovik *Tetrahedron* **1985**, *41*, 2567-2624. For the preparation of **10**, see Thomsen; Clausen; Scheibye; Lawesson *Org. Synth. VII*, 372.

[116]Pedersen; Scheibye; Nilsson; Lawesson *Bull. Soc. Chim. Belg.* **1978**, *87*, 223. For a study of the mechanism, see Rauchfuss; Zank *Tetrahedron Lett.* **1986**, *27*, 3445.

[117]For a review of thiono esters RC(=S)OR', see Jones; Bradshaw *Chem. Rev.* **1984**, *84*, 17-30.

[118]Scheibye; Pedersen; Lawesson *Bull. Soc. Chim. Belg.* **1978**, *87*, 229; Ghattas; El-Khrisy; Lawesson *Sulfur Lett.* **1982**, *1*, 69; Yde; Yousif; Pedersen; Thomsen; Lawesson *Tetrahedron* **1984**, *40*, 2047; Thomsen et al., Ref. 115.

[119]Steliou; Mrani *J. Am. Chem. Soc.* **1982**, *104*, 3104.

[120]Corey; Wright *Tetrahedron Lett.* **1984**, *25*, 2639.

[120a]For a review of dithiocarboxylic esters, see Kato; Ishida *Sulfur Rep.* **1988**, *8*, 155-323.

[121]Davy; Metzner *Chem. Ind. (London)* **1985**, 824.

[122]See, for example, Scheeren; Ooms; Nivard *Synthesis* **1973**, 149.

[123]See for example, Kimura; Niwa; Motoki *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2751; de Mayo; Petrašiūnas; Weedon *Tetrahedron Lett.* **1978**, 4621; Okazaki; Inoue; Inamoto *Tetrahedron Lett.* **1979**, 3673.

[124]For a review of the preparation of *gem*-dithiols, see Mayer; Hiller; Nitzschke; Jentzsch *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 370-373 [*Angew. Chem. 75*, 1011-1014].

[125]Cairns; Evans; Larchar; McKusick *J. Am. Chem. Soc.* **1952**, *74*, 3982.

[126]Ref. 109; Demuynck; Vialle *Bull. Soc. Chim. Fr.* **1967**, 1213.

[127]See, for example, Fournier; Lamaty; Nata; Roque *Tetrahedron* **1975**, *31*, 809.

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

[129]Truce; Roberts *J. Org. Chem.* **1963**, *28*, 961.

with ethanedithiol to give a cyclic dithioketal.[130] After subsequent reactions involving the R or R' group, the protecting group can then be removed by **0-6.** Alternatively, the dithioketal can be desulfurized with Raney nickel (**4-36**), giving the overall conversion C=O → CH$_2$. Dithioacetals can also be prepared from aldehydes or ketones by treatment with thiols in the presence of TiCl$_4$,[131] SiCl$_4$,[132] or polyphosphoric acid trimethylsilyl ester;[133] with a disulfide RSSR (R = alkyl or aryl),[134] or with methylthiotrimethylsilane MeSSiMe$_3$.[135]

If an aldehyde or ketone possesses an α hydrogen, it can be converted to the corresponding enol thioether by treatment with a thiol in the presence of TiCl$_4$:[136]

$$\underset{\displaystyle O}{\overset{\displaystyle \|}{-C}}-CH- + RSH \xrightarrow{\text{TiCl}_4} -C=\underset{\displaystyle SR}{\overset{\displaystyle |}{C}}-$$
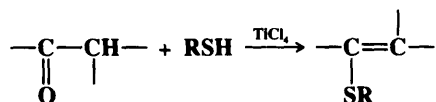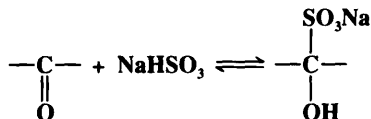
Aldehydes and ketones have been converted to sulfides by treatment with thiols and pyridine–borane, RCOR' + R''SH $\xrightarrow{\text{BH}_3}$ RR'CHSR'',[137] in a reductive alkylation reaction, analogous to **6-7.**

OS **II,** 610; **IV,** 927; **VI,** 109; **VII,** 124, 372. Also see OS **III,** 332; **IV,** 967; **V,** 780; **VI,** 556; **65,** 215.

6-12   Formation of Bisulfite Addition Products
       O-**Hydro-***C*-**sulfonato-addition**

$$\underset{\displaystyle O}{\overset{\displaystyle \|}{-C}}- + \text{NaHSO}_3 \;\rightleftharpoons\; \underset{\displaystyle OH}{\overset{\displaystyle SO_3Na}{-C-}}$$

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[138])[139] 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.[140]

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

[130]For a review, see Olsen; Currie, in Patai *The Chemistry of the Thiol Group*, pt. 2; Wiley: New York, 1974, pp. 521-532.
[131]Kumar; Dev *Tetrahderon Lett.* **1983,** 24, 1289.
[132]Ku; Oh *Synth. Commun.* **1989,** 433.
[133]Kakimoto; Seri; Imai *Synthesis* **1987,** 164.
[134]Tazaki; Takagi *Chem. Lett.* **1979,** 767.
[135]Evans; Grimm; Truesdale *J. Am. Chem. Soc.* **1975,** 97, 3229.
[136]Mukaiyama; Saigo *Chem. Lett.* **1973,** 479.
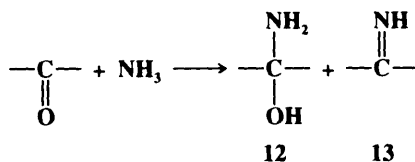[137]Kikugawa *Chem. Lett.* **1981,** 1157.
[138]For cleavage with ion-exchange resins, see Khusid; Chizhova *J. Org. Chem. USSR* **1985,** 21, 37.
[139]For a discussion of the mechanism, see Young; Jencks *J. Am. Chem. Soc.* **1978,** 100, 1228.
[140]The reaction has also been used to protect an aldehyde group in the presence of a keto group: Chihara; Wakabayashi; Taya *Chem. Lett.* **1981,** 1657.

D. Attack by NH₂, NHR, or NR₂ (Addition of NH₃, RNH₂, R₂NH)

6-13 The Addition of Ammonia to Aldehydes and Ketones
Formaldehyde–hexamethylenetetramine transformation

$$HCHO + NH_3 \longrightarrow \text{(structure)} $$

11
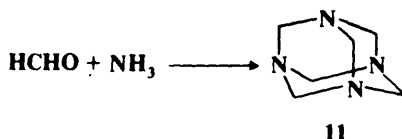
The addition of ammonia[141] to aldehydes or ketones does not generally give useful products. According to the pattern followed by analogous nucleophiles, the initial products would be expected to be *hemiaminals*[142] (also called "aldehyde ammonias") (**12**) and/or imines (**13**):

$$\underset{\underset{O}{\|}}{-C-} + NH_3 \longrightarrow \underset{\underset{OH}{|}}{\overset{\overset{NH_2}{|}}{-C-}} + \underset{}{\overset{\overset{NH}{\|}}{-C-}}$$

12   **13**

However, these compounds are generally unstable. Most imines with a hydrogen on the nitrogen spontaneously polymerize.[143] Stable hemiaminals can be prepared from polychlorinated and polyfluorinated aldehydes and ketones, and diaryl ketones do give stable imines $Ar_2C\!\!=\!\!NH$.[144] Aside from these, when stable compounds *are* prepared in this reaction, they are the result of combinations and condensations of one or more molecules of **12** and/or **13** with each other or with additional molecules of ammonia or carbonyl compound. The most important example of such a product is hexamethylenetetramine[145] (**11**), prepared from ammonia and formaldehyde.[146] Aromatic aldehydes give hydrobenzamides $ArCH(N\!\!=\!\!CHAr)_2$ derived from three molecules of aldehyde and two of ammonia.[147]

OS **II**, 214, 219; **IV**, 451; **VI**, 664, 976. Also see OS **III**, 471; **V**, 897.

6-14 The Addition of Amines to Aldehydes and Ketones
Alkylimino-de-oxo-bisubstitution

$$\underset{\underset{O}{\|}}{-C-} + RNH_2 \longrightarrow \underset{\underset{N-R}{\|}}{-C-}$$
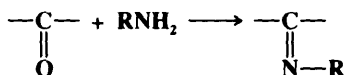
Primary, secondary, and tertiary amines can add to aldehydes[148] and ketones to give different kinds of products. Primary amines give imines.[149] In contrast to imines in which the nitrogen

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[141]For a review of this reagent in organic synthesis, see Jeyaraman, in Pizey *Synthetic Reagents*, vol. 5; Wiley: New York, 1983, pp. 9-83.

[142]These compounds have been detected by ¹³C nmr: Chudek; Foster; Young *J. Chem. Soc., Perkin Trans. 2* **1985**, 1285.

[143]Methanimine CH₂=NH is stable in solution for several hours at −95°C, but rapidly decomposes at −80°C: Braillon; Lasne; Ripoll; Denis *Nouv. J. Chim.* **1982**, *6*, 121. See also Bock; Dammel *Chem. Ber.* **1987**, *120*, 1961.

[144]Verardo; Giumanini; Strazzolini; Poiana *Synth. Commun.* **1988**, *18*, 1501.

[145]For a review of this compound, see Blažević; Kolbah; Belin; Šunjić; Kajfež *Synthesis* **1979**, 161-176.
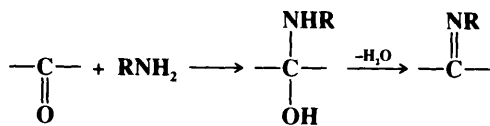
[146]For a discussion of the mechanism, see Nielsen; Moore; Ogan; Atkins *J. Org. Chem.* **1979**, *44*, 1678.

[147]Ogata; Kawasaki; Okumura *J. Org. Chem.* **1964**, *29*, 1985; Crowell; McLeod *J. Org. Chem.* **1967**, *32*, 4030.

[148]For a review of the reactions between amines and formaldehyde, see Farrar *Rec. Chem. Prog.* **1968**, *29*, 85-101.

[149]For reviews of reactions of carbonyl compounds leading to the formation of C=N bonds, see Dayagi; Degani, in Patai *The Chemistry of the Carbon–Nitrogen Double Bond*; Ref. 40, pp. 64-83; Reeves, in Patai, Ref. 2, pp. 600-614.

is attached to a hydrogen (**6-13**), 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. The reaction is straightforward and proceeds in high yields. The initial N-substituted hemiaminals[150] lose water to give the stable Schiff bases:

$$ -\overset{\displaystyle ||}{\underset{\displaystyle O}{C}}-\ +\ RNH_2\ \longrightarrow\ -\overset{\displaystyle NHR}{\underset{\displaystyle OH}{C}}-\ \xrightarrow{-H_2O}\ -\overset{\displaystyle NR}{\underset{\displaystyle}{C}}- $$

In general, ketones react more slowly than aldehydes, and higher temperatures and longer reaction times are often required.[151] 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 $TiCl_4$,[152] or with a molecular sieve.[153]

The reaction is often used to effect ring closure.[154] The *Friedländer quinoline synthesis*[155] is an example:
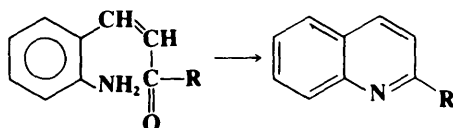
Pyrylium ions react with ammonia or primary amines to give pyridinium ions[156] (see p. 354).

When secondary amines are added to aldehydes or ketones, the initially formed N,N-disubstituted hemiaminals (**14**) cannot lose water in the same way, and it is possible to isolate them.[157] However, they are generally unstable, and under the reaction conditions
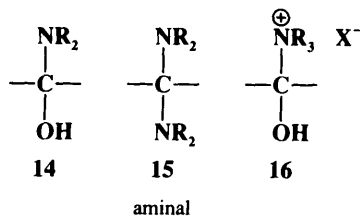
usually react further. If no α hydrogen is present, **14** is converted to the more stable *aminal* (**15**).[158] However, if an α hydrogen is present, water (from **14**) or RNH_2 (from **15**) can be lost in that direction to give an enamine:[159]

[150]Some of these have been observed spectrally; see Forlani; Marianucci; Todesco *J. Chem. Res. (S)* **1984**, 126.
[151]For improved methods, see Morimoto; Sekiya *Chem. Lett.* **1985**, 1371; Eisch; Sanchez *J. Org. Chem.* **1986**, *51*, 1848.
[152]Weingarten; Chupp; White *J. Org. Chem.* **1967**, *32*, 3246.
[153]Bonnett; Emerson *J. Chem. Soc.* **1965**, 4508; Roelofsen; van Bekkum *Recl. Trav. Chim. Pays-Bays* **1972**, *91*, 605.
[154]For a review of such ring closures, see Katritzky; Ostercamp; Yousaf *Tetrahedron* **1987**, *43*, 5171-5186.
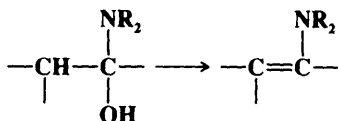[155]For a review, see Cheng; Yan *Org. React.* **1982**, *28*, 37-201.
[156]For a review, see Zvezdina; Zhadonva; Dorofeenko *Russ. Chem. Rev.* **1982**, *51*, 469-484.
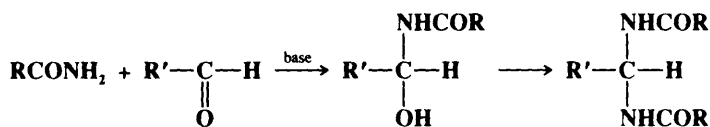[157]For example, see Duhamel; Cantacuzène *Bull. Soc. Chim. Fr.* **1962**, 1843.
[158]For a review of aminals, see Duhamel, in Patai *The Chemistry of Functional Groups, Supplement F*, pt. 2; Wiley: New York, 1982, pp. 849-907.
[159]For reviews of the preparation of enamines, see Haynes; Cook, in Cook, Ref. 45, pp. 103-163; Pitacco; Valentin, in Patai, Ref. 158, pt. 1, pp. 623-714.

$$\underset{\overset{|}{\text{OH}}}{-\overset{\overset{\displaystyle NR_2}{|}}{\text{CH}}-\overset{|}{\text{C}}-} \longrightarrow -\overset{\overset{\displaystyle NR_2}{|}}{\text{C}}=\overset{|}{\text{C}}-$$

This is the most common method[160] 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,[161] but molecular sieves can also be used.[162] Secondary amine perchlorates react with aldehydes and ketones to give iminium salts (**2**, p. 885).[163] Tertiary amines can only give salts (**16**).
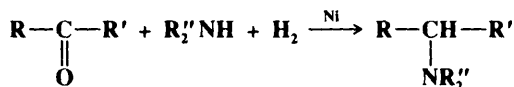
Amides can add to aldehydes in the presence of bases (so the nucleophile is actually RCONH⁻) or acids to give acylated amino alcohols, which often react further to give alkylidene or arylidene bisamides:[164]

$$\text{RCONH}_2 + \text{R}'-\underset{\overset{\|}{\text{O}}}{\text{C}}-\text{H} \xrightarrow{\text{base}} \text{R}'-\underset{\overset{|}{\text{OH}}}{\overset{\overset{\displaystyle NHCOR}{|}}{\text{C}}}-\text{H} \longrightarrow \text{R}'-\underset{\overset{|}{\text{NHCOR}}}{\overset{\overset{\displaystyle NHCOR}{|}}{\text{C}}}-\text{H}$$

If the R' group contains an α hydrogen, water may split out.

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; **65**, 108, 119, 146, 183; **66**, 133, 142, 203; **68**, 206. Also see OS **IV**, 283, 464; **VII**, 197; **66**, 52; **69**, 55, 158.

6-15 Reductive Alkylation of Ammonia or Amines
Hydro,dialkylamino-de-oxo-bisubstitution

$$\text{R}-\underset{\overset{\|}{\text{O}}}{\text{C}}-\text{R}' + \text{R}_2''\text{NH} + \text{H}_2 \xrightarrow{\text{Ni}} \text{R}-\underset{\overset{|}{\text{NR}_2''}}{\text{CH}}-\text{R}'$$

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), *reductive alkylation* of ammonia or the amine (or *reductive amination* of the carbonyl compound) takes place.[165] 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:[166]

---

[160]For another method, see Katritzky; Long; Lue; Jozwiak *Tetrahedron* **1990**, *46*, 8153.

[161]For example, TiCl₄: White; Weingarten *J. Org. Chem.* **1967**, *32*, 213; Kuo; Daly *J. Org. Chem.* **1970**, *35*, 1861; Nilsson; Carlson *Acta Chem. Scand. Sect. B* **1984**, *38*, 523.
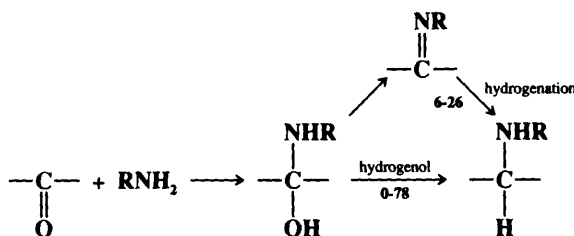
[162]Brannock; Bell; Burpitt; Kelly *J. Org. Chem.* **1964**, *29*, 801; Taguchi; Westheimer *J. Org. Chem.* **1971**, *36*, 1570; Roelofsen; van Bekkum, Ref. 153; Carlson; Nilsson; Strömqvist *Acta Chem. Scand., Ser. B* **1983**, *37*, 7.

[163]Leonard; Paukstelis *J. Org. Chem.* **1964**, *28*, 3021.

[164]For reviews, see Challis; Challis, in Zabicky, Ref. 65, pp. 754-759; Zaugg; Martin *Org. React.* **1965**, *14*, 52-269, pp. 91-95, 104-112. For a discussion, see Gilbert *Synthesis* **1972**, 30.

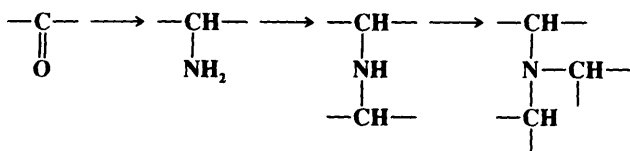[165]For reviews, see Rylander *Hydrogenation Methods*; Academic Press: New York, 1985, pp. 82-93; Klyuev; Khidekel *Russ. Chem. Rev.* **1980**, *49*, 14-27; Rylander, *Catalytic Hydrogenation over Platinum Metals*; Academic Press: New York, 1967, pp. 291-303.

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

$$
\begin{array}{c}
\overset{\displaystyle NR}{\underset{\displaystyle 6\text{-}26}{\overset{\displaystyle \|}{-C-}}} \\
\nearrow \qquad \searrow \text{hydrogenation}
\end{array}
$$

$$
\underset{\displaystyle O}{-\overset{\displaystyle \|}{C}-} \; + \; RNH_2 \;\longrightarrow\; \underset{\displaystyle OH}{-\overset{\displaystyle NHR}{\overset{|}{C}}-} \; \xrightarrow[\displaystyle 0\text{-}78]{\text{hydrogenol}} \; \underset{\displaystyle H}{-\overset{\displaystyle NHR}{\overset{|}{C}}-}
$$

For ammonia and primary amines there are two possible pathways, but when secondary amines are involved, only the hydrogenolysis pathway is possible. Other reducing agents[167] can be used instead of hydrogen and a catalyst, among them zinc and HCl, sodium cyanoborohydride $NaBH_3CN$,[168] sodium triacetoxyborohydride,[169] sodium borohydride,[170] iron pentacarbonyl and alcoholic KOH,[171] BH_3–pyridine,[172] and formic acid. When the last is used, the process is called the *Wallach reaction*. 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*. It is possible to use ammonium (or amine) salts of formic acid,[173] or formamides, as a substitute for the Wallach conditions. This method is called the *Leuckart reaction*,[174] and in this case the products obtained are often the N-formyl derivatives of the amines instead of the free amines. Primary and secondary amines can be N-ethylated (e.g., $ArNHR \rightarrow ArNREt$) by treatment with $NaBH_4$ in acetic acid.[175]

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:

$$
\underset{\displaystyle O}{-\overset{\displaystyle \|}{C}-} \;\longrightarrow\; \underset{\displaystyle NH_2}{-\overset{|}{C}H-} \;\longrightarrow\; \underset{\underset{\displaystyle -CH-}{\displaystyle |}}{\underset{\displaystyle NH}{-\overset{|}{C}H-}} \;\longrightarrow\; \underset{\underset{\displaystyle -CH-}{\displaystyle |}}{\underset{\displaystyle N-CH-}{-\overset{|}{C}H-}}
$$

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).

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

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[167]For a list of many of these, with references, see Ref. 64, pp. 421-423.

[168]Borch; Bernstein; Durst *J. Am. Chem. Soc.* **1971**, *93*, 2897; Mattson; Pham; Leuck; Cowen *J. Org. Chem.* **1990**, *55*, 2552. See also Barney; Huber; McCarthy *Tetrahedron Lett.* **1990**, *31*, 5547. For reviews of $NaBH_3CN$, see Hutchins; Natale *Org. Prep. Proced. Int.* **1979**, *11*, 201-246; Lane *Synthesis* **1975**, 135-146.

[169]Abdel-Magid; Maryanoff; Carson *Tetrahedron Lett.* **1990**, *31*, 5595.

[170]Schellenberg *J. Org. Chem.* **1963**, *28*, 3259; Gribble; Nutaitis *Synthesis* **1987**, 709.

[171]Watanabe; Yamashita; Mitsudo; Tanaka; Takegami *Tetrahedron Lett.* **1974**, 1879; Watanabe; Mitsudo; Yamashita; Shim; Takegami *Chem. Lett.* **1974**, 1265.

[172]Pelter; Rosser; Mills *J. Chem. Soc., Perkin Trans. 1* **1984**, 717.

[173]For a review of ammonium formate in organic synthesis, see Ram; Ehrenkaufer *Synthesis* **1988**, 91-95.

[174]For a review, see Moore, *Org. React.* **1949**, *5*, 301-330; for discussions of the mechanism, see Lukasiewicz *Tetrahedron* **1963**, *19*, 1789; Ito; Oba; Sekiya *Bull. Chem. Soc. Jpn.* **1976**, *49*, 2485; Awachie; Agwada *Tetrahedron* **1990**, *46*, 1899.

[175]Gribble; Lord; Skotnicki; Dietz; Eaton; Johnson *J. Am. Chem. Soc.* **1974**, *96*, 7812; Gribble; Jasinski; Pellicone; Panetta *Synthesis* **1978**, 766. See also Marchini; Liso; Reho; Liberatore; Moracci *J. Org. Chem.* **1975**, *40*, 3453. For a review, see Gribble; Nutaitis *Org. Prep. Proced. Int.* **1985**, *17*, 317-384, pp. 336-350.
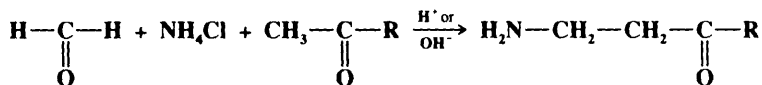
been prepared by both possible procedures: 2 moles of ammonia and 1 mole of aldehyde or ketone, and 1 mole of primary amine and 1 mole of carbonyl compound, the latter method being better for all but aromatic aldehydes. Tertiary amines can be prepared in three ways, but the method is seldom carried out with 3 moles of ammonia and 1 mole of carbonyl compound. Much more often they are prepared from primary or secondary amines.[176] The most common method for this purpose is the Eschweiler-Clarke procedure, i.e., treatment of the primary or secondary amine with formaldehyde and formic acid. Amines of the form $RNMe_2$ and R_2NMe are prepared in this manner.[177] Another method for accomplishing the conversions $RNH_2 \rightarrow RNMe_2$ and $R_2NH \rightarrow R_2NMe$ is to treat the amine with aqueous formaldehyde and $NaBH_4$[178] or $NaBH_3CN$.[179]

Reductive alkylation has also been carried out on nitro, nitroso, azo, and other compounds that are reduced in situ to primary or secondary amines.
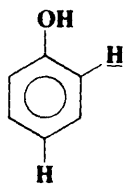
OS **I**, 347, 528, 531; **II**, 503; **III**, 328, 501, 717, 723; **IV**, 603; **V**, 552; **VI**, 499; **VII**, 27.

6-16   The Mannich Reaction
Acyl,amino-de-oxo-bisubstitution, etc.

$$H\!-\!\underset{\underset{O}{\|}}{C}\!-\!H \;+\; NH_4Cl \;+\; CH_3\!-\!\underset{\underset{O}{\|}}{C}\!-\!R \;\xrightarrow[OH^-]{H^+ \text{ or}}\; H_2N\!-\!CH_2\!-\!CH_2\!-\!\underset{\underset{O}{\|}}{C}\!-\!R$$

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.[180] This can formally be considered as an addition of ammonia to give H_2NCH_2OH, followed by a nucleophilic substitution. Instead of ammonia, the reaction can be carried out with salts of primary or secondary amines,[181] or with amides,[182] in which cases the product is substituted on the nitrogen with R, R_2, and RCO, respectively. Arylamines do not normally give the reaction. The product is referred to as a *Mannich base*. Many active hydrogen compounds give the reaction. Among these are the following types, with the active hydrogen underlined:

$$-\underset{|}{\overset{|}{C}}H\!-\!COR \text{ (or H)} \quad -\underset{|}{\overset{|}{C}}H\!-\!COOR \text{ (or H)} \quad -\underset{|}{\overset{|}{C}}H\!-\!NO_2 \quad -\underset{|}{\overset{|}{C}}H\!-\!CN$$

$$RC\!\equiv\!CH \quad HCN \quad ROH \quad RSH$$
See **6-50**

See **1-25**

---

[176]For a review of the preparation of tertiary amines by reductive alkylation, see Spialter; Pappalardo *The Acyclic Aliphatic Tertiary Amines*; Macmillan: New York, 1965, pp. 44-52.

[177]For a discussion, see Pine; Sanchez *J. Org. Chem.* **1971**, *36*, 829.

[178]Sondengam; Hentchoya Hémo; Charles *Tetrahedron Lett.* **1973**, 261.

[179]Borch; Hassid *J. Org. Chem.* **1972**, *37*, 1673; Kapnang; Charles; Sondengam; Hentchoya Hémo *Tetrahedron Lett.* **1977**, 3469. See also Ref. 168.

[180]For reviews, see Tramontini; Angiolini *Tetrahedron* **1990**, *46*, 1791-1837; Gevorgyan; Agababyan; Mndzhoyan *Russ. Chem. Rev.* **1984**, *53*, 561-581; Tramontini *Synthesis* **1973**, 703-775; House *Modern Synthetic Reactions*, 2nd ed.; W.A. Benjamin: New York, 1972, pp. 654-660. For reviews of Mannich reactions in which the active-hydrogen component is a thiol, see Massy *Synthesis* **1987**, 589-603; Dronov; Nikitin *Russ. Chem. Rev.* **1985**, *54*, 554-561; in which it is a nitro compound, see Baer; Urbas, in Feuer *The Chemistry of the Nitro and Nitroso Groups*; Wiley: New York, 1970, pp. 117-130. For reviews on the reactions of Mannich bases, see Tramontini; Angeloni, cited above; Gevorgyan; Agababyan; Mndzhoyan *Russ. Chem. Rev.* **1985**, *54*, 495-514.

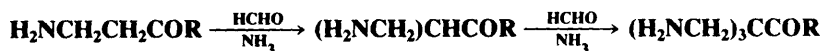[181]For a review where the amine component is an amino acid, see Agababyan; Gevorgyan; Mndzhoyan *Russ. Chem. Rev.* **1982**, *51*, 387-396.

[182]Hellmann, *Angew. Chem.* **1957**, *69*, 463, *Newer Methods Prep. Org. Chem.* **1963**, *2*, 277-302.

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, e.g.,

$$\text{H}_2\text{NCH}_2\text{CH}_2\text{COR} \xrightarrow[\text{CH}_3\text{COR}]{\text{HCHO}} \text{HN(CH}_2\text{CH}_2\text{COR)}_2 \xrightarrow[\text{CH}_3\text{COR}]{\text{HCHO}} \text{N(CH}_2\text{CH}_2\text{COR)}_3$$

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, e.g,

$$\text{H}_2\text{NCH}_2\text{CH}_2\text{COR} \xrightarrow[\text{NH}_3]{\text{HCHO}} \text{(H}_2\text{NCH}_2)\text{CHCOR} \xrightarrow[\text{NH}_3]{\text{HCHO}} \text{(H}_2\text{NCH}_2)_3\text{CCOR}$$

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

$$\text{H}_2\text{NCH}_2\text{CH}_2\text{COR} + \text{HCHO} \longrightarrow \text{H}_2\text{C}{=}\text{NCH}_2\text{CH}_2\text{COR}$$
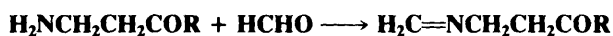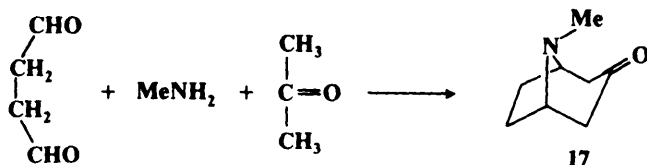
Sometimes it is possible to obtain these products of further condensation as the main products of the reaction. At other times they are side products.

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, etc.:

$$\text{H}_2\text{NCH}_2\text{CH}_2\text{COR} \xrightarrow{\Delta} \text{H}_2\text{C}{=}\text{CHCOR}$$
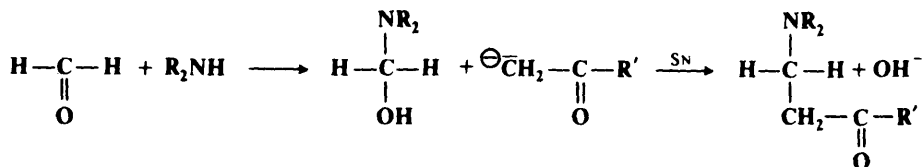
The Mannich reaction is an important biosynthetic route to natural products, mainly alkaloids, and some of these routes have been duplicated in the laboratory. A classic example is the synthesis of tropinone (**17**) by Robinson in 1917. Robinson synthesized tropinone by a Mannich reaction involving succindialdehyde, methylamine, and acetone:[183]

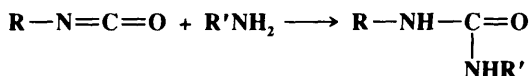Studies of the reaction kinetics have led to the following proposals for the mechanism of the Mannich reaction.[184]

The base-catalyzed reaction

[183]Robinson *J. Chem. Soc.* **1917**, *111*, 762.
[184]Cummings; Shelton *J. Org. Chem.* **1960**, *25*, 419.

The acid-catalyzed reaction

$$H-\underset{\underset{O}{\|}}{C}-H \ + \ R_2NH \ \longrightarrow \ H-\underset{\underset{OH}{|}}{\overset{\overset{NR_2}{|}}{C}}-H \ \underset{-H_2O}{\overset{H^+}{\rightleftharpoons}} \ \underset{\mathbf{18}}{H-\overset{\overset{\oplus NR_2}{\|}}{C}-H} \ + \ \underset{\underset{OH}{|}}{CH_2{=}C-R'} \ \longrightarrow$$

$$H-\underset{\underset{\underset{\underset{R'}{|}}{C=OH}}{\overset{\overset{NR_2}{|}}{\underset{CH_2}{|}}}}{\overset{\overset{NR_2}{|}}{C}}-H \ \xrightarrow{-H^+} \ H-\underset{\underset{\underset{\underset{R'}{|}}{C=O}}{\overset{\overset{NR_2}{|}}{\underset{CH_2}{|}}}}{\overset{\overset{NR_2}{|}}{C}}-H$$

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 **2-4**. There is kinetic evidence for the intermediacy of the iminium ion (**18**).[185]

When it is desired to use an unsymmetrical ketone as the active-hydrogen component, it is possible to get two products. Regioselectivity has been obtained by treatment of the ketone with preformed iminium ions:[186] the use of $Me_2\overset{\oplus}{N}{=}CH_2$ CF_3COO^- in CF_3COOH gives substitution at the more highly substituted position, while with iso-$Pr_2\overset{\oplus}{N}{=}CH_2$ ClO_4^- the reaction takes place at the less highly substituted position.[187] The preformed iminium compound dimethyl(methylene)ammonium iodide $CH_2{=}NMe_2{}^+$ I^-, called *Eschenmoser's salt*,[188] has also been used in Mannich reactions.[189]

Another type of preformed reagent (**20**) has been used to carry out diastereoselective Mannich reactions. The lithium salts **19** are treated with $TiCl_4$ to give **20**, which is then treated with the enolate of a ketone.[190]

$$R-\underset{\underset{O}{\|}}{C}-H \ \xrightarrow{R_2'NLi} \ \underset{\mathbf{19}}{R-\underset{\underset{OLi}{|}}{CH}-NR_2'} \ \xrightarrow{TiCl_4} \ \underset{\mathbf{20}}{R-\underset{\underset{OTiCl_3}{|}}{CH}-NR_2'} \ \longrightarrow$$

Also see **6-50** and **1-25**.
OS **III**, 305; **IV**, 281, 515, 816; **VI**, 474, 981, 987; **VII**, 34. See also OS **68**, 188.

[185]Benkovic; Benkovic; Comfort *J. Am. Chem. Soc.* **1969**, *91*, 1860.
[186]For earlier use of preformed iminium ions in the Mannich reaction, see Ahond; Cavé; Kan-Fan; Husson; de Rostolan; Potier *J. Am. Chem. Soc.* **1968**, *90*, 5622; Ahond; Cavé; Kan-Fan; Potier *Bull. Soc. Chim. Fr.* **1970**, 2707; Ref. 188.
[187]Jasor; Luche; Gaudry; Marquet *J. Chem. Soc., Chem. Commun.* **1974**, 253; Gaudry; Jasor; Khac *Org. Synth.* *VI*, 474.
[188]Schreiber; Maag; Hashimoto; Eschenmoser *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 330 [*Angew. Chem. 83*, 355].
[189]See Holy; Fowler; Burnett; Lorenz *Tetrahedron* **1979**, *35* 613; Bryson; Bonitz; Reichel; Dardis *J. Org. Chem.* **1980**, *45*, 524, and references cited in these papers.
[190]Seebach; Betschart; Schweizer *Helv. Chim. Acta* **1984**, *67*, 1593; Seebach; Schiess; Schweizer *Chimia* **1985**, *39*, 272. See also Heaney; Papageorgiou; Wilkins *J. Chem. Soc., Chem. Commun.* **1988**, 1161; Katritzky; Harris *Tetrahedron* **1990**, *46*, 987.

6-17   The Addition of Amines to Isocyanates
          N-Hydro-*C*-alkylamino-addition

$$R-N=C=O + R'NH_2 \longrightarrow R-NH-\underset{\underset{\displaystyle NHR'}{|}}{C}=O$$
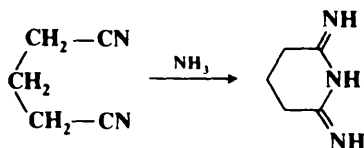
Ammonia and primary and secondary amines can be added to isocyanates[191] to give substituted ureas.[192] Isothiocyanates give thioureas. This is an excellent method for the preparation of ureas and thioureas, and these compounds are often used as derivatives for primary and secondary amines. Isocyanic 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.[193]

OS **II**, 79; **III**, 76, 617, 735; **IV**, 49, 180, 213, 515, 700; **V**, 555, 801, 802, 967; **VI**, 936, 951; **65**, 173.

6-18   The Addition of Ammonia or Amines to Nitriles
          N-Hydro-*C*-amino-addition

$$R-C\equiv N + NH_3 \xrightarrow[\text{pressure}]{\text{NH}_4\text{Cl}} R-\underset{\underset{\displaystyle NH_2}{|}}{C}=NH_2^+ \quad Cl^-$$

Unsubstituted amidines (in the form of their salts) can be prepared by addition of ammonia to nitriles.[194] Many amidines have been made in this way. Dinitriles of suitable chain length can give imidines:[195]

Primary and secondary amines can be used instead of ammonia, to give substituted amidines, but only if the nitrile contains electron-withdrawing groups; e.g., Cl_3CCN gives the reaction. Ordinary nitriles do not react, and, in fact, acetonitrile is often used as a solvent in this reaction.[196] However, ordinary nitriles can be converted to amidines by treatment with an alkylchloroaluminum amide $MeAl(Cl)NR_2$ (R = H or Me).[197] The addition of ammonia to cyanamide NH_2CN gives guanidine $(NH_2)_2C=NH$.

If water is present, and a ruthenium complex catalyst is used, the addition of a

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[191]For a review of the mechanism, see Satchell; Satchell, Ref. 46.
[192]For a review of substituted ureas, see Vishnyakova; Golubeva; Glebova *Russ. Chem. Rev.* **1985**, *54*, 249-261.
[193]For a history of the investigation of the mechanism of the Wöhler synthesis, see Shorter, *Chem. Soc. Rev.* **1978**, *7*, 1-14. See also Williams; Jencks *J. Chem. Soc., Perkin Trans. 2* **1974**, 1753, 1760; Hall; Watts *Aust. J. Chem.* **1977**, *30*, 781, 903.
[194]For reviews of amidines, see Granik *Russ. Chem. Rev.* **1983**, *52*, 377-393; Gautier; Miocque; Farnoux, in Patai, Ref. 103, pp. 283-348.
[195]Elvidge; Linstead; Salaman *J. Chem. Soc.* **1959**, 208.
[196]Grivas; Taurins *Can. J. Chem.* **1961**, *39*, 761.
[197]Garigipati *Tetrahedron Lett.* **1990**, *31*, 1969.

primary or secondary amine to a nitrile gives an amide: $RCN + R'NHR'' + H_2O \rightarrow$
$RCONR'R'' + NH_3$ (R'' may be H).[198]

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

6-19 The Addition of Amines to Carbon Disulfide and Carbon Dioxide
**S-Metallo-C-alkylamino-addition**

$$S{=}C{=}S + RNH_2 \xrightarrow{\text{base}} RNH{-}\underset{\underset{S}{\|}}{C}{-}S^-$$
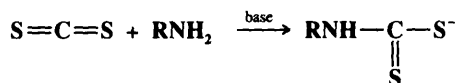
Salts of dithiocarbamic acid can be prepared by the addition of primary or secondary amines
to carbon disulfide.[199] This reaction is similar to **6-10**. H_2S can be eliminated from the product,
directly or indirectly, to give isothiocyanates RNCS. Isothiocyanates can be obtained directly
by the reaction of primary amines and CS_2 in pyridine in the presence of dicyclohexylcar-
bodiimide.[200] 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:[201]

$$RNH_2 + CO_2 \xrightarrow[\text{HPO(OPh)}_2]{\text{pyridine}} RHN{-}\underset{\underset{O}{\|}}{C}{-}NHR$$
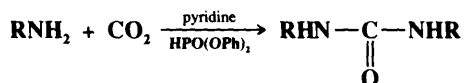
OS **I**, 447; **III**, 360, 394, 599, 763; **V**, 223.

E. Other Nitrogen Nucleophiles

6-20 The Addition of Hydrazine Derivatives to Carbonyl Compounds
Hydrazono-de-oxo-bisubstitution

$$-\underset{\underset{O}{\|}}{C}{-} \xrightarrow{RNHNH_2} -\underset{\underset{N{-}NHR}{\|}}{C}{-}$$
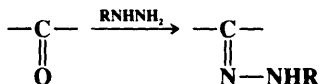
The product of condensation of a hydrazine and an aldehyde or ketone is called a *hydrazone*.
Hydrazine itself gives hydrazones only with aryl ketones. With other aldehydes and ketones,
either no useful product can be isolated, or the remaining NH_2 group condenses with a
second mole of carbonyl compound to give an *azine*. This type of product is especially
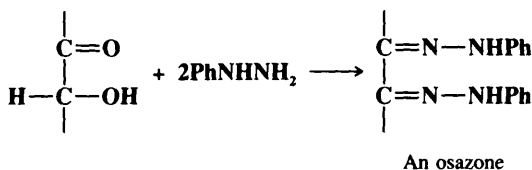important for aromatic aldehydes:

$$ArCH{=}N{-}NH_2 + ArCHO \longrightarrow ArCH{=}N{-}N{=}CHAr$$

An azine
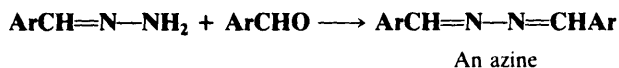
[198]Murahashi; Naota; Saito *J. Am. Chem. Soc.* **1986**, *108*, 7846.
[199]For reviews, see Ref. 106, pp. 226-315; Katritzky; Faid-Allah; Marson *Heterocycles* **1987**, *26*, 1657-1670; Yo-
koyama; Imamoto *Synthesis* **1984**, 797-824, pp. 804-812. For a review of the addition of heterocyclic amines to CO_2
to give, e.g., salts of pyrrole-1-carboxylic acids, see Katritzky; Marson; Faid-Allah *Heterocycles* **1987**, *26*, 1333-1344.
[200]Jochims *Chem. Ber.* **1968**, *101*, 1746. For other methods, see Sakai; Fujinami; Aizawa *Bull. Chem. Soc. Jpn.*
1975, *48*, 2981; Gittos; Davies; Iddon; Suschitzky *J. Chem. Soc., Perkin Trans. 1* **1976**, 141; Shibanuma; Shiono;
Mukaiyama *Chem. Lett.* **1977**, 573; Molina; Alajarin; Arques *Synthesis* **1982**, 596.
[201]Yamazaki; Higashi; Iguchi *Tetrahedron Lett.* **1974**, 1191. For other methods for the conversion of amines and
CO_2 to ureas, see Ogura; Takeda; Tokue; Kobayashi *Synthesis* **1978**, 394; Fournier; Bruneau; Dixneuf; Lécolier *J.
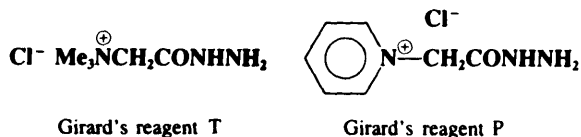Org. Chem.* **1991**, *56*, 4456.

However, in some cases azines can be converted to hydrazones by treatment with excess hydrazine and NaOH.[202] Arylhydrazines, especially phenyl, p-nitrophenyl, and 2,4-dinitrophenyl,[203] are used much more often and give the corresponding hydrazones with most aldehydes and ketones.[204] Since these are usually solids, they make excellent derivatives and are commonly employed for this purpose. α-Hydroxy aldehydes and ketones and α-dicarbonyl compounds give *osazones*, in which two adjacent carbons have carbon–nitrogen double bonds:

$$\begin{array}{c} | \\ C{=}O \\ | \\ H{-}C{-}OH \\ | \end{array} \ + \ 2PhNHNH_2 \ \longrightarrow \ \begin{array}{c} | \\ C{=}N{-}NHPh \\ | \\ C{=}N{-}NHPh \\ | \end{array}$$

An osazone

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):

$$R{-}\underset{O}{\underset{\|}{C}}{-}CH_2{-}\underset{O}{\underset{\|}{C}}{-}OEt \ + \ PhNHNH_2 \ \longrightarrow$$
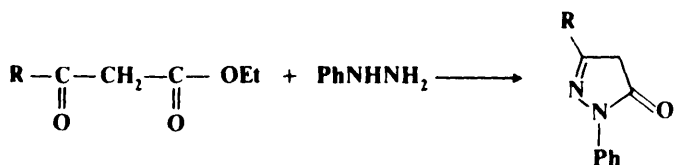
Other hydrazine derivatives frequently used to prepare the corresponding hydrazone are semicarbazide $NH_2NHCONH_2$, in which case the hydrazone is called a semicarbazone, and *Girard's reagents T and P*, in which case the hydrazone is water-soluble because of the ionic

$$Cl^- \ Me_3\overset{\oplus}{N}CH_2CONHNH_2 \qquad\qquad Cl^- \quad \langle\!\langle\bigcirc\rangle\!\rangle \ \overset{\oplus}{N}{-}CH_2CONHNH_2$$

Girard's reagent T   Girard's reagent P

group. Girard's reagents are often used for purification of carbonyl compounds.[205]

Simple N-unsubstituted hydrazones can be obtained by an exchange reaction. The N,N-dimethylhydrazone is prepared first and then treated with hydrazine:[206]

$$\underset{O}{\overset{\|}{\underset{}{C}}}{-} \ + \ NH_2{-}NMe_2 \ \longrightarrow \ \underset{N{-}NMe_2}{\overset{\|}{\underset{}{C}}}{-} \ \xrightarrow{NH_2-NH_2} \ \underset{N{-}NH_2}{\overset{\|}{\underset{}{C}}}{-}$$
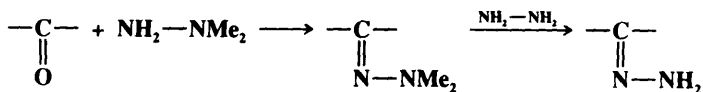
No azines are formed under these conditions.

[202]For example, see Day; Whiting *Org. Synth. VI*, 10.
[203]For an improved procedure for the preparation of 2,4-dinitrophenylhydrazones, see Behforouz; Bolan; Flynt *J. Org. Chem.* **1985,** *50,* 1186.
[204]For a review of arylhydrazones, see Buckingham *Q. Rev., Chem. Soc.* **1969,** *23,* 37-56.
[205]For a study of the mechanism with Girard's reagent T, see Stachissini; do Amaral *J. Org. Chem.* **1991,** *56,* 1419.
[206]Newkome; Fishel *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; **66**, 142.
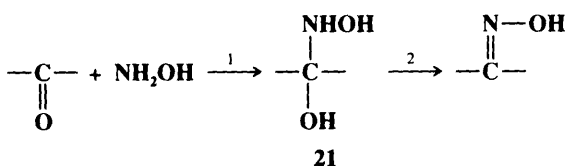
6-21   The Formation of Oximes
Hydroxyimino-de-oxo-bisubstitution

$$-\overset{\parallel}{\underset{O}{C}}- \;+\; NH_2OH \;\longrightarrow\; -\overset{\parallel}{\underset{N-OH}{C}}-$$
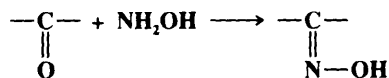
In a reaction very much like **6-20**, oximes can be prepared by the addition of hydroxylamine to aldehydes or ketones. Derivatives of hydroxylamine, e.g., H_2NOSO_3H and $HON(SO_3Na)_2$, have also been used. For hindered ketones, such as hexamethylacetone, high pressures, e.g., 10,000 atm, may be necessary.[207]

It has been shown[208] that the rate of formation of oximes is at a maximum at a pH which depends on the substrate but is usually about 4, and that the rate decreases as the pH is either raised or lowered from this point. We have previously seen (p. 332) 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 is slow (and rate-

$$-\overset{\parallel}{\underset{O}{C}}- \;+\; NH_2OH \;\xrightarrow{\;1\;}\; -\overset{NHOH}{\underset{OH}{C}}- \;\xrightarrow{\;2\;}\; -\overset{N-OH}{C}-$$

21

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 about 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 about 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 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 about 4. It is likely that similar considerations apply to the reaction of aldehydes and ketones with amines, hydrazines, and other nitrogen nucleophiles.[209] There is evidence that when the nucleophile is 2-methylthiosemicarbazide, there is a second change in the rate-determining step: above pH about 10 *basic* catalysis of step 2 has increased the rate of this step to the point where step 1 is again rate-determining.[210] Still a third change in the rate-determining step has been found at about pH = 1, showing

[207]Jones; Tristram; Benning *J. Am. Chem. Soc.* **1959**, *81*, 2151.
[208]Jencks *J. Am. Chem. Soc.* **1959**, *81*, 475, *Prog. Phys. Org. Chem.* **1964**, *2*, 63-128.
[209]For reviews of the mechanism of such reactions, see Cockerill; Harrison, in Patai *The Chemistry of Functional Groups: Supplement A*, pt. 1; Wiley: New York, 1977, pp. 288-299; Sollenberger; Martin, in Patai *The Chemistry of the Amino Group*; Wiley: New York, 1968, pp. 367-392. For isotope effect studies, see Rossi; Stachissini; do Amaral *J. Org. Chem.* **1990**, *55*, 1300.
[210]Sayer; Jencks *J. Am. Chem. Soc.* **1972**, *94*, 3262.

that at least in some cases step 1 actually consists of two steps: formation of a zwitterion,

e.g., $\overset{\oplus}{HO\overset{|}{N}H_2}\overset{|}{-}\overset{|}{C}\overset{|}{-}O^{\ominus}$ in the case shown above, and conversion of this to **21**.[211] The in-

termediate **21** has been detected by nmr in the reaction between NH_2OH and acetaldehyde.[212]

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.[213] Ketones can also be converted to oximes by treatment with other oximes, in a transoximation reaction.[214]

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

6-22   The Conversion of Aldehydes to Nitriles
Nitrilo-de-hydro,oxo-tersubstitution

$$R\overset{|}{\underset{\overset{||}{O}}{-C-}}H + NH_2OH\cdot HCl \xrightarrow{\text{HCOOH}} R-C{\equiv}N$$
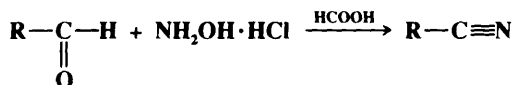
Aldehydes can be converted to nitriles in one step by treatment with hydroxylamine hy-drochloride and either formic acid,[215] concentrated HCl,[216] SeO_2,[217] $MeNO_2$–polyphosphoric acid,[218] or pyridine–toluene.[219] The reaction is a combination of **6-21** and **7-37**. Direct nitrile formation has also been accomplished with certain derivatives of NH_2OH, notably, N,O-bistrifluoroacetylhydroxylamine $F_3CCONHOCOCF_3$[220] and NH_2OSO_2OH.[221] Another method involves treatment with hydrazoic acid, though the Schmidt reaction (**8-17**) may compete.[222] Aromatic aldehydes have been converted to nitriles in good yield with $NH_4H_2PO_4$ and nitropropane in acetic acid,[223] with trimethylsilyl azide,[224] with S,S-di-methylsulfurdiimide,[225] with NH_4Cl–O_2–Cu in pyridine,[226] with hydroxylamine hydrochlo-ride, $MgSO_4$, and TsOH,[227] and with ammonia and iodine or lead tetraacetate.[228]

[211]Rosenberg; Silver; Sayer; Jencks *J. Am. Chem. Soc.* **1974**, *96*, 7986; Sayer; Pinsky; Schonbrunn; Washticn *J. Am. Chem. Soc.* **1974**, *96*, 7998; Sayer; Edman *J. Am. Chem. Soc.* **1979**, *101*, 3010.

[212]Cocivera; Fyfe; Effio; Vaish; Chen *J. Am. Chem. Soc.* **1976**, *98*, 1573; Cocivera; Effio *J. Am. Chem. Soc.* **1976**, *98*, 7371.

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

[214]For example, see Block; Newman *Org. Synth. V*, 1031.

[215]Olah; Keumi *Synthesis* **1979**, 112.

[216]Findlay; Tang *Can. J. Chem.* **1967**, *45*, 1014.

[217]Sosnovsky; Krogh; Umhoefer *Synthesis* **1979**, 722.

[218]Ganboa; Palomo *Synth. Commun.* **1983**, *13*, 999.

[219]Saednya *Synthesis* **1982**, 190.

[220]Pomeroy; Craig *J. Am. Chem. Soc.* **1959**, *81*, 6340.

[221]Streith; Fizet; Fritz *Helv. Chim. Acta* **1976**, *59*, 2786.

[222]For additional methods, see Glass; Hoy *Tetrahedron Lett.* **1976**, 1781; Ikeda; Machii; Okahara *Synthesis* **1978**, 301; Nakagawa; Mineo; Kawamura; Horikawa; Tokumoto; Mori *Synth. Commun.* **1979**, *9*, 529; Furukawa; Fukumura; Akasaka; Yoshimura; Oae *Tetrahedron Lett.* **1980**, *21*, 761; Gelas-Mialhe; Vessière *Synthesis* **1980**, 1005; Arques; Molina; Soler *Synthesis* **1980**, 702; Sato; Itoh; Itoh; Nishina; Goto; Saito *Chem. Lett.* **1984**, 1913; Reddy; Reddy *Synth. Commun.* **1988**, *18*, 2179; Neunhoeffer; Diehl; Karafiat *Liebigs Ann. Chem.* **1989**, 105; Said; Skarżewski; Młochowski *Synthesis* **1989**, 223.

[223]Blatter; Lukaszewski; de Stevens, *J. Am. Chem. Soc.* **1961**, *83*, 2203. See also Dauzonne; Demerseman; Royer *Synthesis* **1981**, 739; Karmarkar; Kelkar; Wadia *Synthesis* **1985**, 510.

[224]Nishiyama; Oba; Watanabe *Tetrahedron* **1987**, *43*, 693.

[225]Georg; Pfeifer; Haake *Tetrahedron Lett.* **1985**, *26*, 2739.

[226]Capdevielle; Lavigne; Maumy *Synthesis* **1989**, 451. See also Yamazaki; Yamazaki *Chem. Lett.* **1990**, 571.

[227]Ganboa; Palomo *Synth. Commun.* **1983**, *13*, 219.

[228]Misono; Osa; Koda *Bull. Chem. Soc. Jpn.* **1966**, *39*, 854, **1967**, *40*, 2875; Parameswaran; Friedman *Chem. Ind. (London)* **1965**, 988.

On treatment with two equivalents of dimethylaluminum amide Me_2AlNH_2, carboxylic esters can be converted to nitriles: $RCOOR' \rightarrow RCN$.[229] This is very likely a combination of **0-55** and **7-39**.
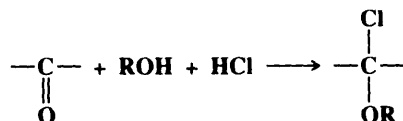
See also **9-5**.

OS **V**, 656.

F. Halogen Nucleophiles

6-23 The Formation of α-Halo Ethers

Alkoxy, halo-de-oxo-bisubstitution

$$-\overset{\text{O}}{\underset{\text{||}}{C}}- \ + \ ROH \ + \ HCl \ \longrightarrow \ -\overset{\text{Cl}}{\underset{\text{OR}}{C}}-$$

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. Aromatic aldehydes and ketones react poorly.[230]

The addition of HX to an aldehyde or ketone gives α-halo alcohols, which are usually unstable, though exceptions are known, especially with perfluoro and perchloro species.[231] Unstable α-halo alcohols may be quite stable in the dimeric form $2XCR_2OH \rightarrow XCR_2OCR_2X$.

OS **I**, 377; **IV**, 101 (see, however, OS **V**, 218), 748; **VI**, 101.

6-24 The Formation of *gem*-Dihalides from Aldehydes and Ketones

Dihalo-de-oxo-bisubstitution

$$-\overset{\text{O}}{\underset{\text{||}}{C}}- \ + \ PCl_5 \ \longrightarrow \ -\overset{\text{Cl}}{\underset{\text{Cl}}{C}}-$$
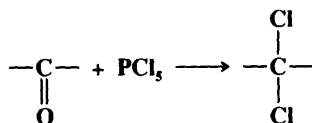
Aliphatic aldehydes and ketones can be converted to *gem*-dichlorides[232] by treatment with PCl_5. The reaction fails for perhalo ketones.[233] If the aldehyde or ketone has an α hydrogen, elimination of HCl may follow and a vinylic chloride is a frequent side product:[234]

$$-\overset{\text{Cl}}{\underset{\text{Cl}}{C}}-\overset{\text{}}{\underset{\text{H}}{C}}- \ \longrightarrow \ -C=\overset{\text{}}{\underset{\text{Cl}}{C}}-$$
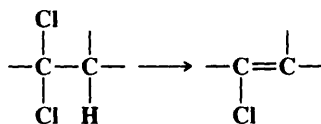
[229]Wood; Khatri; Weinreb *Tetrahedron Lett.* **1979**, 4907.

[230]Klages; Mühlbauer *Chem. Ber.* **1959**, *92*, 1818.

[231]For example, see Andreades; England *J. Am Chem. Soc.* **1961**, *83*, 4670; Clark; Emsley; Hibbert *J. Chem. Soc., Perkin Trans. 2* **1988**, 1107.
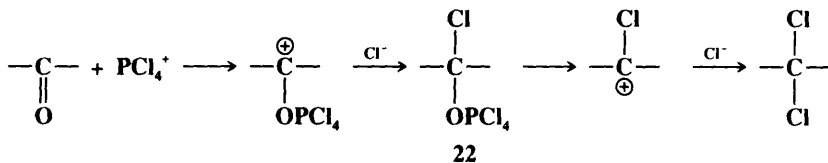
[232]For a list of reagents that convert aldehydes and ketones to *gem*-dihalides or vinylic halides, with references, see Ref. 64, pp. 372-375.

[233]Farah; Gilbert *J. Org. Chem.* **1965**, *30*, 1241.

[234]See, for example, Nikolenko; Popov *J. Gen. Chem. USSR* **1962**, *32*, 29.

or even the main product.[235] PBr₅ does not give good yields of *gem*-dibromides,[236] but these can be obtained from aldehydes, by the use of Br₂ and triphenyl phosphite.[237]
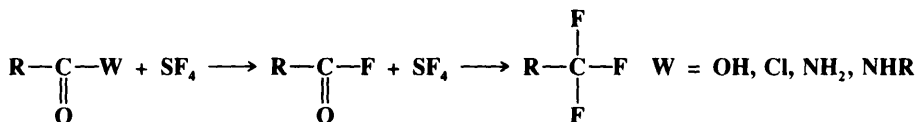
The mechanism of *gem*-dichloride formation involves initial attack of PCl_4^+ (which is present in solid PCl_5) at the oxygen, followed by addition of Cl^- to the carbon:[238]

$$
\underset{O}{\overset{\|}{-C-}} + PCl_4^+ \longrightarrow \underset{OPCl_4}{\overset{\oplus}{-C-}} \xrightarrow{Cl^-} \underset{OPCl_4}{\overset{Cl}{\underset{|}{-C-}}} \longrightarrow \underset{\oplus}{\overset{Cl}{\underset{|}{-C-}}} \xrightarrow{Cl^-} \underset{Cl}{\overset{Cl}{\underset{|}{-C-}}}
$$

22

This chloride ion may come from PCl_6^- (which is also present in solid PCl_5). There follows a two-step SN1 process. Alternatively, **22** can be converted to the product without going through the chlorocarbocation, by an SNi 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.[239] However, formates commonly give the reaction.

Many aldehydes and ketones have been converted to *gem*-difluoro compounds with sulfur tetrafluoride SF_4,[240] 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.[241] 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:

$$
\underset{O}{\overset{\|}{R-C-W}} + SF_4 \longrightarrow \underset{O}{\overset{\|}{R-C-F}} + SF_4 \longrightarrow \underset{F}{\overset{F}{\underset{|}{R-C-F}}} \quad W = OH, Cl, NH_2, NHR
$$

The acyl fluoride can be isolated. Carboxylic esters also give trifluorides, though more vigorous conditions are required, but in this case the carbonyl group of the ester is attacked first, and RCF_2OR' can be isolated from $RCOOR'$[242] and then converted to the trifluoride. Anhydrides can react in either manner, and both types of intermediate are isolable under the right conditions. 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.[243] Another reagent that is often used to convert aldehydes and ketones to *gem*-difluorides is the commercially available diethylaminosulfur trifluoride (DAST) Et_2NSF_3.[244] Among other

[235]See, for example, Newman; Fraenkel; Kirn *J. Org. Chem.* **1963**, *28*, 1851.

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

[237]Hoffmann; Bovicelli *Synthesis* **1990**, 657. See also Lansinger; Ronald *Synth. Commun.* **1979**, *9*, 341.

[238]Newman; Wood *J. Am. Chem. Soc.* **1959**, *81*, 4300; Newman *J. Org. Chem.* **1969**, *34*, 741.

[239]Kirsanov; Molosnova *J. Gen. Chem. USSR* **1958**, *28*, 31; Clark; Simons *J. Org. Chem.* **1961**, *26*, 5197.

[240]For reviews, see Wang *Org. React.* **1985**, *34*, 319-400; Boswell; Ripka; Scribner; Tullock *Org. React.* **1974**, *21*, 1-124.

[241]Muratov; Mohamed; Kunshenko; Burmakov; Alekseeva; Yagupol'skii *J. Org. Chem. USSR* **1985**, *21*, 1292.

[242]For methods of converting RCOOR' to RCF₂OR', see Boguslavskaya; Panteleeva; Chuvatkin *J. Org. Chem. USSR* **1982**, *18*, 198; Bunnelle; McKinnis; Narayanan *J. Org. Chem.* **1990**, *55*, 768.

[243]Olah; Nojima; Kerekes *J. Am. Chem. Soc.* **1974**, *96*, 925.

[244]Markovskij; Pashinnik; Kirsanov *Synthesis* **1973**, 787; Middleton *J. Org. Chem.* **1975**, *40*, 574. For a review of DAST and related reagents, see Hudlický *Org. React.* **1988**, *35*, 513-637.

reagents[245] used have been phenylsulfur trifluoride PhSF$_3$,[246] and molybdenum hexafluoride MoF$_6$.[247]

The mechanism with SF$_4$ is probably similar in general nature, if not in specific detail, to that with PCl$_5$.

Aromatic aldehydes, ketones, and carboxylic acids and esters can be halogenated and reduced in one operation (e.g., ArCHO → ArCH$_2$Br), by treatment with LiAlH$_4$ followed by HBr.[248]

OS **II**, 549; **V**, 365, 396, 1082; **VI**, 505, 845; **66**, 173. Also see OS **I**, 506.

G. Attack by Hydrogen

6-25   Reduction of Aldehydes and Ketones to Alcohols
C,O-Dihydro-addition

$$\begin{array}{ccc}
 & & \text{H} \\
 & & | \\
-\text{C}- \ + \ \text{LiAlH}_4 & \longrightarrow & -\text{C}- \\
\ \ || & & | \\
\ \ \text{O} & & \text{OH}
\end{array}$$

Aldehydes can be reduced to primary alcohols, and ketones to secondary alcohols, by a number of reducing agents,[249] of which lithium aluminum hydride and other metallic hydrides are the most commonly used.[250] These reagents have two main advantages over many other reducing agents: they do not reduce carbon–carbon double (or triple) bonds, and they generally contain a lot of hydrogen in a small amount of reagent—with LiAlH$_4$, all four hydrogens are usable for reduction. The reaction is broad and general. LiAlH$_4$ easily reduces aliphatic, aromatic, alicyclic, and heterocyclic aldehydes, containing double or triple bonds and/or nonreducible groups such as NR$_3$, OH, OR, F, etc. If the molecule contains a group reducible by LiAlH$_4$ (e.g., NO$_2$, CN, COOR), then it is also reduced. LiAlH$_4$ reacts readily with water and alcohols, so these compounds must be excluded. Common solvents are ether and THF. NaBH$_4$ has a similar scope but is more selective and so may be used with NO$_2$, Cl, COOR, CN, etc. in the molecule. Another advantage of NaBH$_4$ is that it can be used in water or alcoholic solvents and so reduces compounds such as sugars that are not soluble in ethers.[251] The scope of these reagents with ketones is similar to that with aldehydes. LiAlH$_4$ reduces even sterically hindered ketones.

The double bonds that are generally not affected by metallic hydrides may be isolated or conjugated, but double bonds that are conjugated with the C=O group may or may not be reduced, depending on the substrate, reagent, and reaction conditions.[252] Some reagents that reduce only the C=O bonds of α,β-unsaturated aldehydes and ketones are

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[245]For some indirect methods, see Sondej; Katzenellenbogen *J. Org. Chem.* **1986**, *51*, 3508; Prakesh; Reddy; Li; Olah *Synlett* **1990**, 594; Rozen; Zamir *J. Org. Chem.* **1991**, *56*, 4695.

[246]Sheppard *J. Am. Chem. Soc.* **1962**, *84*, 3058.

[247]Mathey; Bensoam *Tetrahedron* **1971**, *27*, 3965, **1975**, *31*, 391.

[248]Bilger; Royer; Demerseman *Synthesis* **1988**, 902.

[249]For a review, see Hudlický *Reductions in Organic Chemistry*; Ellis Horwood: Chichester, 1984, pp. 96-129. For a list of reagents, with references, see Ref. 64, pp. 527-547.

[250]For books on metal hydrides, see Seyden-Penne *Reductions by the Alumino- and Borohydrides*; VCH: New York, 1991; Hajos *Complex Hydrides*; Elsevier: New York, 1979. For reviews, see House, Ref. 180, pp. 49-71; Wheeler, in Patai, Ref. 2, pp. 507-566.

[251]NaBH$_4$ reduces solid ketones in the absence of any solvent (by mixing the powders): Toda; Kiyoshige; Yagi *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 320 [*Angew. Chem. 101*, 329].

[252]For a review of the reduction of α,β-unsaturated carbonyl compounds, see Keinan; Greenspoon, in Patai; Rappoport *The Chemistry of Enones*, pt. 2; Wiley: New York, 1989, pp. 923-1022.

AlH$_3$,[253] NaBH$_4$, or LiAlH$_4$ in the presence of lanthanide salts (e.g., LaCl$_3$, CeBr$_3$),[254] NaBH$_3$(OAc),[255] Et$_3$SiH,[256] lithium n-butylborohydride,[257] and diisobutylaluminium hydride (DIBALH).[258] Also, both LiAlH$_4$[259] and NaBH$_4$[260] predominantly reduce only the C=O bonds of C=C—C=O systems in most cases, though substantial amounts of fully saturated alcohols have been found in some cases[259] (p. 774). For some reagents that reduce only the C=C bonds of conjugated aldehydes and ketones, see **5-9**.

When a functional group is selectively attacked in the presence of a different functional group, the reaction is said to be *chemoselective*. A number of reagents have been found to reduce aldehydes much faster than ketones. Among these[261] are NaBH$_4$ in isopropyl alcohol,[262] sodium triacetoxyborohydride,[263] lithium tris[(3-ethyl-3-pentyl)oxy]aluminum hydride Li(Et$_3$CO)$_3$AlH,[264] zinc borohydride in THF,[264a] and tributyltin hydride.[265] On the other hand, ketones can be chemoselectively reduced in the presence of aldehydes with NaBH$_4$ in aqueous EtOH at −15°C in the presence of cerium trichloride CeCl$_3$.[266] The reagent lithium N-dihydropyridylaluminum hydride reduces diaryl ketones much better than dialkyl or alkyl aryl ketones.[267] Most other hydrides reduce diaryl ketones more slowly than other types of ketones. Saturated ketones can be reduced in the presence of α,β-unsaturated ketones with NaBH$_4$–50% MeOH–CH$_2$Cl$_2$ at −78°C[268] and with zinc borohydride.[269] In general, NaBH$_4$ reduces carbonyl compounds in this order: aldehydes > α,β-unsaturated aldehydes > ketones > α,β-unsaturated ketones, and a carbonyl group of one type can be selectively reduced in the presence of a carbonyl group of a less reactive type.[270] Potassium triphenylborohydride KPh$_3$BH shows 99.4:0.6 selectivity between cyclohexanone and 4-heptanone, and 97:3 selectivity between cyclohexanone and cyclopentanone.[271] A number of reagents will preferentially reduce the less sterically hindered of two carbonyl compounds, but by the use of DIBALH in the presence of the Lewis acid methylaluminum bis(2,6-di-t-butyl-4-methylphenoxide), it was possible selectively to reduce the *more hindered* of a mixture of two ketones.[272] It is obvious that reagents can often be found to reduce one kind of carbonyl

[253]Jorgenson *Tetrahedron Lett.* **1962**, 559; Dilling; Plepys *J. Org. Chem.* **1970**, *35*, 2971.

[254]Gemal; Luche *J. Am. Chem. Soc.* **1981**, *103*, 5454; Fukuzawa; Fujinami; Yamauchi; Sakai *J. Chem. Soc., Perkin Trans. 1* **1986**, 1929. See also Chênevert; Ampleman *Chem. Lett.* **1985**, 1489; Varma; Kabalka *Synth. Commun.* **1985**, *15*, 985.

[255]Nutaitis; Bernardo *J. Org. Chem.* **1989**, *54*, 5629.

[256]Ojima; Kogure *Organometallics* **1982**, *1*, 1390.

[257]Kim; Moon; Ahn *J. Org. Chem.* **1982**, *47*, 3311.

[258]Wilson; Seidner; Masamune *Chem. Commun.* **1970**, 213.

[259]Johnson; Rickborn *J. Org. Chem.* **1970**, *35*, 1041.

[260]Chaikin; Brown *J. Am. Chem. Soc.* **1949**, *71*, 122.

[261]For some others (not all of them metal hydrides) see Hutchins; Kandasamy *J. Am. Chem. Soc.* **1973**, *95*, 6131; Risbood; Ruthven *J. Org. Chem.* **1979**, *44*, 3969; Babler; Invergo *Tetrahedron Lett.* **1981**, *22*, 621; Fleet; Harding *Tetrahedron Lett.* **1981**, *22*, 675; Yamaguchi; Kabuto; Yasuhara *Chem. Lett.* **1981**, 461; Kim; Kang; Yang *Tetrahedron Lett.* **1984**, *25*, 2985; Kamitori; Hojo; Masuda; Yamamoto *Chem. Lett.* **1985**, 253; Borbaruah; Barua; Sharma *Tetrahedron Lett.* **1987**, *28*, 5741.

[262]Brown; Wheeler; Ichikawa *Tetrahedron* **1957**, *1*, 214; Adams *Synth. Commun.* **1984**, *14*, 1349.

[263]Gribble; Ferguson *J. Chem. Soc., Chem. Commun.* **1975**, 535. See also Nutaitis; Gribble *Tetrahedron Lett.* **1983**, *24*, 4287.

[264]Krishnamurthy *J. Org. Chem.* **1981**, *46*, 4628.

[264a]Ranu; Chakraborty *Tetrahedron Lett.* **1990**, *31*, 7663.

[265]Fung; Mayo; Schauble; Weedon *J. Org. Chem.* **1978**, *43*, 3977; Shibata; Yoshida; Baba; Matsuda *Chem. Lett.* **1989**, 619; Adams; Schemenaur *Synth. Commun.* **1990**, *20*, 2359. For a review, see Kuivila *Synthesis* **1970**, 499-509.

[266]Luche; Gemal *J. Am. Chem. Soc.* **1979**, *101*, 5848. See also Gemal; Luche *Tetrahedron Lett.* **1981**, *22*, 4077. For other methods, see Paradisi; Zecchini; Ortar *Tetrahedron Lett.* **1980**, *21*, 5085; Bordoloi; Sarmah *Chem. Ind. (London)* **1987**, 459.

[267]Lansbury; Peterson *J. Am. Chem. Soc.* **1962**, *84*, 1756.

[268]Ward; Rhee; Zoghaib *Tetrahedron Lett.* **1988**, *29*, 517.

[269]Sarkar; Das; Ranu *J. Org. Chem.* **1990**, *55*, 5799.
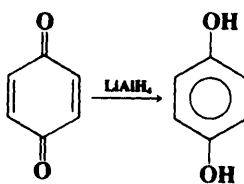
[270]Ward, Rhee *Can. J. Chem.* **1989**, *67*, 1206.

[271]Yoon; Kim; Kang *J. Org. Chem.* **1986**, *51*, 226.

[272]Maruoka; Araki; Yamamoto *J. Am. Chem. Soc.* **1988**, *110*, 2650.

function in the presence of another.[273] For a discussion of selectivity in reduction reactions, see p. 1206.

Quinones are reduced to hydroquinones by $LiAlH_4$, $SnCl_2$–HCl, or sodium hydrosulfite $Na_2S_2O_4$, as well as by other reducing agents.

The reagent lithium tri-*sec*-butylborohydride $LiBH(sec\text{-}Bu)_3$ reduces cyclic and bicyclic ketones in a highly stereoselective manner, giving the less stable isomer.[274] For example, 2-methylcyclohexanone gave *cis*-2-methylcyclohexanol with an isomeric purity greater than 99%. The more usual reagents, e.g., $LiAlH_4$, $NaBH_4$, reduce relatively unhindered cyclic ketones either with little or no stereoselectivity[275] or give predominant formation of the more stable isomer (axial attack).[276] The less stable alcohol is also predominantly formed when cyclohexanones are reduced with (among other reagents) AlH_3 in ether at $-70°C$[277] and with triethyl phosphite and iridium tetrachloride in aqueous isopropyl alcohol.[278] Cyclohexanones that have a large degree of steric hindrance near the carbonyl group usually give predominant formation of the less stable alcohol, even with $LiAlH_4$ and $NaBH_4$.

Among other reagents that reduce aldehydes and ketones to alcohols[279] are the following:

1. *Hydrogen and a catalyst.*[280] The most common catalysts are platinum and ruthenium, but homogeneous catalysts have also been used.[281] Before the discovery of the metal hydrides this was one of the most common ways of effecting this reduction, but it suffers from the fact that C=C, C≡C, C=N and C≡N bonds are more susceptible to attack than C=O bonds.[282] For aromatic aldehydes and ketones, reduction to the hydrocarbon (**9-37**) is a side reaction, stemming from hydrogenolysis of the alcohol initially produced (**0-78**).

[273]For lists of some of these chemoselective reagents, with references, see Ref. 64, pp. 535-537, and references given in Ref. 270.

[274]Brown; Krishnamurthy *J. Am. Chem. Soc.* **1972**, *94*, 7159; Krishnamurthy; Brown *J. Am. Chem. Soc.* **1976**, *98*, 3383.

[275]For reviews of the stereochemistry and mechanism, see Caro; Boyer; Lamaty; Jaouen *Bull. Soc. Chim. Fr.* **1983**, II-281-II-303; Boone; Ashby *Top. Stereochem.* **1979**, *11*, 53-95; Wigfield *Tetrahedron* **1979**, *35*, 449-462. For a review of stereoselective synthesis of amino alcohols by this method, see Tramontini *Synthesis* **1982**, 605-644.

[276]For a discussion of why this isomer is predominantly formed, see Mukherjee; Wu; Fronczek; Houk *J. Am. Chem. Soc.* **1988**, *110*, 3328.

[277]Ayres; Sawdaye *J. Chem. Soc. B* **1967**, 581; Ayres; Kirk; Sawdaye *J. Chem. Soc. B* **1970**, 505.

[278]Henbest; Mitchell *J. Chem. Soc. C* **1970**, 785; Eliel; Doyle; Hutchins; Gilbert *Org. Synth. VI*, 215. See also Henbest; Zurqiyah *J. Chem. Soc., Perkin Trans. 1* **1974**, 604.

[279]This can also be done electrochemically. For a review, see Feoktistov; Lund, in Baizer; Lund *Organic Electochemistry*; Marcel Dekker: New York, 1983, pp. 315-358, pp. 315-326. See also Coche; Moutet *J. Am. Chem. Soc.* **1987**, *109*, 6887.

[280]For reviews, see Parker, in Hartley *The Chemistry of the Metal-Carbon Bond*, vol. 4; Wiley: New York, 1987, pp. 979-1047; Tanaka, in Červený *Catalytic Hydrogenation*; Elsevier: New York, 1986, pp. 79-104; Rylander *Hydrogenation Methods*, Ref. 165, pp. 66-77; Rylander *Catalytic Hydrogenation over Platinum Metals*, Ref. 165, pp. 238-290.

[281]For a review, see Heck *Organotransition Metal Chemistry*; Academic Press: New York, 1974, pp. 65-70.

[282]For catalysts that allow hydrogenation of only the C=O bond of α,β-unsaturated aldehydes, see Galvagno; Poltarzewski; Donato; Neri; Pietropaolo *J. Chem. Soc., Chem. Commun.* **1986**, 1729; Farnetti; Pesce; Kašpar; Spogliarich; Graziani *J. Chem. Soc., Chem. Commun.* **1986**, 746; Narasimhan; Deshpande; Ramnarayan *J. Chem. Soc., Chem. Commun.* **1988**, 99.

2. *Sodium in ethanol.*[283] This is called the *Bouveault–Blanc procedure* and was more popular for the reduction of carboxylic esters (**9-42**) than of aldehydes or ketones before the discovery of $LiAlH_4$.

3. *Isopropyl alcohol and aluminum isopropoxide.* This is called the *Meerwein–Ponndorf–Verley reduction*. It is reversible, and the reverse reaction is known as the *Oppenauer oxidation* (see **9-3**):

$$R-\underset{\underset{O}{\|}}{C}-R' + CH_3-\underset{\underset{OH}{|}}{CH}-CH_3 \underset{\xrightarrow{\hspace{1cm}}}{\overset{Al(OCHMe_2)_3}{\rightleftharpoons}} R-\underset{\underset{OH}{|}}{CH}-R' + CH_3-\underset{\underset{O}{\|}}{C}-CH_3$$
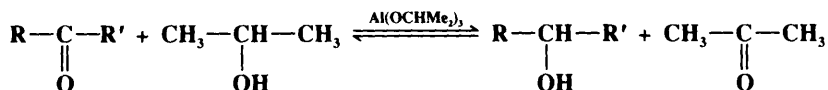
The equilibrium is shifted by removal of the acetone by distillation. The reaction takes place under very mild conditions and is highly specific for aldehydes and ketones, so that C=C bonds (including those conjugated with the C=O bonds) and many other functional groups can be present without themselves being reduced.[284] This includes acetals, so that one of two carbonyl groups in a molecule can be specifically reduced if the other is first converted to an acetal. β-Keto esters, β-diketones, and other ketones and aldehydes with a relatively high enol content do not give this reaction.

4. Borane BH_3 and substituted boranes reduce aldehydes and ketones in a manner similar to their addition to C=C bonds (**5-12**).[285] That is, the boron adds to the oxygen and the hydrogen to the carbon:[286]

$$-\underset{\underset{O}{\|}}{C}- + BH_3-THF \longrightarrow \left(-\underset{\underset{O}{|}}{\overset{\overset{H}{|}}{C}}-\right)_3 B$$
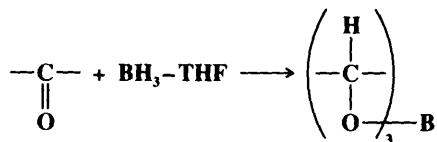
The borate is then hydrolyzed to the alcohol. 9-BBN[287] (p. 785) and BH_3–Me_2S[288] reduce only the C=O group of conjugated aldehydes and ketones.

5. *Diimide* (N_2H_2, see p. 779) reduces aromatic aldehydes[289] and ketones, but aliphatic carbonyl compounds react very poorly.[290]

6. A single carbonyl group of an α-diketone can be reduced (to give an α-hydroxy ketone) by heating with zinc powder in aqueous DMF.[291] This has also been accomplished with aqueous VCl_2[292] and with Zn–$ZnCl_2$–EtOH.[293]

7. In the Cannizzaro reaction (**9-69**) aldehydes without an α hydrogen are reduced to alcohols.

[283]For a discussion, see House, Ref. 180, pp. 152-160.
[284]Diisobornyloxyaluminum isopropoxide gives higher yields under milder conditions than aluminum isopropoxide: Hutton, *Synth. Commun.* **1979**, *9*, 483. For other substitutes for aluminum isopropoxide, see Namy; Souppe; Collin; Kagan *J. Org. Chem.* **1984**, *49*, 2045; Okano; Matsuoka; Konishi; Kiji *Chem. Lett.* **1987**, 181.
[285]For a review, see Cragg *Organoboranes in Organic Synthesis*; Marcel Dekker: New York, 1973, pp. 324-335.
[286]Brown; Subba Rao *J. Am. Chem. Soc.* **1960**, *82*, 681; Brown; Korytnyk *J. Am. Chem. Soc.* **1960**, *J. Am. Chem. Soc.* **1960**, *82*, 3866.
[287]Krishnamurthy; Brown *J. Org. Chem.* **1975**, *40*, 1864; Lane *Aldrichimica Acta* **1976**, *9*, 31.
[288]Mincione *J. Org. Chem.* **1978**, *43*, 1829.
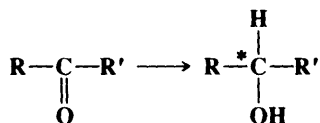[289]Curry; Uff; Ward *J. Chem. Soc. C* **1967**, 1120.
[290]van Tamelen; Davis; Deem *Chem. Commun.* **1965**, 71.
[291]Kreiser *Liebigs Ann. Chem.* **1971**, *745*, 164.
[292]Ho; Olah *Synthesis* **1976**, 815.
[293]Toda; Tanaka; Tange *J. Chem. Soc., Perkin Trans. 1* **1989**, 1555.

Unsymmetrical ketones are prochiral (p. 135); that is, reduction creates a new chiral center:

$$R—\underset{\underset{O}{\parallel}}{C}—R' \longrightarrow R—\overset{\overset{H}{|}}{\underset{\underset{OH}{|}}{\overset{*}{C}}}—R'$$

Much effort has been put into finding optically active reducing agents that will produce one enantiomer of the alcohol enantioselectively, and considerable success has been achieved,[294] both with biologically-derived reducing agents[295] such as baker's yeast,[296] and with synthetic reagents. Each reagent is more effective for certain types of ketones than for others.[297] H.C. Brown and co-workers reduced various types of ketone with a number of reducing agents,[298] and reported in 1987 that of the reagents available at that time, the highest enantiomeric excesses (ee) for acyclic ketones were obtained with (R,R)- or (S,S)-2,5-dimethylborolane (**47** and **48** on p. 787).[299] For cyclic ketones the best reagents were diisopinocampheyl-chloroborane (**23**),[300] (S)-2-amino-1,1-diphenylbutan-1-ol–BH_3,[301] and K-Glucoride, a boron derivative of a carbohydrate.[302] These workers also determined the relative effectiveness of

Me H
BCl
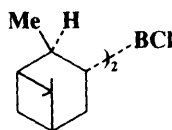
23

various reagents for reduction of 8 other types of ketone, including heterocyclic, aralkyl, β-keto esters, etc.[298] In most cases, ee values of greater than 90% can be obtained with the proper reagent.[303]

Asymmetric reduction with very high ee values has also been achieved with achiral reducing agents and optically active catalysts. The two most important examples are (1) homogeneous catalytic hydrogenation with the catalyst 2,2'-bis(diphenylphosphino)-1,1'-

[294]For reviews, see Midland *Chem. Rev.* **1989**, *89*, 1553-1561; Nógrádi *Stereoselective Synthesis*; VCH: New York, 1986, pp. 105-130; in Morrison *Asymmetric Synthesis*; Academic Press: New York, 1983, the articles by Midland, vol. 2, pp. 45-69, and Grandbois; Howard; Morrison, vol. 2, pp. 71-90; Haubenstock *Top. Stereochem.* **1983**, *14*, 231-300.

[295]For a review, see Sih; Chen *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 570-578 [*Angew. Chem. 96*, 556-565].

[296]See, for example, Fujisawa; Hayashi; Kishioka *Chem. Lett.* **1987**, 129; Nakamura; Kawai; Ohno *Tetrahedron Lett.* **1990**, *31*, 267; Spiliotis; Papahatjis; Ragoussis *Tetrahedron Lett.* **1990**, *31*, 1615.

[297]For a list of many of these reducing agents, with references, see Ref. 64, pp. 540-547.

[298]Brown; Park; Cho; Ramachandran *J. Org. Chem.* **1987**, *52*, 5406.

[299]First used in this way by Imai; Tamura; Yamamuro; Sato; Wollmann; Kennedy; Masamune *J. Am. Chem. Soc.* **1986**, *108*, 7402; Masamune; Kennedy; Petersen; Houk; Wu *J. Am. Chem. Soc.* **1986**, *108*, 7404.

[300]Chandrasekharan; Ramachandran; Brown *J. Org. Chem.* **1985**, *50*, 5446; Brown; Chandrasekharan; Ramachandran *J. Org. Chem.* **1986**, *51*, 3394, *J. Am. Chem. Soc.* **1988**, *110*, 1539; Srebnik; Ramachandran; Brown *J. Org. Chem.* **1988**, *53*, 2916. See also Brown; Srebnik; Ramachandran *J. Org. Chem.* **1989**, *54*, 1577.

[301]For the preparation and use of this and related reagents, see Itsuno; Nakano; Miyazaki; Masuda; Ito; Hirao; Nakahama *J. Chem. Soc., Perkin Trans. 1* **1985**, 2039, and other papers in this series.

[302]Brown; Park; Cho *J. Org. Chem.* **1986**, *51*, 1934, 3278; Brown; Cho; Park *J. Org. Chem.* **1986**, *51*, 3396, **1988**, *53*, 1231.

[303]For some recent examples, see Youn; Lee; Pak *Tetrahedron Lett.* **1988**, *29*, 4453; Meyers; Brown *Tetrahedron Lett.* **1988**, *29*, 5617; Brown; Ramachandran; Weissman; Swaminathan *J. Org. Chem.* **1990**, *55*, 6328; Rama Rao; Gurjar; Sharma; Kaiwar *Tetrahedron Lett.* **1990**, *31*, 2341; Midland; Kazubski; Woodling *J. Org. Chem.* **1991**, *56*, 1068.

binaphthyl–ruthenium acetate [BINAP–Ru(OAc)$_2$],[304] which reduces β-keto esters in >98% ee,[305] and (2) reduction with BH$_3$–THF or catecholborane, using an oxazaborolidine

R(+)-BINAP   **24**
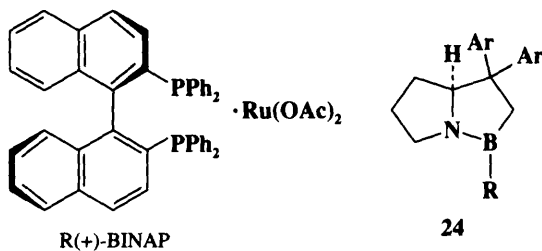
24 (R = H, Me, or n-Bu; Ar = Ph or β-naphthyl) as a catalyst.[306] This method gives high ee values with various types of ketone, especially α,β-unsaturated ketones.

Enantioselective reduction is not possible for aldehydes, since the products are primary alcohols in which the reduced carbon is not chiral, but deuterated aldehydes RCDO give a chiral product, and these have been reduced enantioselectively with B-(3-pinanyl)-9-bora-bicyclo[3.3.1]nonane (Alpine–Borane) with almost complete optical purity.[307]

Alpine – Borane

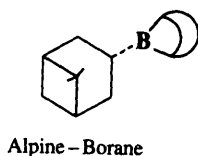In the above cases an optically active reducing agent or catalyst interacts with a prochiral substrate. Asymmetric reduction of ketones has also been achieved with an achiral reducing agent, if the ketone is complexed to an optically active transition metal Lewis acid.[308]

There are other stereochemical aspects to the reduction of aldehydes and ketones. If there is a chiral center α to the carbonyl group,[309] even an achiral reducing agent can give

diastereomers
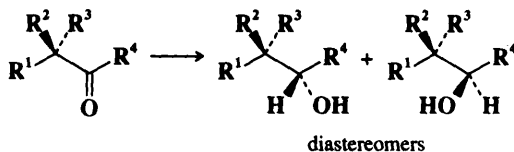
[304]For reviews of BINAP, see Noyori *Science* **1990**, *248*, 1194-1199; Noyori; Takaya *Acc. Chem. Res.* **1990**, *23*, 345-350. For the synthesis of BINAP, see Takaya; Akutagawa; Noyori *Org. Synth. 67*, 20.

[305]Noyori; Ohkuma; Kitamura; Takaya; Sayo; Kumobayashi; Akutagawa *J. Am. Chem. Soc.* **1987**, *109*, 5856; Taber; Silverberg *Tetrahedron Lett.* **1991**, *32*, 4227. See also Kitamura; Ohkuma; Inoue; Sayo; Kumobayashi; Akutagawa; Ohta; Takaya; Noyori; *J. Am. Chem. Soc.* **1988**, *110*, 629.

[306]Corey; Bakshi; Shibata *J. Am. Chem. Soc.* **1987**, *109*, 5551; Corey; Bakshi; Shibata; Chen; Singh *J. Am. Chem. Soc.* **1987**, *109*, 7924; Corey; Link; *Tetrahedron Lett.* **1989**, *30*, 6275; Corey; Bakshi *Tetrahedron Lett.* **1990**, *31*, 611.

[307]Midland; Greer; Tramontano; Zderic *J. Am. Chem. Soc.* **1979**, *101*, 2352. See also Noyori; Tomino; Tanimoto *J. Am. Chem. Soc.* **1979**, *101*, 3129; Brown; Jadhav; Mandal *Tetrahedron* **1981**, *37*, 3547-3587; Midland; Zderic *J. Am. Chem. Soc.* **1982**, *104*, 525.

[308]Dalton; Gladysz *J. Organomet. Chem.* **1989**, *370*, C17.

[309]In theory, the chiral center can be anywhere in the molecule, but in practice, reasonable diastereoselectivity is most often achieved when it is in the α position. For examples of high diastereoselectivity when the chiral center is further away, especially in reduction of β-hydroxy ketones, see Narasaka; Pai *Tetrahedron* **1984**, *40*, 2233; Hassine; Gorsane; Pecher; Martin *Bull. Soc. Chim. Belg.* **1985**, *94*, 597; Bloch; Gilbert; Girard *Tetrahedron Lett.* **1988**, *53*, 1021; Evans; Chapman; Carreira *J. Am. Chem. Soc.* **1988**, *110*, 3560.

more of one diastereomer than of the other. Such diastereoselective reductions have been carried out with considerable success.[310] In most such cases Cram's rule (p. 117) is followed, but exceptions are known.[311]

With most reagents there is an initial attack on the carbon of the carbonyl group by H^- or some carrier of it, though with BH_3[312] the initial attack is on the oxygen. Detailed mechanisms are not known in most cases.[275] With AlH_4^- (or BH_4^-) compounds, the attacking species is the AlH_4^- (or BH_4^-) ion, which, in effect, transfers H^- to the carbon. The following mechanism has been proposed for $LiAlH_4$:[313]

S = solvent molecules
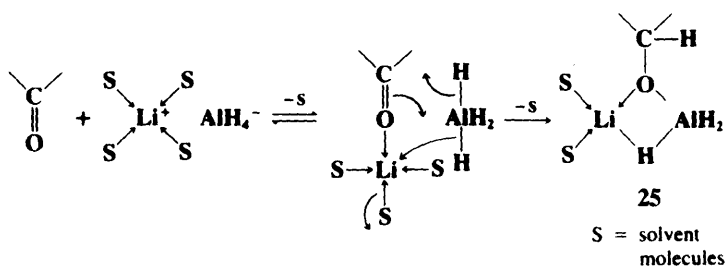
Evidence that the cation plays an essential role, at least in some cases, is that when the Li^+ was effectively removed from $LiAlH_4$ (by the addition of a crown ether), the reaction did not take place.[314] The complex **25** must now be hydrolyzed to the alcohol. For $NaBH_4$ the Na^+ does not seem to participate in the transition state, but kinetic evidence shows that an OR group from the solvent does participate and remains attached to the boron:[315]
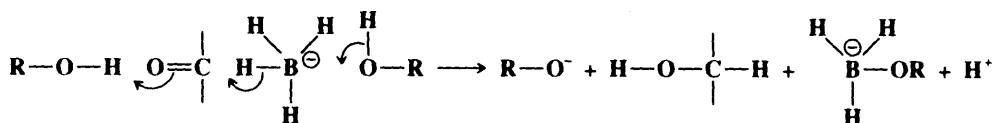
Free H^- cannot be the attacking entity in most reductions with boron or aluminum hydrides because the reactions are frequently sensitive to the size of the MH_4^- [or $MR_mH_n^-$ or $M(OR)_mH_n^-$, etc.].

There has been much controversy about whether the initial complex in the $LiAlH_4$ reduction (**25**, which can be written as $H{-}\overset{|}{\underset{|}{C}}{-}OAlH_3^-$, **26**) can reduce another carbonyl to give $(H{-}\overset{|}{\underset{|}{C}}{-}O)_2AlH_2^-$, and so on. It has been shown[316] that this is probably not the

[310]For reviews, see Nógrádi, Ref. 294, pp. 131-148; Oishi; Nakata *Acc. Chem. Res.* **1984**, *17*, 338-344.

[311]One study showed that the Cram's rule product predominates with metal hydride reducing agents, but the other product with Bouveault-Blanc and dissolving metal reductions: Yamamoto; Matsuoka; Nemoto *J. Am. Chem. Soc.* **1988**, *110*, 4475.

[312]For a discussion of the mechanism with boranes, see Brown, Wang, Chandrasekharan *J. Am. Chem. Soc.* **1983**, *105*, 2340.

[313]Ashby; Boone *J. Am. Chem. Soc.* **1976**, *98*, 5524.

[314]Pierre; Handel *Tetrahedron Lett.* **1974**, 2317. See also Loupy, Seyden-Penne; Tchoubar *Tetrahedron Lett.* **1976**, 1677; Ref. 313.

[315]Wigfield; Gowland *J. Org. Chem.* **1977**, *42*, 1108, *Tetrahedron Lett.* **1976**, 3373. See however Adams; Gold; Reuben *J. Chem. Soc., Chem. Commun.* **1977**, 182, *J. Chem. Soc., Perkin Trans 2* **1977**, 1466, 1472; Kayser; Eliev; Eisenstein *Tetrahedron Lett.* **1983**, *24*, 1015.

[316]Haubenstock; Eliel *J. Am. Chem. Soc.* **1962**, *84*, 2363; Malmvik; Obenius; Henriksson *J. Chem. Soc., Perkin Trans. 2* **1986**, 1899, 1905.

case but that, more likely, **26** disproportionates to $(H\text{—}\overset{\textstyle |}{\underset{\textstyle |}{C}}\text{—}O)_4Al^-$ and $AlH_4{}^-$, which is the only attacking species. Disproportionation has also been reported in the $NaBH_4$ reaction.[317]

26 is essentially $LiAlH_4$ with one of the hydrogens replaced by an alkoxy group, i.e., $LiAlH_3OR$. The fact that **26** and other alkoxy derivatives of $LiAlH_4$ are less reactive than $LiAlH_4$ itself has led to the use of such compounds as reducing agents that are less reactive and more selective than $LiAlH_4$.[318] We have already met some of these, e.g., $LiAlH(O\text{-}t\text{-}Bu)_3$ (reactions **0-83** to **0-85**; see also Table 19.5). As an example of chemoselectivity in this reaction it may be mentioned that $LiAlH(O\text{-}t\text{-}Bu)_3$ has been used to reduce only the keto group in a molecule containing both keto and carboxylic ester groups.[319] However, the use of such reagents is sometimes complicated by the disproportionation mentioned above, which may cause $LiAlH_4$ to be the active species, even if the reagent is an alkoxy derivative. Another highly selective reagent (reducing aldehydes and ketones, but not other functional groups), which does not disproportionate, is potassium triisopropoxyborohydride.[320]

The Meerwein–Ponndorf–Verley reaction usually[321] involves a cyclic transition state:[322]
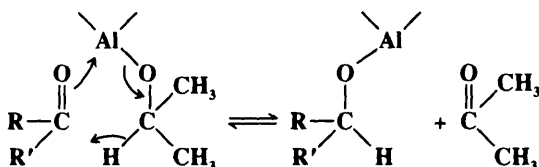
but in some cases 2 moles of aluminum alkoxide are involved—one attacking the carbon and the other the oxygen, a conclusion that stems from the finding that in these cases the reaction was 1.5 order in alkoxide.[323] Although, for simplicity, we have shown the alkoxide as a monomer, it actually exists as trimers and tetramers, and it is these that react.[324]

For the reaction with sodium in ethanol the following mechanism[325] has been suggested:[326]
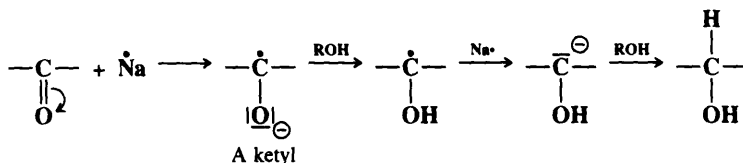
A ketyl

The ketyl intermediate can be isolated.[327]

[317]Malmvik; Obenius; Henriksson *J. Org. Chem.* **1988**, *53*, 221.

[318]For reviews of reductions with alkoxyaluminum hydrides, see Málek *Org. React.* **1988**, *36*, 249-590, **1985**, *34*, 1-317; Málek; Černý *Synthesis* **1972**, 217-234.

[319]Levine; Eudy *J. Org. Chem.* **1970**, *35*, 549; Heusler; Wieland; Meystre *Org. Synth.* V, 692.

[320]Brown; Krishnamurthy; Kim *J. Chem. Soc., Chem. Commun.* **1973**, 391.

[321]It has been that shown in some cases reduction with metal alkoxides, including aluminum isopropoxide, involves free-radical intermediates (SET mechanism): Screttas; Cazianis *Tetrahedron* **1978**, *34*, 933; Ashby; Goel; Argyropoulos *Tetrahedron Lett.* **1982**, *23*, 2273; Nasipuri; Gupta; Banerjee *Tetrahedron Lett.* **1984**, *25*, 5551; Ashby; Argyropoulos *Tetrahedron Lett.* **1986**, *27*, 465, *J. Org. Chem.* **1986**, *51*, 3593; Yamataka; Hanafusa *Chem. Lett.* **1987**, 643.

[322]See, for example, Shiner; Whittaker *J. Am. Chem. Soc.* **1963**, *85*, 2337; Warnhoff; Reynolds-Warnhoff; Wong *J. Am. Chem. Soc.* **1980**, *102*, 5956.

[323]Moulton; Van Atta; Ruch *J. Org. Chem.* **1961**, *26*, 290.

[324]Williams; Krieger; Day *J. Am. Chem. Soc.* **1953**, *75*, 2404; Shiner; Whittaker *J. Am. Chem. Soc.*, **1969**, *91*, 394.

[325]For reviews of the mechanisms of these reactions, see Pradhan *Tetrahedron* **1986**, *42*, 6351-6388; Huffman *Acc. Chem. Res.* **1983**, *16*, 399-405. For discussions of the mechanism in the absence of protic solvents, see Huffman; Liao; Wallace *Tetrahedron Lett.* **1987**, *28*, 3315; Rautenstrauch *Tetrahedron* **1988**, *44*, 1613; Song; Dewald *J. Chem. Soc., Perkin Trans. 2* **1989**, 269. For a review of the stereochemistry of these reactions in liquid NH_3, see Rassat *Pure Appl. Chem.* **1977**, *49*, 1049-1058.

[326]House, Ref. 180, p. 151. See, however Giordano; Perdoncin; Castaldi *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 499 [*Angew. Chem. 97*, 510].

[327]For example, see Rautenstrauch; Geoffroy *J. Am. Chem. Soc.* **1976**, *98*, 5035, **1977**, *99*, 6280.

The mechanism of catalytic hydrogenation of aldehydes and ketones is probably similar to that of reaction **5-9**, though not much is known about it.[328]

For other reduction reactions of aldehydes and ketones, see **9-37, 9-62,** and **9-69.**

OS **I**, 90, 304, 554; **II**, 317, 545, 598; **III**, 286; **IV**, 15, 25, 216, 660; **V**, 175, 294, 595, 692; **VI**, 215, 769, 887; **VII**, 129, 215, 241, 402, 417; **65,** 203, 215; **68,** 56; **69,** 44.

6-26   Reduction of the Carbon–Nitrogen Double Bond
C,N-Dihydro-addition

$$\underset{\overset{\|}{\underset{N-}{}}}{-C-} \quad \xrightarrow{\text{LiAlH}_4} \quad \underset{\overset{|}{\underset{NH-}{}}}{-CH-}$$
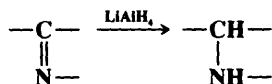
Imines, Schiff bases, hydrazones, and other C≡N compounds can be reduced with $LiAlH_4$, $NaBH_4$, Na–EtOH, hydrogen and a catalyst, as well as with other reducing agents.[329] Iminium salts are also reduced by $LiAlH_4$, though here there is no "addition" to the nitrogen:[330]

$$\underset{\overset{\|}{\underset{\underset{\oplus}{N-}}{}}}{-C-} \quad + \text{ LiAlH}_4 \quad \longrightarrow \quad \underset{\overset{|}{\underset{-N-}{}}}{-\overset{\overset{H}{|}}{C}-}$$
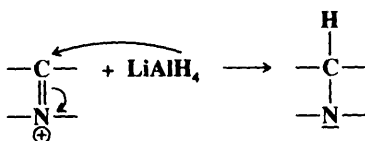
Reduction of imines has been carried out enantioselectively.[331]

Isocyanates have been catalytically hydrogenated to N-substituted formamides: RNCO → R—NH—CHO.[332]

Oximes are generally reduced to amines (**9-51**), but simple addition of H_2 to give hydroxylamines can be accomplished with borane[333] or sodium cyanoborohydride.[168]

$$\underset{\overset{\|}{\underset{\underset{OH}{\diagdown}}{N}}}{R-C-R'} \quad \xrightarrow{\text{BH}_3\text{-THF}} \quad \underset{\underset{NHOH}{|}}{R-CH-R'}$$
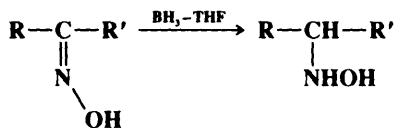
OS **III**, 328, 827; **VI**, 905; **66,** 185; **69,** 154. Also see OS **IV**, 283.

6-27   The Reduction of Nitriles to Amines
CC,NN-Tetrahydro-biaddition

$$R-C\equiv N + \text{ LiAlH}_4 \longrightarrow R-CH_2-NH_2$$

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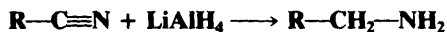
[328]For a review of the mechanism of gas-phase hydrogenation, see Pavlenko *Russ. Chem. Rev.* **1989,** *58,* 453-469.

[329]For a review, see Harada, in Patai *The Chemistry of the Carbon–Nitrogen Double Bond,* Ref. 40, pp. 276-293. For a review with respect to catalytic hydrogenation, see Rylander, *Catalytic Hydrogenation over Platinum Metals,* Ref. 165, pp. 123-138.

[330]For a review of nucleophilic addition to iminium salts, see Paukstelis; Cook, in Cook, Ref. 45, pp. 275-356.

[331]See Cho; Chun *J. Chem. Soc., Perkin Trans. 1* **1990,** 3200; Chan; Osborn *J. Am. Chem. Soc.* **1990,** *112,* 9400, and references cited in these papers.

[332]Howell *Synth. Commun.* **1983,** *13,* 635.

[333]Feuer; Vincent *J. Am. Chem. Soc.* **1962,** *84,* 3771; Feuer; Vincent; Bartlett *J. Org. Chem.* **1965,** *30,* 2877; Ioffe; Tartakovskii; Medvedeva; Novikov *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1964,** 1446; Kawase; Kikugawa, *J. Chem. Soc., Perkin Trans. 1* **1979,** 643.

Nitriles can be reduced to primary amines with many reducing agents,[334] including $LiAlH_4$, BH_3-Me_2S,[335] NaOEt, and hydrogen and a catalyst.[336] $NaBH_4$ does not generally reduce nitriles but does so in alcoholic solvents when a $CoCl_2$ catalyst is added[337] or in the presence of Raney nickel.[338] The reaction is of wide scope and has been applied to many nitriles. When catalytic hydrogenation is used, secondary amines $(RCH_2)_2NH$ are often side products.[339] These can be avoided by adding a compound such as acetic anhydride, which removes the primary amine as soon as it is formed,[340] or by the use of excess ammonia to drive the equilibria backward.[341]

It is not possible to stop with the addition of only 1 mole of hydrogen, i.e., to convert the nitrile to an imine, except where the imine is subsequently hydrolyzed (**6-28**).

N-Alkylnitrilium ions are reduced to secondary amines by $NaBH_4$.[342]

$$RCN \xrightarrow{R_3O^+ \ BF_4^-} R\!-\!C\!\equiv\!\overset{\oplus}{N}\!-\!R' \xrightarrow[\text{diglyme}]{NaBH_4} RCH_2\!-\!NH\!-\!R'$$

Since nitrilium salts can be prepared by treatment of nitriles with trialkyloxonium salts (see **6-9**), this is a method for the conversion of nitriles to secondary amines.

OS **III**, 229, 358, 720; **VI**, 223.

6-28   The Reduction of Nitriles to Aldehydes
Hydro,oxy-de-nitrilo-tersubstitution

$$R\!-\!C\!\equiv\!N \xrightarrow[\text{2. hydrolysis}]{\text{1. HCl, SnCl}_2} R\!-\!CH\!=\!O$$
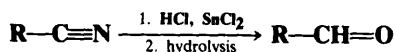
There are two principal methods for the reduction of nitriles to aldehydes.[343] In one of these, known as the *Stephen reduction*, the nitrile is treated with HCl to form

$$RCH\!=\!NH_2^+ \ Cl^-$$

27
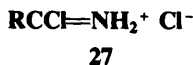
This is reduced with anhydrous $SnCl_2$ to $RCH\!=\!NH$, which precipitates as a complex with $SnCl_4$ and is then hydrolyzed (**6-2**) to the aldehyde. The Stephen reduction is most successful when R is aromatic, but it can be done for aliphatic R up to about six carbons.[344] It is also possible to prepare **27** in a different way, by treating ArCONHPh with PCl_5. The **27** obtained in this way can then be converted to the aldehyde. This is known as the *Sonn–Müller method*.

The other way of reducing nitriles to aldehydes involves using a metal hydride reducing agent to add 1 mole of hydrogen and hydrolysis, in situ, of the resulting imine (which is undoubtedly coordinated to the metal). This has been carried out with $LiAlH_4$,

[334]For a review, see Rabinovitz, in Rappoport *The Chemistry of the Cyano Group*; Wiley: New York, 1970, pp. 307-340. For a list of reagents, with references, see Ref. 64, pp. 437-438.

[335]See Brown; Choi; Narasimhan *Synthesis* **1981**, 605.

[336]For reviews of catalytic hydrogenation of nitriles, see Volf; Pašek, in Červený, Ref. 280, pp. 105-144; Rylander, Ref. 329, pp. 203-226; Freidlin; Sladkova *Russ. Chem. Rev.* **1964**, *33*, 319-330.

[337]Satoh; Suzuki *Tetrahedron Lett.* **1969**, 4555. For a discussion of the mechanism, see Heinzman; Ganem *J. Am. Chem. Soc.* **1982**, *104*, 6801.

[338]Egli *Helv. Chim. Acta* **1970**, *53*, 47.

[339]For a method of making secondary amines the main products, see Galán; de Mendoza; Prados; Rojo; Echavarren *J. Org. Chem.* **1991**, *56*, 452.

[340]For example, see Carothers; Jones *J. Am. Chem. Soc.* **1925**, *47*, 3051; Gould; Johnson; Ferris *J. Org. Chem.* **1960**, *25*, 1658.

[341]For example, see Freifelder *J. Am. Chem. Soc.* **1960**, *82*, 2386.

[342]Borch *Chem. Commun.* **1968**, 442.

[343]For a review, see Rabinovitz, Ref. 334. For a list of reagents, with references, see Ref. 64, pp. 624-625.

[344]Zil'berman; Pyryalova *J. Gen. Chem. USSR* **1963**, *33*, 3348.

LiAlH(OEt)$_3$,[345] DIBALH,[346] and NaAlH$_4$.[347] The metal hydride method is useful for ali-
phatic and aromatic nitriles. Reduction to the aldehyde has also been accomplished by
treatment of the nitrile with sodium hypophosphate and Raney nickel in aqueous acetic
acid–pyridine or formic acid,[348] and with zinc and a Cob(I)alamin catalyst in aqueous acetic
acid.[349]

OS **III**, 626, 818; **VI**, 631.

H. Carbon Attack by Organometallic Compounds[350]

6-29 The Addition of Organometallic Compounds to Aldehydes and Ketones
O-Hydro-C-alkyl-addition
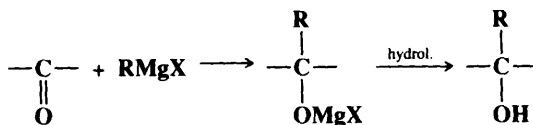
The addition of Grignard reagents to aldehydes and ketones is known as the *Grignard
reaction*.[351] Formaldehyde gives primary alcohols; other aldehydes give secondary alcohols;
and ketones give tertiary alcohols. The reaction is of very broad scope, and hundreds of
alcohols have been prepared in this manner. R may be alkyl or aryl. In many cases the
hydrolysis step is carried out with dilute HCl or H$_2$SO$_4$, 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 (**7-1**). In such cases (and often for other alcohols as well) an aqueous
solution of ammonium chloride is used instead of a strong acid. Other organometallic
compounds can also be used,[352] but in general only of active metals; e.g., alkylmercurys do
not react. In practice, the only organometallic compounds used to any extent, besides
Grignard reagents, are alkyl- and aryllithiums,[353] and alkylzinc reagents[354] where enantio-
selective addition is desired (see below). For the addition of acetylenic groups, sodium may
be the metal used: RC≡CNa (**6-41**); while vinylic alanes (prepared as in **5-13**) are the
reagents of choice for the addition of vinylic groups.[355] Many methods have been reported

[345]Brown; Shoaf *J. Am. Chem. Soc.* **1964**, *86*, 1079. For a review of reductions with this and related reagents, see
Málek *Org. React.* **1988**, *36*, 249-590, pp. 287-289, 438-448.
[346]Miller; Biss; Schwartzman *J. Org. Chem.* **1959**, *24*, 627; Marshall; Andersen; Schlicher *J. Org. Chem.* **1970**,
35, 858.
[347]Zakharkin; Maslin; Gavrilenko *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1964**, 1415.
[348]Backeberg; Staskun *J. Chem. Soc.* **1962**, 3951; van Es; Staskun *J. Chem. Soc.* **1965**, 5775, *Org. Synth. VI*, 631.
For a related method, see Khai; Arcelli *J. Org. Chem.* **1989**, *54*, 949.
[349]Fischli *Helv. Chim. Acta* **1978**, *61*, 2560.
[350]Discussions of most of the reactions in this section are found in Hartley; Patai *The Chemistry of the Metal–
Carbon Bond*, vols. 2, 3 and 4; Wiley: New York, 1985-1987.
[351]For reviews of the addition of organometallic compounds to carbonyl groups, see Eicher, in Patai, Ref. 2, pp.
621-693; Kharasch; Reinmuth *Grignard Reactions of Nonmetallic Substances*; Prentice-Hall: Englewood Cliffs, NJ,
1954, pp. 138-528. For a review of reagents that extend carbon chains by 3 carbons, with some functionality at the
new terminus, see Stowell *Chem. Rev.* **1984**, *84*, 409-435.
[352]For a list of reagents, with references, see Ref. 64, pp. 559-567.
[353]For a discussion, see Wakefield *Organolithium Methods*; Academic Press: New York, 1988, pp. 67-75.
[354]For a review with respect to organozinc compounds, see Furukawa; Kawabata *Adv. Organomet. Chem.* **1974**,
12, 103-112. For a review with respect to organocadmium compounds, see Jones; Desio *Chem. Rev.* **1978**, *78*, 491-
516.
[355]Newman *Tetrahedron Lett.* **1971**, 4571. Vinylic groups can also be added with 9-vinylic-9-BBN compounds:
Jacob; Brown *J. Org. Chem.* **1977**, *42*, 579.

for the addition of allylic groups.[356] Among these are the use of allyltrialkyltin compounds (in the presence of BF$_3$–etherate),[357] allyltrialkylsilanes (in the presence of a Lewis acid),[358] as well as other allylic metal compounds.[359] Although organoboranes do not generally add to aldehydes and ketones,[360] allylic boranes are exceptions.[361] When they add, an allylic rearrangement always takes place, e.g.,

$$
\text{RCH}{=}\text{CH}{-}\text{CH}_2\text{Br}'_2 + \text{R}''{-}\underset{\underset{\text{O}}{\|}}{\text{C}}{-}\text{H} \longrightarrow \text{R}''{-}\underset{\underset{\text{OH}}{|}}{\text{CH}}{-}\underset{\underset{|}{\overset{\text{R}}{|}}}{\text{CH}}{-}\text{CH}{=}\text{CH}_2
$$
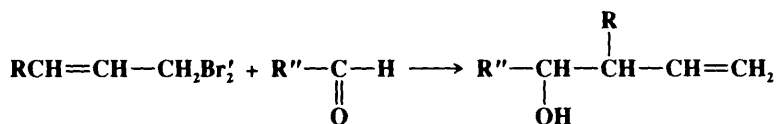
indicating a cyclic mechanism:
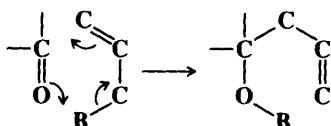
Allylic rearrangements sometimes take place with the other reagents as well.

Certain functional groups (COOEt, CONMe$_2$, CN) can be present in the R group when organotin reagents RSnEt$_3$ are added to aldehydes.[362] A trifluoromethyl group can be added with Me$_3$SiCF$_3$, with Bu$_4$NF as a catalyst, in THF.[363]

The reaction with alkyl- and aryllithium reagents has also been carried out without preliminary formation of RLi: a mixture of RX and the carbonyl compound was added to a suspension of lithium pieces in THF.[364] Yields were generally satisfactory. The magnesium analog of this process is called the *Barbier reaction*.[365] Lithium dimethylcopper Me$_2$CuLi

[356]For a list of reagents and references, see Ref. 64, pp. 567-572.

[357]Naruta; Ushida; Maruyama *Chem. Lett.* **1979**, 919. For a review, see Yamamoto *Aldrichimica Acta* **1987**, *20*, 45-49.

[358]For reviews, see Fleming; Dunoguès; Smithers *Org. React.* **1989**, *37*, 57-575, pp. 113-125, 290-328; Parnes; Bolestova *Synthesis* **1984**, 991-1008, pp. 997-1000. For studies of the mechanism, see Denmark; Wilson; Willson *J. Am. Chem. Soc.* **1988**, *110*, 984; Denmark; Weber; Wilson; Willson *Tetrahedron* **1989**, *45*, 1053; Keck; Andrus; Castellino *J. Am. Chem. Soc.* **1989**, *111*, 8136.

[359]See, for example, Furuta; Ikeda; Meguriya; Ikeda; Yamamoto *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2781; Pétrier; Luche *J. Org. Chem.* **1985**, *50*, 910; Tanaka; Yamashita; Hamatani; Ikemoto; Torii *Chem. Lett.* **1986**, 1611, *Synth. Commun.* **1987**, *17*, 789; Guo; Doubleday; Cohen *J. Am. Chem. Soc.* **1987**, *109*, 4710; Hosomi *Acc. Chem. Res.* **1988**, *21*, 200-206; Araki; Butsugan *Chem. Lett.* **1988**, 457; Minato; Tsuji *Chem. Lett.* **1988**, 2049; Coxon; van Eyk; Steel *Tetrahedron* **1989**, *45*, 1029; Knochel; Rao *J. Am. Chem. Soc.* **1990**, *112*, 6146; Wada; Ohki; Akiba *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1738; Marton; Tagliavini; Zordan; Wardell *J. Organomet. Chem.* **1990**, *390*, 127; Wang; Shi; Xu; Huang *J. Chem. Soc., Perkin Trans. 1* **1990**, 424; Shono; Ishifune; Kashimura *Chem. Lett.* **1990**, 449.

[360]For another exception, involving a vinylic borane, see Satoh; Tayano; Hara; Suzuki *Tetrahedron Lett.* **1989**, *30*, 5153.

[361]For reviews, see Hoffmann; Niel; Schlapbach *Pure Appl. Chem.* **1990**, *62*, 1993-1998; Pelter; Smith; Brown *Borane Reagents*; Academic Press: New York, 1988, pp. 310-318. For a review of allylic boranes, see Bubnov *Pure Appl. Chem.* **1987**, *21*, 895-906.

[362]Kashin; Tulchinsky; Beletskaya *J. Organomet. Chem.* **1985**, *292*, 205.

[363]Prakash; Krishnamurti; Olah *J. Am. Chem. Soc.* **1989**, *111*, 393.

[364]Pearce; Richards; Scilly *J. Chem. Soc., Perkin Trans 1* **1972**, 1655; de Souza-Barboza; Pétrier; Luche; *J. Org. Chem.* **1988**, *53*, 1212.

[365]For a review, with Mg, Li, and other metals, see Blomberg; Hartog *Synthesis* **1977**, 18-30. For a discussion of the mechanism, see Molle; Bauer *J. Am. Chem. Soc.* **1982**, *104*, 3481. For a list of Barbier-type reactions, with references, see Ref. 64, pp. 553-555.

reacts with aldehydes[366] and with certain ketones[367] to give the expected alcohols. The similar reagents RCu(CN)ZnI also react with aldehydes, in the presence of BF_3–etherate, to give secondary alcohols. Carboxylic ester, nitrile, and imide groups in the R are not affected by the reaction conditions.[368]

Trimethylaluminum[369] and dimethyltitanium dichloride[370] exhaustively methylate ketones to give *gem*-dimethyl compounds[371] (see also **0-90**):

$$R-\underset{\underset{O}{\|}}{C}-R' \xrightarrow[\underset{Me_2TiCl_2}{or}]{Me_3Al} R-\underset{\underset{Me}{|}}{\overset{\overset{Me}{|}}{C}}-R'$$
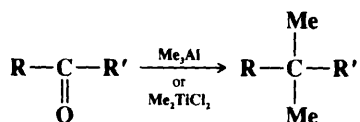
The titanium reagent also dimethylates aromatic aldehydes.[372]

α,β-Unsaturated aldehydes or ketones can give 1,4-addition as well as normal 1,2 addition (see **5-18**). In general, alkyllithiums give less 1,4 addition than the corresponding Grignard reagents.[373] Quinones add Grignard reagents on one or both sides or give 1,4 addition. In a compound containing both an aldehyde and a ketone function it is possible to add RMgX chemoselectively to the aldehyde function without significantly disturbing the ketonic group[374] (see also p. 927). On the other hand, chemoselective addition to a ketonic group can be carried out if the aldehyde is protected with a titanium tetrakis(dialkylamide).[375]

As with the reduction of aldehydes and ketones (**6-25**), the addition of organometallic compounds to these substrates can be carried out enantioselectively and diastereoselectively.[376] Chiral secondary alcohols have been obtained with high ee values by addition to aromatic aldehydes of Grignard and organolithium compounds in the presence of optically active amino alcohols as ligands.[377] High ee values have also been obtained with other organometallics,[378] including organotitanium compounds (methyl, aryl, allylic) in which an optically active ligand is coordinated to the titanium,[379] allylic boron compounds, and organozinc compounds.

[366]Barreiro; Luche; Zweig; Crabbé *Tetrahedron Lett.* **1975**, 2353; Zweig; Luche; Barreiro; Crabbé *Tetrahedron Lett.* **1975**, 2355.

[367]House; Prabhu; Wilkins; Lee *J. Org. Chem.* **1976**, *41*, 3067; Matsuzawa; Isaka; Nakamura; Kuwajima *Tetrahedron Lett.* **1989**, *30*, 1975.

[368]Yeh; Knochel; Santa *Tetrahedron Lett.* **1988**, *29*, 3887.

[369]Meisters; Mole *Aust. J. Chem.* **1974**, *27*, 1655. See also Jeffery; Meisters; Mole *Aust. J. Chem.* **1974**, *27*, 2569. For discussions of the mechanism of this reaction, see Ashby; Goel *J. Organomet. Chem.* **1981**, *221*, C15; Ashby; Smith *J. Organomet. Chem.* **1982**, *225*, 71. For a review of organoaluminum compounds in organic synthesis, see Maruoka; Yamamoto *Tetrahedron* **1988**, *44*, 5001-5032.

[370]Reetz; Westermann; Kyung *Chem. Ber.* **1985**, *118*, 1050.

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

[372]Reetz; Kyung *Chem. Ber.* **1987**, *120*, 123.

[373]An example was given on p. 799.

[374]Vaskan; Kovalev *J. Org. Chem. USSR* **1973**, *9*, 501.

[375]Reetz; Wenderoth; Peter *J. Chem. Soc., Chem. Commun.* **1983**, 406. For another method, see Maruoka; Araki; Yamamoto *Tetrahedron Lett.* **1988**, *29*, 3101.

[376]For reviews, see Solladié, in Morrison, Ref. 294, vol. 2, pp. 157-199, pp. 158-183; Nógrádi, Ref. 294, pp. 160-193; Noyori; Kitamura *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 49-69 [*Angew. Chem. 103*, 34-55].

[377]Mukaiyama; Soai; Sato; Shimizu; Suzuki *J. Am. Chem. Soc.* **1979**, *101*, 1455; Mazaleyrat; Cram *J. Am. Chem. Soc.* **1981**, *103*, 4585; Eleveld; Hogeveen *Tetrahedron Lett.* **1984**, *25*, 5187.

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

[379]Reetz; Kükenhöhner; Weinig *Tetrahedron Lett.* **1986**, *27*, 5711; Wang; Fan; Feng; Quian *Synthesis* **1989**, 291; Riediker; Duthaler *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 494 [*Angew. Chem. 101*, 488]; Riediker; Hafner; Piantini; Rihs; Togni *Angew. Chem. Int. Ed. Engl.* **1989**, *30*, 499 [*Angew. Chem. 101*, 493].

A number of optically active allylic boron compounds have been used, including[380] B-allylbis(2-isocaranyl)borane (**28**),[381] E- and Z-crotyl-(R,R)-2,5-dimethylborolanes (**29**),[382]

28

29

30
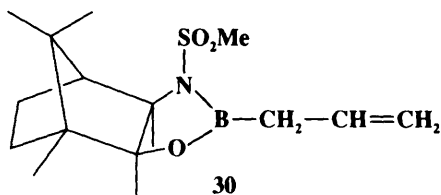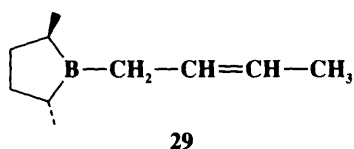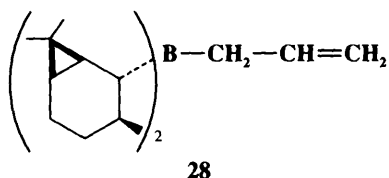
and the borneol derivative **30**,[383] all of which allylate aldehydes with ee values of 90% or more. Where the substrate possesses an aryl group or a triple bond, enantioselectivity is enhanced by using a a metal carbonyl complex of the substrate.[384]

As for the organozinc reagents, very high ee values (90-98%) were obtained from R_2Zn reagents (R = alkyl) and aromatic[385] aldehydes by the use of a small amount (2 mole percent) of the catalyst[386] (−)-3-exo-(dimethylamino)isoborneol (DAIB).[387] High ee values

(−)-DAIB

31
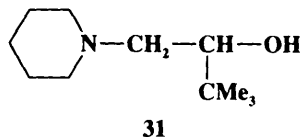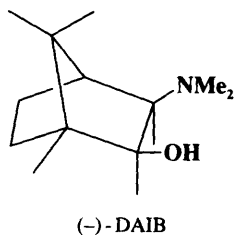
were also achieved with divinylzinc and both aromatic and aliphatic aldehydes, with other optically active amino alcohols as catalysts.[388] When benzaldehyde was treated with Et_2Zn

[380]For some others, see Hoffmann Pure Appl. Chem. **1988**, 60, 123; Corey; Yu; Kim J. Am. Chem. Soc. **1989**, 111, 5495; Roush; Ando; Powers, Palkowitz; Halterman J. Am. Chem. Soc. **1990**, 112, 6339; Brown; Randad Tetrahedron Lett. **1990**, 31, 455; Stürmer; Hoffmann Synlett **1990**, 759.

[381]Brown; Randad Tetrahedron **1990**, 46, 4457; Racherla; Brown J. Org. Chem. **1991**, 56, 401, and references cited in these papers.

[382]Garcia; Kim; Masamune J. Org. Chem. **1987**, 52, 4831.

[383]Reetz; Zierke Chem. Ind. (London) **1988**, 663.

[384]Roush; Park J. Org. Chem. **1990**, 55, 1143.

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

[386]For some other optically active catalysts used with R_2Zn and ArCHO, see Smaardijk; Wynberg J. Org. Chem. **1987**, 52, 135; Joshi; Srebnik; Brown Tetrahedron Lett. **1989**, 30, 5551; Soai; Watanabe; Yamamoto J. Org. Chem. **1990**, 55, 4832; Soai; Hori; Kawahara Tetrahedron: Asymmetry **1990**, 1, 769; Chelucci; Falorni; Giacomelli Tetrahedron: Asymmetry **1990**, 1, 843; Chaloner; Langadianou Tetrahedron Lett. **1990**, 31, 5185; Corey; Yuen; Hannon; Wierda J. Org. Chem. **1990**, 55, 784.

[387]Kitamura; Okada; Suga; Noyori J. Am. Chem. Soc. **1989**, 111, 4028; Noyori; Suga; Kawai; Okada; Kitamura; Oguni; Hayashi; Kaneko; Matsuda J. Organomet. Chem. **1990**, 382, 19.

[388]Oppolzer; Radinov Tetrahedron Lett. **1988**, 29, 5645; Watanabe; Araki; Butsugan; Uemura J. Org. Chem. **1991**, 56, 2218; Soai; Watanabe Tetrahedron: Asymmetry **1991**, 2, 97; Asami; Inoue Chem. Lett. **1991**, 685.

in the presence of the optically active catalyst 1-piperidino-3,3-dimethyl-2-butanol (**31**), a surprising result was obtained. Although the catalyst had only 10.7% excess of one enantiomer, the product PhCH(OH)Me had an ee of 82%.[389] 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[390] 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.

Diastereoselective addition[391] has been carried out with achiral reagents and chiral substrates,[392] similar to the reduction shown on p. 915,[393] but 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.[394] Use of suitable reactants creates, in the most general case, two new chiral centers, so the product can exist as two pairs of enantiomers:

$$R^1{-}\underset{\underset{R^2}{|}}{CHM} + R^3{-}\underset{\underset{O}{\|}}{C}{-}R^4 \longrightarrow$$

diastereomers

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.[395]

In some cases the Grignard reaction can be performed intramolecularly.[396] For example, treatment of 5-bromo-2-pentanone with magnesium and a small amount of mercuric chloride in THF produced 1-methyl-1-cyclobutanol in 60% yield.[397] Other four- and five-membered

$$BrCH_2CH_2CH_2{-}\underset{\underset{O}{\|}}{C}{-}CH_3 \xrightarrow[THF]{Mg} 60\% $$

[389]Oguni; Matsuda; Kaneko *J. Am. Chem. Soc.* **1988**, *110*, 7877.

[390]See Wynberg *Chimia* **1989**, *43*, 150.

[391]For a review, see Yamamoto; Maruyama *Heterocycles* **1982**, *18*, 357-386.

[392]For a review of cases in which the substrate bears a group that can influence the diastereoselectivity by chelating with the metal, see Reetz *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 556-569 [*Angew. Chem. 96*, 542-555]. See also Keck; Castellino *J. Am. Chem. Soc.* **1986**, *108*, 3847.

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

[394]For a review of such reactions with crotylmetallic reagents, see Hoffmann *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 555-566 [*Angew. Chem. 94*, 569-580]. For a discussion of the mechanism, see Denmark; Weber *J. Am. Chem. Soc.* **1984**, *106*, 7970. For some examples, see Hoffmann; Landmann *Chem. Ber.* **1986**, *119*, 2013; Zweifel; Shoup *J. Am. Chem. Soc.* **1988**, *110*, 5578; Gung; Smith; Wolf *Tetrahedron Lett.* **1991**, *32*, 13.

[395]For examples, see Coxon; van Eyk; Steel *Tetrahedron Lett.* **1985**, *26*, 6121; Mukaiyama; Ohshima; Miyoshi *Chem. Lett.* **1987**, 1121; Masuyama; Takahara; Kurusu *Tetrahedron Lett.* **1989**, *30*, 3437.

[396]For a list of reagents, with references, see Ref. 64, p. 557.

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

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.[398] An interesting organometallic ring closure is

base

In this case, because the ketone has no α hydrogen, the base removed a β hydrogen (from a CH_3 group), and the intramolecular addition to the C=O followed.[399]

The gem-disubstituted magnesium compounds formed from CH_2Br_2 or CH_2I_2 (**2-38**) react with aldehydes or ketones to give olefins in moderate-to-good yields.[400] The reaction could
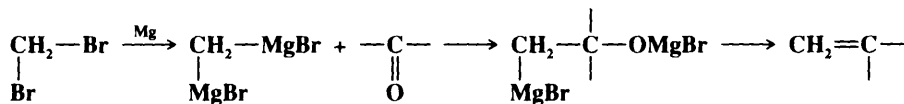
not be extended to other gem-dihalides. Similar reactions with gem-dimetallic compounds prepared with metals other than magnesium have also produced olefins.[401] The α,α-dimetallic derivatives of phenyl sulfones $PhSO_2CM_2R$ (M = Li or Mg) react with aldehydes or ketones R'COR" to give good yields of the α,β-unsaturated sulfones PhSO₂CR=CR'R",[402] which can be reduced with aluminum amalgam (see **0-94**) or with $LiAlH_4$–$CuCl_2$ to give the olefins CHR=CR'R".[403] Olefins can also be obtained from organolithium compounds R^1R^2CHLi, by treating them with ketones R^3COR^4, followed by $SOCl_2$, a procedure which gives $R^1R^2C=CR^3R^4$.[404] These reactions are closely related to the Wittig reaction (**6-47**) and, like it, provide a means of achieving the conversion $R_2C=O \rightarrow R_2C=CR'R"$. On the other hand, gem-dihalides treated with a carbonyl compound and Li or BuLi give epoxides[405] (see also **6-61**).
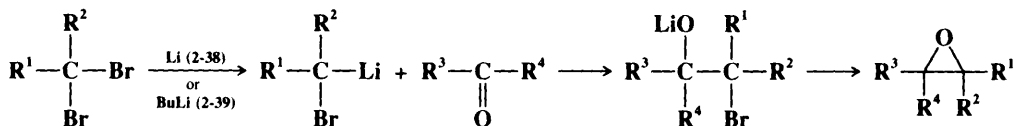
[398]Corey; Kuwajima J. Am. Chem. Soc. **1970**, 92, 395. For another method, see Molander; Etter; Zinke J. Am. Chem. Soc. **1987**, 109, 453; Molander; McKie J. Org. Chem. **1991**, 56, 4112.
[399]Shiner; Berks; Fisher J. Am. Chem. Soc. **1988**, 110, 957.
[400]Bertini; Grasselli; Zubiani; Cainelli Tetrahedron **1970**, 26, 1281.
[401]For example, see Zweifel; Steele Tetrahedron Lett. **1966**, 6021; Cainelli; Bertini; Grasselli; Zubiani Tetrahedron Lett. **1967**, 1581; Takai; Hotta; Oshima; Nozaki Bull. Chem. Soc. Jpn. **1980**, 53, 1698; Knochel; Normant Tetrahedron Lett. **1986**, 27, 1039; Barluenga; Fernández-Simón; Concellón; Yus J. Chem. Soc., Chem. Commun. **1986**, 1665; Okazoe; Takai; Utimoto J. Am. Chem. Soc. **1987**, 109, 951; Piotrowski; Malpass; Boleslawski; Eisch J. Org. Chem. **1988**, 53, 2829; Tour; Bedworth; Wu Tetrahedron Lett. **1989**, 30, 3927; Lombardo Org. Synth. 65, 81.
[402]Pascali; Tangari; Umani-Ronchi J. Chem. Soc., Perkin Trans. 1 **1973**, 1166.
[403]Pascali; Umani-Ronchi J. Chem. Soc., Chem. Commun. **1973**, 351.
[404]Olah; Wu; Farooq J. Org. Chem. **1989**, 54, 1375.
[405]Cainelli; Umani-Ronchi; Bertini; Grasselli; Zubiani Tetrahedron **1971**, 27, 6109; Cainelli; Tangari; Umani-Ronchi Tetrahedron **1972**, 28, 3009.

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[406] and the CHX_2 group when treated with methylene halides and lithium dicyclohexylamide at low temperatures.[407]

$$CH_2X_2 \ + \ \overset{\displaystyle |}{\underset{\displaystyle \underset{O}{\|}}{-C-}} \ \xrightarrow[\text{2. H}_2\text{O}]{\overset{\text{1. LiN(C}_6\text{H}_{11}\text{)}_2}{-78°C}} \ \overset{\displaystyle |}{\underset{\displaystyle \underset{OH}{|}}{-C}}-CHX_2 \quad X = Cl, Br, I$$

A hydroxymethyl group can be added to an aldehyde or ketone with the masked reagent $Me_2(i\text{-}PrO)SiCH_2MgCl$, which with R_2CO gives $R_2C(OH)CH_2Si(O\text{-}i\text{-}Pr)Me_2$, which, with H_2O_2, give 1,2-diols $R_2C(OH)CH_2OH$.[408]
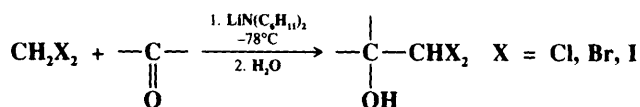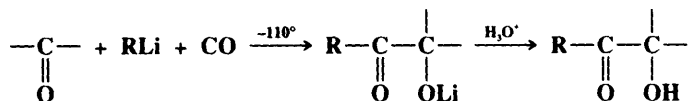
It is possible to add an acyl group to a ketone to give (after hydrolysis) an α-hydroxy ketone.[409] This can be done by adding RLi and CO to the ketone at $-110°C$:[410]

$$\overset{\displaystyle |}{\underset{\displaystyle \underset{O}{\|}}{-C-}} \ + \ RLi \ + \ CO \ \xrightarrow{-110°} \ R-\overset{\displaystyle |}{\underset{\displaystyle \underset{O}{\|}}{C}}-\overset{\displaystyle |}{\underset{\displaystyle \underset{OLi}{|}}{C}}- \ \xrightarrow{H_2O} \ R-\overset{\displaystyle |}{\underset{\displaystyle \underset{O}{\|}}{C}}-\overset{\displaystyle |}{\underset{\displaystyle \underset{OH}{|}}{C}}-$$

When the same reaction is carried out with carboxylic esters R'COOR", α-diketones RCOCOR' are obtained.[410] Another way to add RCO to aldehydes and ketones is to treat the substrate with ArCOLi, generated by treating ArCOTeBu with BuLi.[411]

Although most aldehydes and ketones react very nicely with most Grignard reagents, there are several types of side reaction 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

$$RMgX \ + \ \overset{\displaystyle |}{\underset{\displaystyle \underset{H}{|}}{-C}}-\overset{\displaystyle |}{\underset{\displaystyle \underset{O}{\|}}{C}}-R' \ \longrightarrow \ RH \ + \ \overset{\displaystyle |}{-C}=\overset{\displaystyle |}{\underset{\displaystyle |\underline{O}|^{\ominus}}{C}}-R \ \xrightarrow{\text{hydrol.}} \ \overset{\displaystyle |}{-C}=\overset{\displaystyle |}{\underset{\displaystyle \underset{OH}{|}}{C}}-R' \ \rightleftharpoons \ \overset{\displaystyle |}{\underset{\displaystyle \underset{H}{|}}{-C}}-\overset{\displaystyle |}{\underset{\displaystyle \underset{O}{\|}}{C}}-R'$$

Reduction

$$\overset{\displaystyle |}{\underset{\displaystyle \underset{H}{|}}{-C}}-\overset{\displaystyle |}{\underset{\displaystyle \underset{|}{|}}{C}}-MgX \ + \ \overset{\displaystyle |}{\underset{\displaystyle \underset{O}{\|}}{-C-}} \ \longrightarrow \ \overset{\displaystyle |}{-C}=\overset{\displaystyle |}{C}- \ + \ \overset{\displaystyle H}{\underset{\displaystyle \underset{OMgX}{|}}{-C-}} \ \xrightarrow{\text{hydrol.}} \ \overset{\displaystyle H}{\underset{\displaystyle \underset{OH}{|}}{-C-}}$$
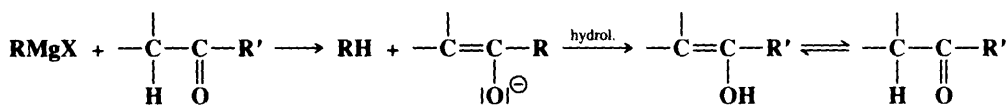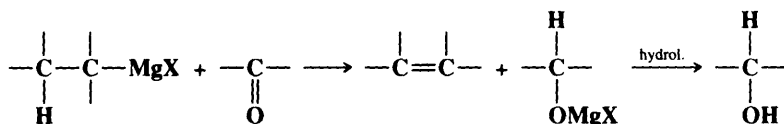
Enolization is an acid–base reaction (2-24) in which a proton is transferred from the α carbon to the Grignard reagent. The carbonyl compound is converted to its enolate ion form, which, on hydrolysis, gives the original ketone or aldehyde. Enolization is important not only for hindered ketones but also for those that have a relatively high percentage of enol form, e.g., β-keto esters, etc. In reduction, the carbonyl compound is reduced to an alcohol (6-25)

[406]Imamoto; Takeyama; Koto *Tetrahedron Lett.* **1986**, *27*, 3243.

[407]Taguchi; Yamamoto; Nozaki *J. Am. Chem. Soc.* **1974**, *96*, 3010 *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1588.

[408]Tamao; Ishida *Tetrahedron Lett.* **1984**, *25*, 4245. For another method, see Imamoto; Takeyama; Yokoyama *Tetrahedron Lett.* **1984**, *25*, 3225.

[409]For a review, see Seyferth; Weinstein; Wang; Hui; Archer *Isr. J. Chem.* **1984**, *24*, 167-175.

[410]Seyferth; Weinstein; Wang *J. Org. Chem.* **1983**, *48*, 1144; Seyferth; Weinstein; Wang; Hui; *Tetrahedron Lett.* **1983**, *24*, 4907.

[411]Hiiro; Morita; Inoue; Kambe; Ogawa; Ryu; Sonoda *J. Am. Chem. Soc.* **1990**, *112*, 455.

by the Grignard reagent, which itself undergoes elimination to give an olefin. Two other side reactions are condensation (between enolate ion and excess ketone) and Wurtz-type coupling (**0-92**). Such highly hindered tertiary alcohols as triisopropylcarbinol, tri-*t*-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.[412] However, these carbinols can be prepared by the use of alkyllithiums at $-80°C$,[413] under which conditions enolization and reduction are much less important.[414] Other methods of increasing the degree of addition at the expense of reduction consist of complexing the Grignard reagent with $LiClO_4$ or $Bu_4N^+ Br^-$,[415] or using benzene or toluene instead of ether as solvent.[416] Both reduction and enolization can be avoided by adding $CeCl_3$ to the Grignard reagent.[417]

Another way to avoid complications is to add $(RO)_3TiCl$, $TiCl_4$,[418] $(RO)_3ZrCl$, 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.[419] 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. Furthermore, organotitanium reagents can be made to add chemoselectively to aldehydes in presence of ketones.[420] Organomanganese compounds are also chemoselective in this way.[421]

There has been much controversy regarding the mechanism of addition of Grignard reagents to aldehydes and ketones.[422] The reaction is difficult to study because of the variable nature of the species present in the Grignard solution (p. 183) 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.[423] 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,[424] based on the discovery that this reaction proceeds by two paths—one first order in MeMgBr and the other first order in Me_2Mg.[425] According to this proposal, both MeMgBr and Me_2Mg add to the carbonyl

[412]Whitmore; George *J. Am. Chem. Soc.* **1942**, *64*, 1239.

[413]Bartlett; Lefferts *J. Am. Chem. Soc.* **1955**, *77*, 2804; Zook; March; Smith *J. Am. Chem. Soc.* **1959**, *81*, 1617; Bartlett; Tidwell *J. Am. Chem. Soc.* **1968**, *90*, 4421. See also Lomas *Nouv. J. Chim.* **1984**, *8*, 365; Molle; Briand; Bauer; Dubois *Tetrahedron* **1984**, *40*, 5113.

[414]Buhler *J. Org. Chem.* **1973**, *38*, 904.

[415]Chastrette; Amouroux *Chem. Commun.* **1970**, 470, *Bull. Soc. Chim. Fr.* **1970**, 4348. See also Richey; DeStephano *J. Org. Chem.* **1990**, *55*, 3281.

[416]Canonne; Foscolos; Caron; Lemay *Tetrahedron* **1982**, *38*, 3563.

[417]Imamoto; Takiyama; Nakamura; Hatajima; Kamiya *J. Am. Chem. Soc.* **1989**, *111*, 4392.

[418]See Reetz; Kyung; Hüllmann *Tetrahedron* **1986**, *42*, 2931.

[419]For a monograph, see Reetz *Organotitanium Reagents in Organic Synthesis*; Springer: New York, 1986. For reviews, see Weidmann; Seebach *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 31-45 [*Angew. Chem. 95*, 12-26]; Reetz *Top. Curr. Chem.* **1982**, *106*, 1-54.

[420]Reetz, Ref. 419 (monograph), pp. 75-86. See also Reetz; Maus *Tetrahedron* **1987**, *43*, 101.

[421]Cahiez; Figadere *Tetrahedron Lett.* **1986**, *27*, 4445. For other organometallic reagents with high selectivity towards aldehyde functions, see Kauffmann; Hamsen; Beirich *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 144 [*Angew. Chem. 94*, 145]; Takai; Kimura; Kuroda; Hiyama; Nozaki *Tetrahedron Lett.* **1983**, *24*, 5281; Soai; Watanabe; Koyano *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2124.

[422]For reviews, see Holm *Acta Chem. Scand., Ser. B* **1983**, *37*, 567-584; Ashby *Pure Appl. Chem.* **1980**, *52*, 545-569, *Bull Soc. Chim. Fr.* **1972**, 2133-2142, *Q. Rev. Chem. Soc.* **1967**, *21*, 259-285; Ashby; Laemmle; Neumann *Acc. Chem. Res.* **1974**, *7*, 272-280; Blomberg *Bull. Soc. Chim. Fr.* **1972**, 2143-2149. For a review of the stereochemistry of the reaction, see Ashby; Laemmle, Ref. 5. For a review of the effects of the medium and the cation, see Solv'yanov; Beletskaya *Russ. Chem. Rev.* **1987**, *56*, 465-476.

[423]See, for example, Ashby; Walker; Neumann *Chem. Commun.* **1970**, 330; Ashby; Neumann; Walker; Laemmle; Chao *J. Am. Chem. Soc.* **1973**, *95*, 3330.

[424]Ashby; Laemmle; Neumann *J. Am. Chem. Soc.* **1972**, *94*, 5421.

[425]Ashby; Laemmle; Neumann *J. Am. Chem. Soc.* **1971**, *93*, 4601; Laemmle; Ashby; Neumann *J. Am. Chem. Soc.* **1971**, *93*, 5120.

carbon, though the exact nature of the step by which MeMgBr or Me$_2$Mg reacts with the substrate is not certain. One possibility is a four-centered cyclic transition state:[426]

$$\begin{array}{cc} \text{Me} \overset{\frown}{\leftharpoondown} \text{Mg} - \text{Br} & \text{Me} \quad \text{MgBr} \\ \text{R}_2\text{C} \overset{\frown}{=\!\!\!=} \text{O} & \longrightarrow \quad \text{R}_2\text{C} - \text{O} \end{array}$$
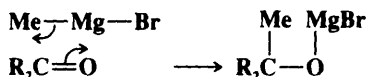
The other type of mechanism is a single electron transfer (SET) process[427] with a ketyl intermediate:[428]

$$R - Mg - X + Ar - \underset{\underset{O}{\|}}{C} - Ar \longrightarrow \left[R\cdot + Ar - \overset{\cdot}{\underset{\underset{OMgX}{|}}{C}} - Ar \right] \overset{A}{\longrightarrow} \underset{Solvent \atop cage}{} Ar - \overset{\overset{R}{|}}{\underset{\underset{OMgX}{|}}{C}} - Ar$$

$$ketyl$$

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 strictly aliphatic ones. Among the evidence[429] for the SET mechanism are esr spectra[430] and the obtention of Ar$_2$C—CAr$_2$ side products (from dimerization of the ketyl).[431] In the case of addition of
 | |
OH OH
RMgX to benzil PhCOCOPh, esr spectra of two different ketyl radicals were observed, both reported to be quite stable at room temperature.[432] 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.[433]

Mechanisms for the addition of organolithium reagents have been investigated much less.[434] Addition of a cryptand that binds Li$^+$ inhibited the normal addition reaction, showing that the lithium is necessary for the reaction to take place.[435]

There is general agreement that the mechanism leading to reduction[436] is usually as follows:

[426]Tuulmets *Org. React.* (*USSR*) **1967**, *4*, 5; House; Oliver *J. Org. Chem.* **1968**, *33*, 929; Ashby; Yu; Roling; *J. Org. Chem.* **1972**, *37*, 1918. See also Billet; Smith *J. Am. Chem. Soc.* **1968**, *90*, 4108; Lasperas; Perez-Rubalcaba; Quiroga-Feijoo *Tetrahedron* **1980**, *36*, 3403.

[427]For a review, see Dagonneau *Bull. Soc. Chim. Fr.* **1982**, II-269-II-280.

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

[429]For other evidence, see Savin; Kitaev *J. Org. Chem. USSR* **1975**, *11*, 2622; Ōkubo *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2379; Ashby; Bowers *J. Am. Chem. Soc.* **1981**, *103*, 2242; Holm *Acta. Chem. Scand., Ser. B* **1982**, *36*, 266, **1988**, *42*, 685; Liotta; Saindane; Waykole *J. Am. Chem. Soc.* **1983**, *105*, 2922; Zhang; Wenderoth; Su; Ashby *J. Organomet. Chem.* **1985**, *292*, 29; Yamataka; Miyano; Hanafusa *J. Org. Chem.* **1991**, *56*, 2573.
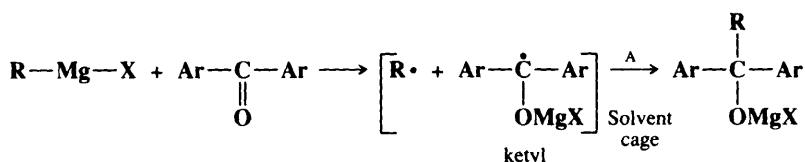
[430]Fauvarque; Rouget, *C. R. Acad. Sci.*, *Ser C* **1968**, *267*, 1355; Maruyama; Katagiri *Chem. Lett.* **1987**, 731, 735, *J. Phys. Org. Chem.* **1988**, *1*, 21.

[431]Blomberg; Mosher *J. Organomet. Chem.* **1968**, *13*, 519; Holm; Crossland *Acta Chem. Scand.* **1971**, *25*, 59.

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

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

[434]See, for example, Al-Aseer; Smith *J. Org. Chem.* **1984**, *49*, 2608; Yamataka; Kawafuji; Nagareda; Miyano; Hanafusa *J. Org. Chem.* **1989**, *54*, 4706.

[435]Perraud; Handel; Pierre *Bull. Soc. Chim. Fr.* **1980**, II-283.

[436]For discussions of the mechanism of reduction, see Singer; Salinger; Mosher *J. Org. Chem.* **1967**, *32*, 3821; Denise; Fauvarque; Ducom *Tetrahedron Lett.* **1970**, 335; Cabaret; Welvart *J. Organomet. Chem.* **1974**, *80*, 199; Holm *J. Organomet. Chem.* **1971**, *29*, C45, *Acta Chem. Scand.* **1973**, *27*, 1552; Morrison; Tomaszewski; Mosher; Dale; Miller; Elsenbaumer *J. Am. Chem. Soc.* **1977**, *99*, 3167; Okuhara *J. Am. Chem. Soc.* **1980**, *102*, 244.
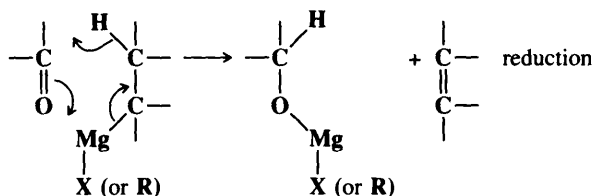
There is evidence that the mechanism leading to enolization is also cyclic, but involves prior coordination with magnesium:[437]
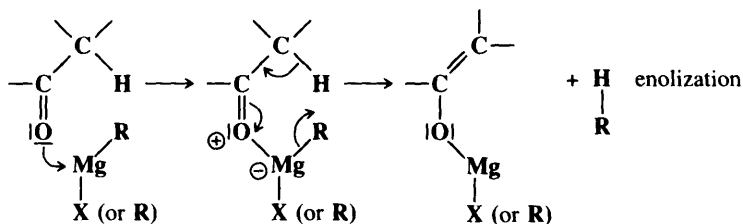
Aromatic aldehydes and ketones can be alkylated and reduced in one reaction vessel by treatment with an alkyl- or aryllithium, followed by lithium and ammonia and then by ammonium chloride.[438]
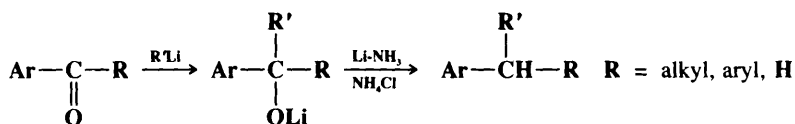
A similar reaction has been carried out with N,N-disubstituted amides: $RCONR_2' \rightarrow$ $RR''CHNR_2'$.[439] When the reagent is $MeNbCl_4$, ketones R_2CO are converted to $R_2C(Cl)Me$.[440]

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; 65, 81; 67, 180, 210; 69, 96, 106, 114, 120, 220.

6-30 The Reformatsky Reaction
O-Hydro-C-α-ethoxycarbonylalkyl-addition
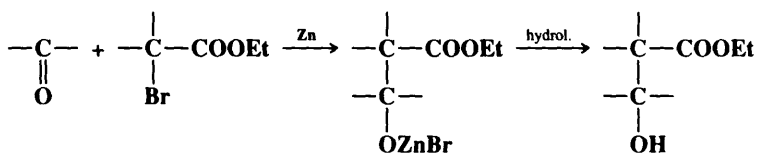
[437]Pinkus; Servoss J. Chem. Soc., Perkin Trans. 2 1979, 1600; Pinkus; Sabesan J. Chem. Soc., Perkin Trans. 2. 1981, 273.
[438]Hall; Lipsky J. Org. Chem. 1973, 38, 1735; Lipsky; Hall Org. Synth. VI, 537; McEnroe; Sha; Hall J. Org. Chem. 1976, 41, 3465.
[439]Hwang; Chu; Fowler J. Org. Chem. 1985, 50, 3885.
[440]Kauffmann; Abel; Neiteler; Schreer Tetrahedron Lett. 1990, 503.

The *Reformatsky reaction* is very similar to **6-29.**[441] 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,[442] α-halo ketones,[443] α-halo N,N-disubstituted amides, and the zinc salts of α-halo carboxylic acids[444] have also been used. With the last reagent the product is a β-hydroxy acid. Especially high reactivity can be achieved with activated zinc,[445] with zinc/silver–graphite,[446] and with zinc and ultrasound.[447] The reaction has also been carried out with other metals instead of zinc (e.g., In,[448] Mn[449]) and with certain other compounds, including SmI_2,[450] Bu_2Te,[451] and Bu_3Sb.[452] 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.

Formally, the reaction can be regarded as if it were analogous to the Grignard reaction

(**6-29**), with EtOOC—C̵—ZnBr (**32**) as an intermediate analogous to RMgX. There *is* an

intermediate derived from zinc and the ester, the structure of which has been shown to be **33**, by x-ray crystallography of the solid intermediate prepared from *t*-BuOCOCH$_2$Br and

33
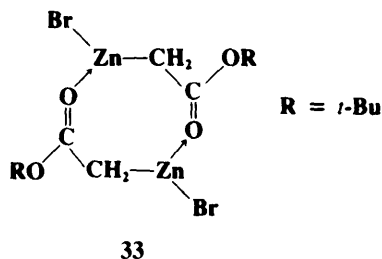
Zn. As can be seen, it has some of the characteristics of **32.**

Usually, after hydrolysis, the alcohol is the product, but sometimes (especially with aryl aldehydes) elimination follows directly and the product is an olefin. By the use of Bu_3P along with Zn, the olefin can be made the main product,[454] making this an alternative to the Wittig reaction (**6-47**). 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:[455]

[441]For reviews, see Fürstner *Synthesis* **1989**, 571-590; Rathke *Org. React.* **1975**, *22*, 423-460; Gaudemar *Organomet. Chem. Rev., Sect A* **1972**, *8*, 183-233.

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

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

[444]Bellassoued; Gaudemar *J. Organomet. Chem.* **1975**, *102*, 1.

[445]Rieke; Uhm *Synthesis* **1975**, 452; Bouhlel; Rathke *Synth. Commun.* **1991**, *21*, 133.

[446]Csuk; Fürstner; Weidmann *J. Chem. Soc., Chem. Commun.* **1986**, 775. See also Bortolussi; Seyden-Penne *Synth. Commun.* **1989**, *19*, 2355.

[447]Han; Boudjouk *J. Org. Chem.* **1982**, *47*, 5030.

[448]Chao; Rieke *J. Org. Chem.* **1975**, *40*, 2253; Araki; Ito; Butsugan *Synth. Commun.* **1988**, *18*, 453.

[449]Cahiez; Chavant *Tetrahedron Lett.* **1989**, *30*, 7373.

[450]Kagan; Namy; Girard *Tetrahedron Suppl.* **1981**, *37*, 175; Tabuchi; Kawamura; Inanaga; Yamaguchi *Tetrahedron Lett.* **1986**, *27*, 3889; Molander; Etter *J. Am. Chem. Soc.* **1987**, *109*, 6556.

[451]Huang; Xie; Wu *Tetrahedron Lett.* **1987**, *28*, 801.

[452]Chen; Huang; Shen; Liao *Heteroat. Chem.* **1990**, *1*, 49.

[453]Dekker; Budzelaar; Boersma; van der Kerk; Spek *Organometallics* **1984**, *3*, 1403.

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

[455]See Cason; Rinehart; Thornton *J. Org. Chem.* **1953**, *18*, 1594; Bellassoued; Gaudemar *J. Organomet. Chem.* **1974**, *81*, 139; Hannick; Kishi *J. Org. Chem.* **1983**, *48*, 3833.

$$\underset{\overset{|}{Br}}{R-C\equiv N} + -\overset{|}{\underset{|}{C}}-COOEt \xrightarrow{Zn} \underset{R-C=NZnBr}{-\overset{|}{\underset{|}{C}}-COOEt} \xrightarrow{hydrol.} \underset{R-C=O}{-\overset{|}{\underset{|}{C}}-COOEt}$$
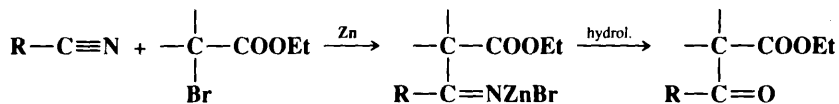
Carboxylic esters have also been used as substrates, but then, as might be expected (p. 881), the result is substitution and not addition:

$$\underset{\overset{||}{O}}{R-C-OR'} + -\overset{|}{\underset{\overset{|}{Br}}{C}}-COOEt \xrightarrow{Zn} \underset{R-C=O}{-\overset{|}{\underset{|}{C}}-COOEt}$$

The product in this case is the same as with the corresponding nitrile, though the pathways are different.

Addition of *t*-butyl acetate to lithium diisopropylamide (LDA) in hexane at $-78°C$ gives the lithium salt of *t*-butyl acetate[456] (2-22) as a stable solid. The nmr and ir spectra of this

$$LiN(iso\text{-}Pr)_2 + CH_3COOCMe_3 \xrightarrow{-78°C} \underset{H}{\overset{H}{}}\!\!>\!\!C\!\!=\!\!C\!\!<\!\!\underset{OCMe_3}{\overset{OLi}{}} + -\overset{}{\underset{\overset{||}{O}}{C}}- \xrightarrow[hydrol.]{after} -\overset{|}{\underset{\overset{|}{OH}}{C}}-CH_2COOCMe_3$$

34
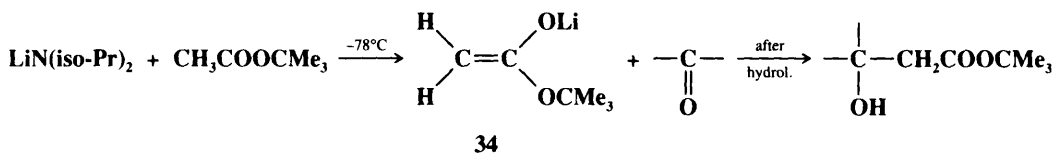
salt in benzene show it to have the enolate structure **34**. Reaction of **34** with a ketone provides a simple rapid alternative to the Reformatsky reaction as a means of preparing β-hydroxy *t*-butyl esters. A similar reaction involves treatment of a ketone with a silyl ketene acetal $R_2C=C(OSiMe_3)OR'$ in the presence of $TiCl_4$[457] (see also the reaction between silyl enol ethers and aldehydes and ketones, in **6-39**).

OS **III**, 408; **IV**, 120, 444.

6-31 The Conversion of Carboxylic Acid Salts to Ketones with Organometallic
         Compounds
         Alkyl-de-oxido-substitution

$$RCOOLi + R'Li \longrightarrow R-\overset{\overset{OLi}{|}}{\underset{\overset{|}{OLi}}{C}}-R' \xrightarrow{H_2O} R-\overset{\overset{}{}}{\underset{\overset{||}{O}}{C}}-R'$$
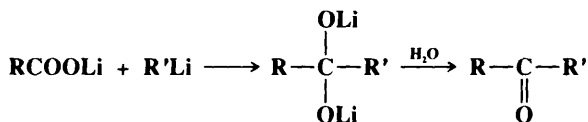
Good yields of ketones can often be obtained by treatment of the lithium salt of a carboxylic acid with an alkyllithium reagent, followed by hydrolysis.[458] R' may be aryl or primary, secondary, or tertiary alkyl. MeLi and PhLi have been employed most often. R may be

[456]Rathke; Sullivan *J. Am. Chem. Soc.* **1973**, *95*, 3050.

[457]See for example. Saigo; Osaki; Mukaiyama *Chem. Lett.* **1975**, 989; Palazzi; Colombo; Gennari *Tetrahedron Lett.* **1986**, *27*, 1735; Oppolzer; Marco-Contelles *Helv. Chim. Acta* **1986**, *69*, 1699; Hara; Mukaiyama *Chem. Lett.* **1989**, 1909. For a list of references, see Ref. 64, pp. 885-887. For methods of preparing silyl ketene acetals, see Revis; Hilty *Tetrahedron Lett.* **1987**, *28*, 4809, and references cited therein.

[458]For a review, see Jorgenson *Org. React.* **1970**, *18*, 1-97. For an improved procedure, see Rubottom; Kim *J. Org. Chem.* **1983**, *48*, 1550.

alkyl or aryl, though lithium acetate generally gives low yields. Tertiary alcohols are side products.

OS **V**, 775.

6-32   The Addition of Grignard Reagents to Acid Derivatives
Dialkyl,hydroxy-de-alkoxy,oxo-tersubstitution

$$
\underset{O}{\overset{\displaystyle R-\overset{\displaystyle}{\underset{\|}{C}}-OR'}}{} + 2R''MgX \longrightarrow R-\underset{OMgX}{\overset{\displaystyle R''}{\underset{|}{\overset{|}{C}}}}-R'' \xrightarrow{\text{hydrol.}} R-\underset{OH}{\overset{\displaystyle R''}{\underset{|}{\overset{|}{C}}}}-R''
$$
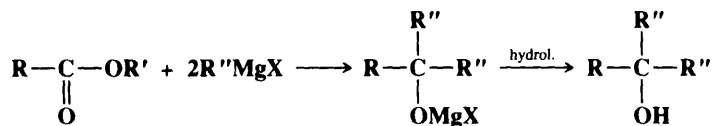
When carboxylic esters are treated with Grignard reagents, there is usually concomitant addition to the carbonyl (**6-29**) and substitution of R″ for OR′ (**0-104**), so that tertiary alcohols are formed in which two R groups are the same. Formates give secondary alcohols and carbonates give tertiary 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.[459] There are many side reactions 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 (**0-104**), which in some cases can be made to predominate. When 1,4-dimagnesium compounds are used, carboxylic esters are converted to cyclopentanols.[460]

$$
\underset{O}{\overset{\displaystyle R-\overset{\displaystyle}{\underset{\|}{C}}-OR'}}{} + BrMg(CH_2)_4MgBr \xrightarrow[\text{hydrol.}]{\text{after}} \text{(cyclopentane ring)}\!-\!\overset{R}{\underset{}{}}\!OH
$$
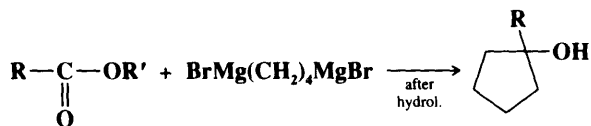
1,5-Dimagnesium compounds give cyclohexanols, but in lower yields.[460]

Trimethylaluminum, which exhaustively methylates ketones (**6-29**), also exhaustively methylates carboxylic acids to give *t*-butyl compounds[461] (see also **0-90**):

$$
RCOOH + \text{excess } Me_3Al \xrightarrow{120^\circ C} RCOOAlMe_2 \xrightarrow{Me_3Al} RCMe_3
$$
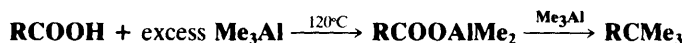
Disubstituted formamides can give addition of 2 moles of Grignard reagent. The products of this reaction (called *Bouveault reaction*) are an aldehyde and a tertiary amine.[462] The use

$$
\underset{O}{\overset{\displaystyle H-\overset{\displaystyle}{\underset{\|}{C}}-NR_2}}{} + 3R'MgX \longrightarrow H-\underset{R'}{\overset{\displaystyle R'}{\underset{|}{\overset{|}{C}}}}-NR_2 + R'CHO
$$
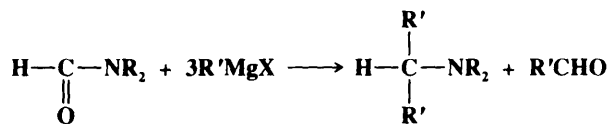
of an amide other than a formamide can give a ketone instead of an aldehyde, but yields are generally low. It has proven possible to add two different R groups by sequential addition

---

[459]For a review of these reactions, see Kharasch; Reinmuth, Ref. 351, pp. 549-766, 846-869.
[460]Canonne; Bernatchez *J. Org. Chem.* **1986**, *51*, 2147, **1987**, *52*, 4025.
[461]Meisters; Mole *Aust. J. Chem.* **1974**, *27*, 1665.
[462]For a review, see Ref. 176, pp. 59-63.

of two Grignard reagents.[463] Alternatively, if R' contains an α hydrogen, the product may be an enamine, and enamines have been synthesized in goods yields by this method.[464]

$$H\overset{\displaystyle |}{\underset{\displaystyle \|}{\underset{\displaystyle O}{C}}}NR_2 \ + \ R'\overset{\displaystyle |}{\underset{\displaystyle R''}{CH}}MgX \ \longrightarrow \ \left[R'\overset{\displaystyle |}{\underset{\displaystyle R''}{CH}}\overset{\displaystyle |}{\underset{\displaystyle OMgX}{CH}}NR_2\right] \ \xrightarrow{-MgXOH} \ R'\overset{\displaystyle |}{\underset{\displaystyle R''}{C}}{=}CHNR_2$$
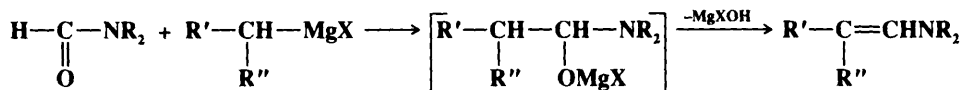
OS **I**, 226; **II**, 179, 602; **III**, 237, 831, 839; **IV**, 601; **VI**, 240, 278; **65**, 42; **67**, 125.

6-33   Conversion of Carboxylic Esters to Enol Ethers
Methylene-de-oxo-bisubstitution

$$R\overset{\displaystyle |}{\underset{\displaystyle OR'}{C}}{=}O \ + \ Cp_2Ti\overset{\diagup CH_2\diagdown}{\underset{\diagdown Cl\diagup}{}}AlMe_2 \ \longrightarrow \ R\overset{\displaystyle |}{\underset{\displaystyle OR'}{C}}{=}CH_2 \qquad Cp = \text{cyclopentadienide}$$

35
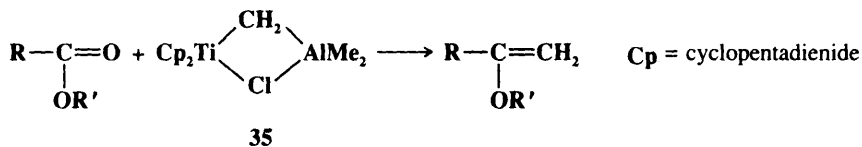
Carboxylic esters and lactones can be converted in good yields to the corresponding enol ethers by treatment with the titanium cyclopentadienide complex **35** (Tebbe's reagent) in toluene-THF containing a small amount of pyridine.[465] **35** is prepared from dicyclopentadienyltitaniumdichloride and trimethylaluminum.[466] Dimethyltitanocene has been used instead of **35**.[467] There are several methods for the conversion C=O to C=CH$_2$ when the substrate is an aldehyde or ketone (see **6-29**, **6-30**, **6-39** to **6-44**, **6-47**), but very few ways to make the same conversion for a carboxylic ester. (Tebbe's reagent also gives good results with ketones.[468]) The enol ether can be hydrolyzed to a ketone (**0-6**), so this is also an indirect method for making the conversion RCOOR' $\rightarrow$ RCOCH$_3$ (see also **0-105**).

Carboxylic esters undergo the conversion C=O $\rightarrow$ C=CHR (R = primary or secondary alkyl) when treated with RCHBr$_2$, Zn, and TiCl$_4$ in the presence of N,N,N',N'-tetramethylethylenediamine.[469] Metal carbene complexes[470] R$_2$C=ML$_n$ (L = ligand), where M is a transition metal such as Zr, W, or Ta, have also been used to convert the C=O of carboxylic esters and lactones to CR$_2$.[471] It is likely that the complex Cp$_2$Ti=CH$_2$ is an intermediate in the reaction with Tebbe's reagent.

OS **69**, 72.

6-34   The Addition of Organometallic Compounds to CO$_2$
C-Alkyl-O-halomagnesio-addition

$$O{=}C{=}O \ + \ RMgX \ \longrightarrow \ R\overset{\displaystyle |}{\underset{\displaystyle OMgX}{C}}{=}O$$
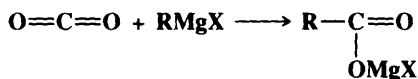
[463]Comins; Dernell *Tetrahedron Lett.* **1981**, *22*, 1085.

[464]Hansson; Wickberg *J. Org. Chem.* **1973**, *38*, 3074.

[465]Tebbe; Parshall; Reddy *J. Am. Chem. Soc.* **1978**, *100*, 3611; Pine; Pettit; Geib; Cruz; Gallego; Tijerina; Pine *J. Org. Chem.* **1985**, *50*, 1212. See also Clawson; Buchwald; Grubbs *Tetrahedron Lett.* **1984**, *25*, 5733; Clift; Schwartz *J. Am. Chem. Soc.* **1984**, *106*, 8300.

[466]For a method of generating this reagent in situ, see Cannizzo; Grubbs *J. Org. Chem.* **1985**, *50*, 2386.

[467]Petasis; Bzowej *J. Am. Chem. Soc.* **1990**, *112*, 6392.

[468]Pine; Shen; Hoang *Synthesis* **1991**, 165.

[469]Okazoe; Takai; Oshima; Utimoto *J. Org. Chem.* **1987**, *52*, 4410. This procedure is also successful for silyl esters, to give silyl enol ethers: Takai; Kataoka; Okazoe; Utimoto *Tetrahedron Lett.* **1988**, *29*, 1065.

[470]For a review of the synthesis of such complexes, see Aguero; Osborn *New J. Chem.* **1988**, *12*, 111-118.

[471]See, for example, Schrock *J. Am. Chem. Soc.* **1976**, *98*, 5399; Aguero; Kress; Osborn *J. Chem. Soc., Chem. Commun.* **1986**, 531; Hartner; Schwartz; Clift *J. Am. Chem. Soc.* **1990**, *105*, 640.

Grignard reagents add to one C=O bond of CO_2 exactly as they do to an aldehyde or a ketone.[472] 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, along with the sequence **0-101—6-5** and reaction **8-8**, this constitutes an important way of increasing a carbon chain by one unit. Since labeled CO_2 is commercially 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, RNa, RCaX, 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 **6-43**).

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

6-35 The Addition of Organometallic Compounds to C=N Compounds
N-Hydro-C-alkyl-addition
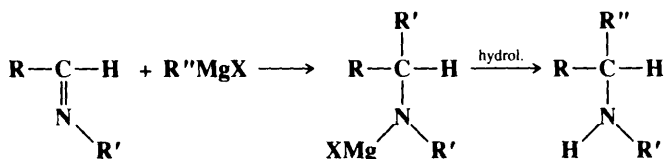
Aldimines can be converted to secondary amines by treatment with Grignard reagents.[473] Ketimines generally give reduction instead of addition. However, organolithium compounds give the normal addition product with both aldimines and ketimines.[474] Other organometallic compounds,[475] including RCu-BF$_3$,[476] allylic boranes[477] (see **6-29**), and allylic stannanes[478] also add to aldimines in the same manner. The addition of organolithiums has been done enantioselectively, with an optically active amino ether as catalyst.[478a] Many other C=N systems (phenylhydrazones, oxime ethers, etc.) give normal addition when treated with Grignard reagents; others give reductions; others give miscellaneous reactions. Oximes can be converted to hydroxylamines by treatment with 2 moles of an alkyllithium reagent, followed by methanol.[479]
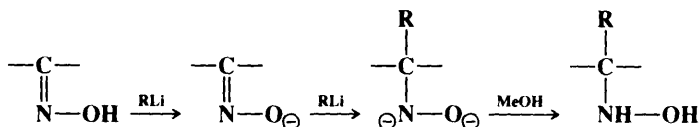
[472]For reviews of the reaction between organometallic compounds and CO$_2$, see Volpin; Kolomnikov; *Organomet. React.* **1975**, *5*, 313-386; Sneeden, in Patai *The Chemistry of Carboxylic Acids and Esters*; Wiley: New York, 1969, pp. 137-173; Kharasch; Reinmuth, Ref. 351, pp. 913-948. For a more general review, see Lapidus; Ping *Russ. Chem. Rev.* **1981**, *50*, 63-75.
[473]For reviews of the addition of organometallic reagents to C=N bonds, see Harada, in Patai *The Chemistry of the Carbon–Nitrogen Double Bond*, Ref. 40, pp. 266-272; Kharasch; Reinmuth, Ref. 451, pp. 1204-1227.
[474]Huet *Bull. Soc. Chim. Fr.* **1964**, 952, 960, 967, 973.
[475]For a list of reagents, with references, see Ref. 64, pp. 425-427.
[476]Wada; Sakurai; Akiba *Tetrahedron Lett.* **1984**, *25*, 1079.
[477]Yamamoto; Nishii; Maruyama; Komatsu; Ito *J. Am. Chem. Soc.* **1986**, *108*, 7778. See also Yamamoto *Acc. Chem. Res.* **1987**, *20*, 243-249.
[478]Keck; Enholm *J. Org. Chem.* **1985**, *50*, 146.
[478a]Tomioka; Inoue; Shindo; Koga *Tetrahedron Lett.* **1991**, *32*, 3095.
[479]Richey; McLane; Phillips *Tetrahedron Lett.* **1976**, 233.

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: $RCH=N(O)OLi + R'MgX \rightarrow RR'C=NOH$.[480]

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 (**6-13**). 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''MgX or R''Li to these compounds gives $ArCHR''NH_2$ after hydrolysis.[481]

Iminium salts[330] give tertiary amines directly, with just R adding:

$$\begin{array}{c} R \\ | \\ -C- + RMgX \longrightarrow -C- \\ \| | \\ \oplus NR'_2 NR'_2 \end{array}$$
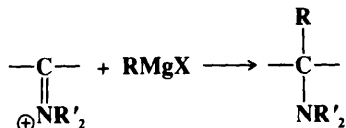
Chloroiminium salts $ClCH=\overset{\oplus}{N}R'_2Cl^-$ (generated in situ from an amide $HCONR'_2$ and phosgene $COCl_2$) react with 2 moles of a Grignard reagent RMgX, one adding to the $C=N$ and the other replacing the Cl, to give tertiary amines $R_2CHNR'_2$.[482]

An alkyl group (primary, secondary, or tertiary) can be added to the oxime ether $CH_2=NOCH_2Ph$ by treatment with the appropriate alkyl halide and an equimolar amount of bis(trimethylstannyl)benzopicolinate.[483] This reaction, which is a free radical addition, is another way to extend a chain by one carbon.

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

6-36 The Addition of Grignard Reagents to Isocyanates
N-Hydro-*C*-alkyl-addition

$$R-N=C=O + R'MgX \longrightarrow R-N=C-OMgX \xrightarrow{\text{hydrol.}} R-N-C=O$$
$$ | | |$$
$$ R' H R'$$
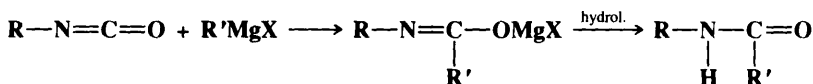
The addition of Grignard reagents to isocyanates gives, after hydrolysis, N-substituted amides.[484] The reaction is written above as involving addition to $C=O$, but the ion is a resonance hybrid and the addition might just as well have been shown as occurring on the $C=N$. Hydrolysis gives the amide. This is a very good reaction and can be used to prepare derivatives of alkyl and aryl halides. The reaction has also been performed with alkyllithium compounds.[485] Isothiocyanates give N-substituted thioamides.

6-37 The Addition of Grignard Reagents to Nitriles
Alkyl,oxo-de-nitrilo-tersubstitution (Overall transformation)

$$R-C\equiv N + R'MgX \longrightarrow R-C-R' \xrightarrow{\text{hydrol.}} R-C-R'$$
$$ \| \|$$
$$ NMgX O$$
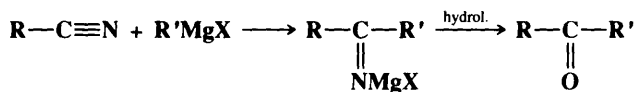
[480]Fujisawa; Kurita; Sato *Chem. Lett.* **1983**, 1537.
[481]Davis; Giangiordano; Starner *Tetrahedron Lett.* **1986**, 27, 3957.
[482]Wieland; Simchen *Liebigs Ann. Chem.* **1985**, 2178.
[483]Hart; Seely *J. Am. Chem. Soc.* **1988**, *110*, 1631.
[484]For a review of this and related reactions, see Screttas; Steele *Org. Prep. Proced. Int.* **1990**, 22, 271-314.
[485]LeBel; Cherluck; Curtis *Synthesis* **1973**, 678. For another method, see Einhorn; Luche *Tetrahedron Lett.* **1986**, 27, 501.

Ketones can be prepared by addition of Grignard reagents to nitriles and subsequent hydrolysis. Many ketones have been made in this manner, though when both R groups are alkyl, yields are not high.[486] Yields can be improved by the use of Cu(I) salts[487] or by using benzene containing one equivalent of ether as the solvent, rather than ether alone.[488] The ketimine salt does not in general react with Grignard reagents: hence tertiary alcohols or tertiary alkyl amines are not often side products.[489] By careful hydrolysis of the salt it is sometimes possible to isolate ketimines R—C—R',[490] especially when R and R' = aryl.

$$\underset{\overset{\|}{\text{NH}}}{\text{R—C—R'}}$$

The addition of Grignard reagents to the C≡N group is normally slower than to the C=O group, and CN-containing aldehydes add the Grignard reagent without disturbing the CN group.[491] In a similar reaction,[492] triethylaluminum[493] reacts with nitriles (in a 2:1 ratio) to give, after hydrolysis, ethyl ketones.[494]

The following mechanism has been proposed for the reaction of the methyl Grignard reagent with benzonitrile:[495]

$$\text{Ph—C}{\equiv}\text{N} \qquad\qquad \text{Ph—C}{\equiv}\text{N}$$
$$\text{Me—Mg—Br} \qquad\qquad \text{Me—Mg—Me}$$
$$\underset{\overset{|}{\text{Me}}}{\text{Ph—C}{=}\text{NMgBr}} \underset{\text{MgBr}_2}{\rightleftharpoons} \underset{\overset{|}{\text{Me}}}{\text{Ph—C}{=}\text{NMgMe}}$$
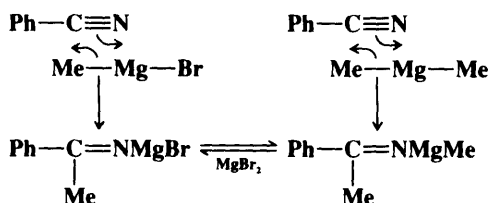
OS **III**, 26, 562; **V**, 520.

6-38   The Addition of Organometallic Reagents to the C=S Bond
C-Alkyl-S-halomagnesio-addition

$$\text{S}{=}\text{C}{=}\text{S} + \text{RMgX} \longrightarrow \underset{\overset{|}{\text{SMgX}}}{\text{S—C}{=}\text{S}}$$
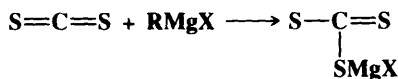
Grignard reagents add to CS_2 to give salts of dithiocarboxylic acids (analogous to **6-34**).[496] Two other reactions are worthy of note. (1) Lithium dialkylcopper reagents react with dithiocarboxylic esters to give tertairy thiols[497] (analogous to **6-32**):

$$\underset{\overset{\|}{\text{S}}}{\text{R—C—SMe}} \xrightarrow[\text{2. H}_2\text{S-NH}_4\text{Cl}]{\text{1. R}'_2\text{CuLi}} \underset{\overset{|}{\text{SH}}}{\overset{\overset{\text{R}'}{|}}{\text{R—C—R'}}}$$
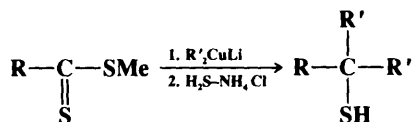
[486]For a review, see Kharasch; Reinmuth, Ref. 351, pp. 767-845.
[487]Weiberth; Hall *J. Org. Chem.* **1987**, *52*, 3901.
[488]Canonne; Foscolos; Lemay *Tetrahedron Lett.* **1980**, 155.
[489]For examples where tertiary amines have been made the main products, see Alvernhe; Laurent *Tetrahedron Lett.* **1973**, 1057; Gauthier; Axiotis; Chastrette *J. Organomet. Chem.* **1977**, *140*, 245.
[490]Pickard; Toblert *J. Org. Chem.* **1961**, *26*, 4886.
[491]Cason; Kraus; McLeod *J. Org. Chem.* **1959**, *24*, 392.
[492]For some other reagents, with references, see Ref. 64, p. 701.
[493]For a review of the reactions of organoaluminum compounds, see Reinheckel; Haage; Jahnke *Organomet. Chem. Rev., Sect. A* **1969**, *4*, 47-136.
[494]Reinheckel; Jahnke *Chem. Ber.* **1964**, *97*, 2661. See also Bagnell; Jeffery; Meisters; Mole *Aust. J. Chem.* **1974**, *27*, 2577.
[495]Ashby; Chao; Neumann *J. Am. Chem. Soc.* **1973**, *95*, 4896, 5186.
[496]For a review of the addition of Grignard reagents to C=S bonds, see Paquer *Bull Soc. Chim. Fr.* **1975**, 1439-1449. For a review of the synthesis of dithiocarboxylic acids and esters, see Ramadas; Srinivasan; Ramachandran; Sastry *Synthesis* **1983**, 605-622.
[497]Bertz; Dabbagh; Williams *J. Org. Chem.* **1985**, *50*, 4414.

(2) Thiono lactones can be converted to cyclic ethers,[498] e.g.:
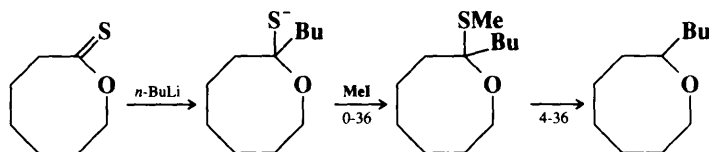
This is a valuable procedure because medium and large ring ethers are not easily made, while the corresponding thiono lactones can be prepared from the readily available lactones (see, for example, **0-22**) by reaction **6-11.**

I.   Carbon Attack by Active Hydrogen Compounds. Reactions **6-39** through **6-48** are base-catalyzed condensations (though some of them are also catalyzed to acids).[499] In **6-39** through **6-47,** 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:
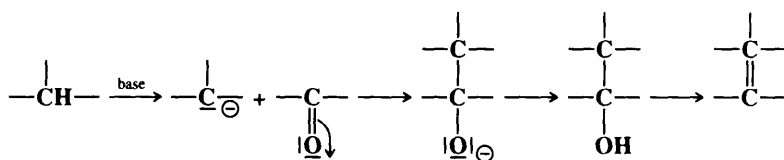
The reactions differ in the nature of the active hydrogen component and the carbonyl component. Table 16.1 illustrates the differences. Reaction **6-48** is an analogous reaction involving addition to C≡N.

6-39   The Aldol Reaction
O-Hydro-*C*-(α-acylalkyl)-addition; α-Acylalkylidene-de-oxo-bisubstitution
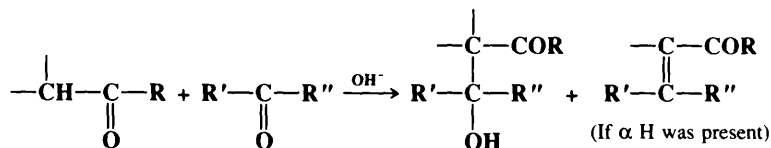
In the *aldol reaction*[500] the α carbon of one aldehyde or ketone molecule adds to the carbonyl carbon of another.[501] The base most often used is OH⁻, though stronger bases, e.g., alu-

[498]Nicolaou; McGarry; Somers; Veale; Furst *J. Am. Chem. Soc.* **1987,** *109,* 2504.
[499]For reviews, see House, Ref. 180, pp. 629-682; Reeves, in Patai, Ref. 2, pp. 567-619. See also Stowell *Carbanions in Organic Synthesis;* Wiley: New York, 1979.
[500]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.
[501]For reviews, see Thebtaranonth; Thebtaranonth, in Patai, Ref. 252, pt. 1, pp. 199-280, pp. 199-212; Hajos, in Augustine *Carbon–Carbon Bond Formation,* vol. 1; Marcel Dekker: New York, 1979; pp. 1-84; Nielsen; Houlihan, *Org. React.* **1968,** *16,* 1-438.

TABLE 16.1   Base-catalyzed condensations showing the active-hydrogen components and the carbonyl components

Reaction	Active-hydrogen component	Carbonyl component	Subsequent reactions
6-39 Aldol reaction	Aldehyde —CH—CHO Ketone —CH—COR	Aldehyde, ketone	Dehydration may follow
6-40	Ester —CH—COOR	Aldehyde, ketone (usually without α-hydrogens)	Dehydration may follow
6-41 Knoevenagel reaction	**Z—CH₂—Z′, Z—CHR—Z′,** and similar molecules	Aldehyde, ketone (usually without α-hydrogens)	Dehydration usually follows
6-42 Peterson reaction	**Me₃Si—CH**	Aldehyde, ketone	Dehydration may follow
6-43	—CH—Z **Z = COR, COOR, NO₂**	**CO₂, CS₂**	
6-44 Perkin reaction	Anhydride —CH—COOCOR	Aromatic aldehyde	Dehydration usually follows
6-45 Darzen's reaction	α-Halo ester XCH—COOR	Aldehyde, ketone	Epoxidation (Sₙ reaction) follows
6-46 Tollens' reaction	Aldehyde —CH—CHO Ketone —CH—COR	Formaldehyde	Crossed Cannizzaro reaction follows
6-47 Wittig reaction	Phosphorous ylide **Ph₃P—C**	Aldehyde, ketone	"Dehydration" always follows
6-48 Thorpe reaction	Nitrile —CH—CN	Nitrile	

minum *t*-butoxide, are sometimes employed. Hydroxide ion is not a strong enough base to convert substantially all of an aldehyde or ketone molecule to the corresponding enolate

$$-\overset{|}{C}H-\underset{\underset{O}{\|}}{C}-R \;\rightleftharpoons\; \left[-\overset{|}{\underset{\ominus}{C}}-\underset{\underset{O}{\|}}{C}-R \;\longleftrightarrow\; -\overset{|}{C}=\underset{\underset{\underset{\ominus}{|\underline{O}|}}{}}{C}-R \right]$$

ion, i.e., the equilibrium lies well to the left, for both aldehydes and ketones. Nevertheless, enough enolate ion is present for the reaction to proceed:
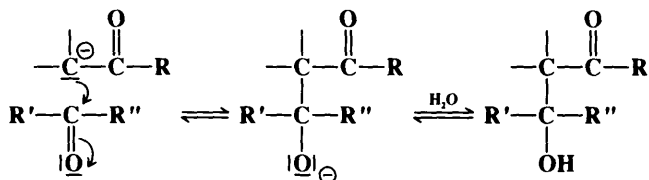
The product is a β-hydroxy aldehyde (called an *aldol*) or ketone, which in some cases is dehydrated during the course of the reaction. Even if the dehydration is not spontaneous, it can usually be done easily, since the new double bond is in conjugation with the C=O bond; so that this is a method of preparing α,β-unsaturated aldehydes and ketones as well as β-hydroxy aldehydes and ketones. 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*). There is evidence that an SET mechanism can intervene when the substrate is an aromatic ketone.[502]

Under the principle of vinylology, the active hydrogen can be one in the γ position of an α,β-unsaturated carbonyl compound:
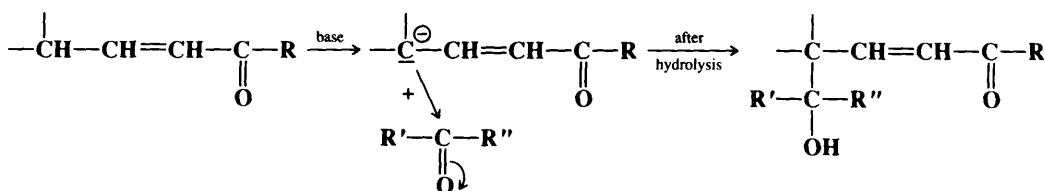
The scope of the aldol reaction may be discussed under five headings:

1. *Reaction between two molecules of the same aldehyde.* The equilibrium lies far to the right,[503] 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.* In this case the equilibrium lies well to the left,[504] 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 (for example, see OS **I,** 199). In this method the ketone is refluxed in such a way that the condensate drips into a separate chamber, in which the base is present. In this chamber the reaction proceeds to the small extent permitted by the unfavorable equilibrium. When the chamber is full, the mixture of the ketone and its dimer is siphoned back into the original flask, out of contact with the base. Since the boiling point of the dimer is higher than that of the ketone, only the ketone is volatilized back to the chamber containing the base, where a little more of it is converted to dimer, and the process is repeated until a reasonable yield of dimer is obtained. Two molecules of the same ketone can also be condensed without a

[502]Ashby; Argyropoulos; Meyer; Goel *J. Am. Chem. Soc.* **1982,** *104,* 6788; Ashby; Argyropoulos *J. Org. Chem.* **1986,** *51,* 472.
[503]For discussions of equilibrium constants in aldol reactions, see Guthrie; Wang *Can. J. Chem.* **1991,** *69,* 339; Guthrie *J. Am. Chem. Soc.* **1991,** *113,* 7249, and references cited in these papers.
[504]The equilibrium concentration of the product from acetone in pure acetone was determined to be 0.01%: Maple; Allerhand *J. Am. Chem. Soc.* **1987,** *109,* 6609.

Soxhlet extractor,[505] by treatment with basic Al_2O_3.[506] 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.)

3. *Reaction between two different aldehydes.* In the most general case, this will produce a mixture of four products (eight, if the olefins 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.*

4. *Reaction between two different ketones.* This is seldom attempted (except with the use of preformed enolates, see below), but similar considerations apply.

5. *Reaction between an aldehyde and a ketone.* This is usually feasible, especially when the aldehyde has no α hydrogen, since there is no competition from ketone condensing with itself.[507] This is also called the *Claisen–Schmidt reaction.* Even when the aldehyde has an α hydrogen, it is the α carbon of the ketone that adds to the carbonyl of the aldehyde, not the other way around. The reaction can be made regioselective by preparing an enol derivative of the ketone separately[508] and then adding this to the aldehyde (or ketone), which assures that the coupling takes place on the desired side of an unsymmetrical ketone. A number of these preformed enolates have been used, the most common of which is the silyl enol ether of the ketone. This can be combined with an aldehyde or ketone, with $TiCl_4$[509]

$$R^1—\underset{\underset{OSiMe_3}{|}}{C}=CHR^2 \;+\; R^3—\underset{\underset{O}{||}}{C}—R^4 \xrightarrow[2.\,H_2O]{1.\,TiCl_4} R^1—\underset{\underset{O}{||}}{C}—\underset{\underset{R^2}{|}}{CH}—\underset{\underset{OH}{|}}{\overset{\overset{R^3}{|}}{C}}—R^4$$

36

(the *Mukaiyama reagent*), with various other catalysts, and even in aqueous solution, with no catalyst at all.[510] The large number of catalysts reported[511] testify to the importance of this method. 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 **36**.[512] Enol acetates and enol ethers also give this product when treated with acetals and $TiCl_4$ or a similar catalyst.[513] When the catalyst is dibutyltin bis(triflate) $Bu_2Sn(OTf)_2$, al-

[505]For another method, see Barot; Sullins; Eisenbraun *Synth. Commun.* **1984**, *14*, 397.

[506]Muzart *Synthesis* **1982**, 60, *Synth. Commun.* **1985**, 285.

[507]For a study of the rate and equilibrium constants in the reaction between acetone and benzaldehyde, see Guthrie; Cossar; Taylor *Can. J. Chem.* **1984**, *62*, 1958.

[508]For some other aldol reactions with preformed enol derivatives, see Schulz; Steglich *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 251 [*Angew. Chem. 89*, 255]; Paterson; Fleming *Tetrahedron Lett.* **1979**, 2179; Itoh; Ozawa; Oshima; Nozaki *Bull. Chem. Soc. Jpn.* **1981**, *54*, 274; Yamamoto; Yatagai; Maruyama *J. Chem. Soc., Chem. Commun.* **1981**, 162; Kowalski; Fields *J. Am. Chem. Soc.* **1982**, *104*, 1777; Fujita; Schlosser *Helv. Chim. Acta* **1982**, *65*, 1258; Kato; Mukaiyama; *Chem. Lett.* **1983**, 1727; Dubois; Axiotis *Tetrahedron Lett.* **1984**, *25*, 2143. For reviews of this subject, see Mukaiyama *Isr. J. Chem.* **1984**, *24*, 162-166; Caine, in Augustine, Ref. 501, pp. 264-276.

[509]Mukaiyama; Banno; Narasaka *J. Am. Chem. Soc.* **1974**, *96*, 7503; Mukaiyama *Pure Appl. Chem.* **1983**, *55*, 1749-1758; Kohler *Synth. Commun.* **1985**, *15*, 39; Mukaiyama; Narasaka *Org. Synth. 65*, 6. For a discussion of the mechanism, see Gennari; Colombo; Bertolini; Schimperna *J. Org. Chem.* **1987**, *52*, 2754. For a review of this and other applications of $TiCl_4$ in organic synthesis, see Mukaiyama *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 817-826 [*Angew. Chem. 89*, 856-866]. See also Reetz, Ref. 419.

[510]Lubineau; Meyer *Tetrahedron* **1988**, *44*, 6065.

[511]See, for example, Noyori; Nishida; Sakata *J. Am. Chem. Soc.* **1981**, *103*, 2106; Nakamura; Shimizu; Kuwajima; Sakata; Yokoyama; Noyori *J. Org. Chem.* **1983**, *48*, 932; Naruse; Ukai; Ikeda; Yamamoto *Chem. Lett.* **1985**, 1451; Sato; Matsuda; Izumi *Tetrahedron Lett.* **1986**, *27*, 5517; Reetz; Vougioukas *Tetrahedron Lett.* **1987**, *28*, 793; Vougioukas; Kagan *Tetrahedron Lett.* **1987**, *28*, 5513; Mukaiyama; Kobayashi; Tamura; Sagawa *Chem. Lett.* **1987**, 491; Iwasawa; Mukaiyama *Chem. Lett.* **1987**, 463; Kawai; Onaka; Izumi *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1237; Ohki; Wada; Akiba *Tetrahedron Lett.* **1988**, *29*, 4719; Mukaiyama; Matsui; Kashiwagi *Chem. Lett.* **1989**, 993.

[512]Mukaiyama; Hayashi *Chem. Lett.* **1974**, 15; Mukaiyama; Kobayashi; Murakami *Chem. Lett.* **1984**, 1759; Murata; Suzuki; Noyori *Tetrahedron* **1988**, *44*, 4259. For a review of cross-coupling reactions of acetals, see Mukaiyama; Murakami *Synthesis* **1987**, 1043-1054.

[513]Mukaiyama; Izawa; Saigo *Chem. Lett.* **1974**, 323; Kitazawa; Imamura; Saigo; Mukaiyama *Chem. Lett.* **1975**, 569.

dehydes react, but not their acetals, while acetals of ketones react, but not the ketones themselves.[514] Other types of preformed derivatives that react with aldehydes and ketones are enamines (with a Lewis acid catalyst),[515] and enol borinates $R'CH{=}CR''{-}OBR_2$[516] (which can be synthesized by **5-19**, or directly from an aldehyde or ketone[517]). Preformed metallic enolates are also used. For example lithium enolates[518] (prepared by **2-22**) react with the substrate in the presence of $ZnCl_2$;[519] in this case the aldol product is stabilized by chelation of its two oxygen atoms with the zinc ion.[520] Among other metallic enolates used for aldol reactions are those of Ti,[521] Zr,[522] and Pd,[523] all of which give products regioselectively. α-Alkoxy ketones react with lithium enolates particularly rapidly.[524]

The reactions with preformed enol derivatives provide a way to control the stereoselectivity of the aldol reaction.[525] As with the Michael reaction (**5-17**), the aldol reaction creates two new chiral centers, and, in the most general case, there are four stereoisomers of the aldol product, which can be represented as

syn (or erythro) ($\pm$) pair   anti (or threo) ($\pm$) pair
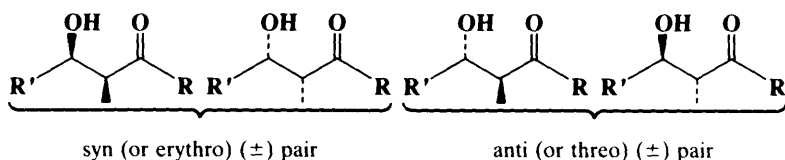
Among the preformed enol derivatives used in this way have been enolates of magnesium, lithium,[526] titanium,[527] rhodium,[528] zirconium,[522] and tin,[529] silyl enol ethers,[530] enol borinates,[531] and enol borates $R'CH{=}CR''{-}OB(OR)_2$.[532] In general, metallic Z enolates give

[514]Sato; Otera; Nozaki *J. Am. Chem. Soc.* **1990**, *112*, 901.
[515]Takazawa; Kogami; Hayashi *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2427.
[516]Inoue; Mukaiyama *Bull. Chem. Soc. Jpn.* **1980**, *53*, 174; Kuwajima; Kato; Mori *Tetrahedron Lett.* **1980**, *21*, 4291; Wada *Chem. Lett.* **1981**, 153; Hooz; Oudenes; Roberts; Benderly *J. Org. Chem.* **1987**, *52*, 1347; Nozaki; Oshima; Utimoto *Tetrahedron Lett.* **1988**, *29*, 1041. For a review, see Pelter; Smith; Brown, Ref. 361, pp. 324-333.
[517]For conversion of ketones to either Z or E enol borinates, see, for example, Evans; Nelson; Vogel; Taber *J. Am. Chem. Soc.* **1981**, *103*, 3099; Brown; Dhar; Bakshi; Pandiarajan; Singaram *J. Am. Chem. Soc.* **1989**, *111*, 3441.
[518]For a complete structure–energy analysis of one such reaction, see Arnett; Fisher; Nichols; Ribeiro *J. Am. Chem. Soc.* **1990**, *112*, 801.
[519]House; Crumrine; Teranishi; Olmstead *J. Am. Chem. Soc.* **1973**, *95*, 3310.
[520]It has been contended that such stabilization is not required: Mulzer; Brüntrup; Finke; Zippel *J. Am. Chem. Soc.* **1979**, *101*, 7723.
[521]Stille; Grubbs *J. Am. Chem. Soc.* **1983**, *105*, 1664.
[522]Evans; McGee *Tetrahedron Lett.* **1980**, *21*, 3975, *J. Am. Chem. Soc.* **1981**, *103*, 2876.
[523]Nokami; Mandai; Watanabe; Ohyama; Tsuji *J. Am. Chem. Soc.* **1989**, *111*, 4126.
[524]Das; Thornton *J. Am. Chem. Soc.* **1990**, *112*, 5360.
[525]For reviews, see Heathcock *Aldrichimica Acta* **1990**, *23*, 99-111; *Science* **1981**, *214*, 395-400; Nógrádi, Ref. 294, pp. 193-220; Heathcock, in Morrison, Ref. 294, vol. 3, 1984, pp. 111-212; Heathcock, in Buncel; Durst *Comprehensive Carbanion Chemistry*, pt. B, Elsevier: New York, 1984, pp. 177-237; Evans; Nelson; Taber *Top. Stereochem.* **1982**, *13*, 1-115; Evans *Aldrichimica Acta* **1982**, *15*, 23-32.
[526]Fellmann; Dubois *Tetrahedron* **1978**, *34*, 1349; Heathcock; Pirrung; Montgomery; Lampe *Tetrahedron* **1981**, *37*, 4087; Masamune; Ellingboe; Choy *J. Am. Chem. Soc.* **1982**, *104*, 5526; Ertas; Seebach *Helv. Chim. Acta* **1985**, *68*, 961.
[527]Siegel; Thornton *Tetrahedron Lett.* **1986**, 27, 457; Nerz-Stormes; Thornton *Tetrahedron Lett.* **1986**, 897; Evans; Rieger; Bilodeau; Urpí *J. Am. Chem. Soc.* **1991**, *113*, 1047.
[528]Slough; Bergman; Heathcock *J. Am. Chem. Soc.* **1989**, *111*, 938.
[529]Mukaiyama; Iwasawa; Stevens; Haga *Tetrahedron* **1984**, *40*, 1381; Labadie; Stille *Tetrahedron* **1984**, *40*, 2329; Yura; Iwasawa; Mukaiyama *Chem. Lett.* **1986**, 187. See also Nakamura; Kuwajima *Tetrahedron Lett.* **1983**, *24*, 3347.
[530]Matsuda; Izumi *Tetrahedron Lett.* **1981**, *22*, 1805; Yamamoto; Maruyama; Matsumoto *J. Am. Chem. Soc.* **1983**, *105*, 6963; Sakurai; Sasaki; Hosomi; *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3195; Hagiwara; Kimura; Uda *J. Chem. Soc., Chem. Commun.* **1986**, 860.
[531]Masamune; Mori; Van Horn; Brooks *Tetrahedron Lett.* **1979**, 1665; Evans et al., Ref. 517; Evans; Bartroli; Shih *J. Am. Chem. Soc.* **1981**, *103*, 2127; Masamune; Choy; Kerdesky; Imperiali *J. Am. Chem. Soc.* **1981**, *103*, 1566; Heathcock; Arseniyadis *Tetrahedron Lett.* **1985**, *26*, 6009; Paterson; Goodman; Lister; Schumann; McClure; Norcross *Tetrahedron* **1990**, *46*, 4663; Walker; Heathcock *J. Org. Chem.* **1991**, *56*, 5747. For reviews, see Paterson *Chem. Ind. (London)* **1988**, 390-394; Pelter; Smith; Brown, Ref. 516.
[532]Hoffmann; Ditrich; Fröch *Liebigs Ann. Chem.* **1987**, 977.

the syn (or erythro) pair, and this reaction is highly useful for the diastereoselective synthesis of these products.[533] The *E* isomers generally react nonstereoselectively. However, anti (or threo) stereoselectivity has been achieved in a number of cases, with titanium enolates,[534] with germanium enolates,[535] with magnesium enolates,[535a] with certain enol borinates,[536] and with lithium enolates at −78°C.[537] High diastereoselectivity was also achieved, without a preformed enolate, in the reaction between ethyl ketones and aldehydes, by performing the reaction in the presence of $PhBCl_2$ and Et_3N.[538]

These reactions can also be made enantioselective (in which case only one of the four isomers predominates) by using[539] chiral enol derivatives,[540] chiral aldehydes or ketones,[541] or both.[542] Since both new chiral centers are formed enantioselectively, this kind of process is called *double asymmetric synthesis*.[543] A single one of the four stereoisomers has also been produced where both the enolate derivative and substrate were achiral, by carrying out the reaction in the presence of an optically active boron compound[544] or a diamine coordinated with a tin compound.[545]

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 $LiN(iso\text{-}Pr)_2$ as the base:[546]

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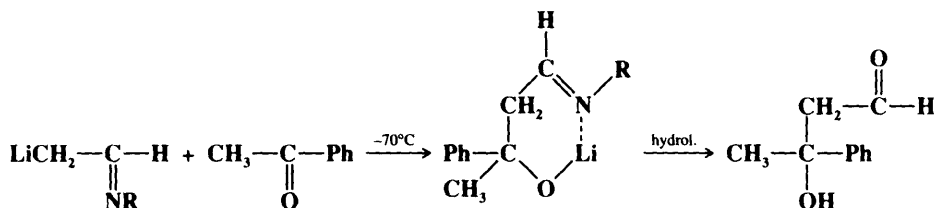
[533]For discussion of transition state geometries in this reaction, see Hoffmann; Ditrich; Froech; Cremer *Tetrahedron* **1985**, *41*, 5517; Anh; Thanh *Nouv. J. Chim.* **1986**, *10*, 681; Li; Paddon-Row; Houk *J. Org. Chem.* **1990**, *55*, 481; Denmark; Henke *J. Am. Chem. Soc.* **1991**, *113*, 2177.

[534]See Murphy; Procter; Russell *Tetrahedron Lett.* **1987**, *28*, 2037; Shirodkar; Nerz-Stormes; Thornton *Tetrahedron Lett.* **1990**, *31*, 4699; Nerz-Stormes; Thornton *J. Org. Chem.* **1991**, *56*, 2489.

[535]Yamamoto; Yamada *J. Chem. Soc., Chem. Commun.* **1988**, 802.

[535a]Swiss; Choi; Liotta; Abdel-Magid; Maryanoff *J. Org. Chem.* **1991**, *56*, 5978.

[536]Masamune; Sato; Kim; Wollmann *J. Am. Chem. Soc.* **1986**, *108*, 8279; Danda; Hansen; Heathcock *J. Org. Chem.* **1990**, *55*, 173. See also Corey; Kim *Tetrahedron Lett.* **1990**, *31*, 3715.

[537]Hirama; Noda; Takeishi; Itô *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2645; Majewski; Gleave *Tetrahedron Lett.* **1989**, *30*, 5681.

[538]Hamana; Sasakura; Sugasawa *Chem. Lett.* **1984**, 1729.

[539]For reviews, see Klein, in Patai *Supplement A: The Chemistry of Double-bonded Functional Groups*, vol. 2, pt. 1; Wiley: New York, 1989, pp. 567-677; Braun *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 24-37 [*Angew. Chem. 99*, 24-37].

[540]For examples, see Eichenauer; Friedrich; Lutz; Enders *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 206 [*Angew. Chem. 90*, 219]; Meyers; Yamamoto *Tetrahedron* **1984**, *40*, 2309; Ando; Shioiri *J. Chem. Soc., Chem. Commun.* **1987**, 1620; Muraoka; Kawasaki; Koga *Tetrahedron Lett.* **1988**, *29*, 337; Paterson; Goodman *Tetrahedron Lett.* **1989**, *30*, 997; Siegel; Thornton *J. Am. Chem. Soc.* **1989**, *111*, 5722; Gennari; Molinari; Cozzi; Oliva *Tetrahedron Lett.* **1989**, *30*, 5163; Faunce; Grisso; Mackenzie *J. Am. Chem. Soc.* **1991**, *113*, 3418.

[541]For example, see Ojima; Yoshida; Inaba *Chem. Lett.* **1977**, 429; Heathcock; Flippin *J. Am. Chem. Soc.* **1983**, *105*, 1667; Reetz; Kesseler; Jung *Tetrahedron* **1984**, *40*, 4327.

[542]For example, see Heathcock; White; Morrison; VanDerveer *J. Org. Chem.* **1981**, *46*, 1296; Short; Masamune *Tetrahedron Lett.* **1987**, *28*, 2841.

[543]For a review, see Masamune; Choy; Petersen; Sita *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 1-30 [*Angew. Chem. 97*, 1-31].

[544]Corey; Imwinkelried; Pikul; Xiang *J. Am. Chem. Soc.* **1989**, *111*, 5493; Corey; Kim *J. Am. Chem. Soc.* **1990**, *112*, 4976; Furuta; Maruyama; Yamamoto *J. Am. Chem. Soc.* **1991**, *113*, 1041; Kiyooka; Kaneko; Komura; Matsuo; Nakano *J. Org. Chem.* **1991**, *56*, 2276.

[545]Mukaiyama; Uchiro; Kobayashi *Chem. Lett.* **1990**, 1147.

[546]Wittig; Frommeld; Suchanek *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 683 [*Angew. Chem. 75*, 303]. For reviews, see Mukaiyama *Org. React.* **1982**, *28*, 203-331; Wittig *Top. Curr. Chem.* **1976**, *67*, 1-14; *Rec. Chem. Prog.* **1967**, *28*, 45-60; Wittig; Reiff *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 7-14; [*Angew. Chem. 80*, 8-15]; Reiff *Newer Methods Prep. Org. Chem.* **1971**, *6*, 48-66.

This is known as the *directed aldol reaction*. Similar reactions have been performed with α-lithiated dimethylhydrazones of aldehydes or ketones[547] and with α-lithiated aldoximes.[548]

The aldol reaction can also be performed with acid catalysts, 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:[549]
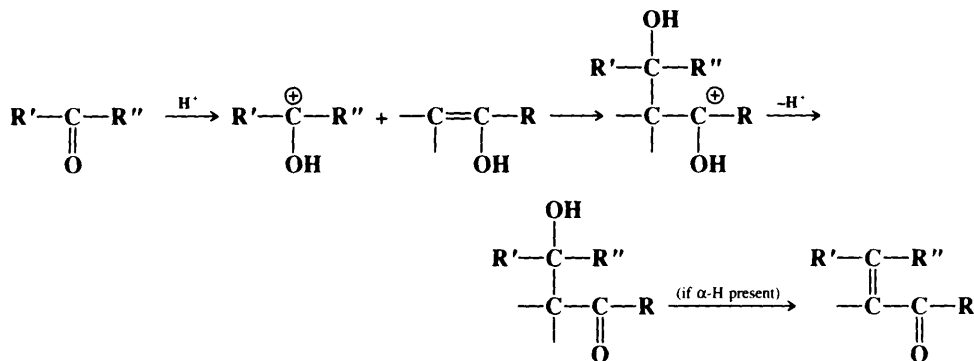
With respect to the enol, this mechanism is similar to that of halogenation (**2-4**).

A side reaction that is sometimes troublesome is further condensation, since the product of an aldol reaction is still an aldehyde or ketone.

Aldol reactions are often used to close five- and six-membered rings. Because of the favorable entropy (p. 211), such ring closures generally take place with ease, even where a ketone condenses with a ketone. An important example is the *Robinson annulation reaction*,[550] which has often been used in the synthesis of steroids and terpenes. In this reaction a cyclic ketone is converted to another cyclic ketone, with one additio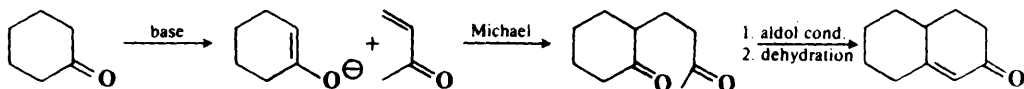nal six-membered ring containing a double bond. The substrate is treated with methyl vinyl ketone (or a simple derivative of methyl vinyl ketone) and a base.[551] The enolate ion of the substrate adds to the methyl vinyl ketone in a Michael reaction (**5-17**) to give a diketone that undergoes or

is made to undergo an internal aldol reaction and subsequent dehydration to give the product.[552] Because methyl vinyl ketone has a tendency to polymerize, precursors are often used instead, i.e., compounds that will give methyl vinyl ketone when treated with a base. One common example, $MeCOCH_2CH_2NEt_2Me^+$ I^- (see **7-8**), is easily prepared by quaternization of $MeCOCH_2CH_2NEt_2$, which itself is prepared by a Mannich reaction (**6-16**)

[547]Corey; Enders *Tetrahedron Lett.* **1976**, 11. See also Beam; Thomas; Sandifer; Foote; Hauser *Chem. Ind. (London)* **1976**, 487; Sugasawa; Toyoda; Sasakura *Synth. Commun.* **1979**, *9*, 515; Depezay; Le Merrer *Bull. Soc. Chim. Fr.* **1981**, II-306.

[548]Hassner; Näumann *Chem. Ber.* **1988**, *121*, 1823.

[549]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; Cox; Slebocka-Tilk; Tencer; Tidwell *J. Am. Chem. Soc.* **1985**, *107*, 3640.

[550]For reviews of this and related reactions, see Gawley *Synthesis* **1976**, 777-794; Jung *Tetrahedron* **1976**, *32*, 1-31; Mundy *J. Chem. Educ.* **1973**, *50*, 110-113. For a list of references, see Ref. 64, pp. 668-670.

[551]Acid catalysis has also been used: see Heathcock; Ellis; McMurry; Coppolino *Tetrahedron Lett.* **1971**, 4995.
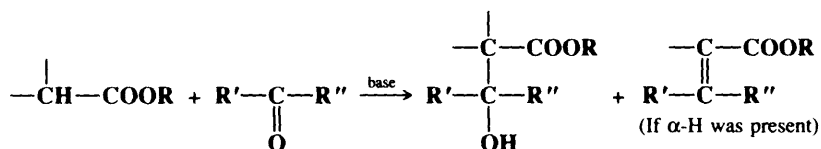
[552]For improved procedures, see Sato; Wakahara; Otera; Nozaki *Tetrahedron Lett.* **1990**, *31*, 1581, and references cited therein.

involving acetone, formaldehyde, and diethylamine. The Robinson annulation reaction has also been carried out with 3-butyn-2-one, in which case the new ring of the product contains two double bonds.[553] α-Silylated vinyl ketones $RCOC(SiMe_3){=}CH_2$ have also been used successfully in annulation reactions.[554] 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.[555]

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; 65, 6, 26; 67, 121; 68, 83; 69, 55, 226. Also see OS 65, 146.

6-40   Aldol-type Reactions between Carboxylic Esters and Aldehydes or Ketones
O-Hydro-C-(α-alkoxycarbonylalkyl)-addition; α-Alkoxycarbonylalkylidene-de-oxo-bisubstitution

$$
-\overset{\displaystyle |}{C}H-COOR + R'-\underset{\displaystyle \underset{O}{\|}}{C}-R'' \xrightarrow{\text{base}} R'-\underset{\displaystyle \underset{OH}{|}}{\overset{\displaystyle \overset{\displaystyle -\overset{|}{C}-COOR}{|}}{C}}-R'' + R'-\underset{\displaystyle \underset{}{\|}}{\overset{\displaystyle -C-COOR}{C}}-R''
$$

(If α-H was present)

In the presence of a strong base, the α carbon of a carboxylic ester can condense with the carbonyl carbon of an aldehyde or ketone to give a β-hydroxy ester,[556] which may or may not be dehydrated to the α,β-unsaturated ester. This reaction is sometimes called the Claisen condensation,[557] an unfortunate usage since that name is more firmly connected to 0-108. 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 (0-109) 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.

Besides ordinary esters (containing an α hydrogen), the reaction can also be carried out with lactones and, as in 6-39, with the γ position of α,β-unsaturated esters (vinylology).

For most esters, a much stronger base is needed than for aldol reactions; (i-Pr)₂NLi, Ph₃CNa and LiNH₂ 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 KOCMe₃. This reaction is called the *Stobbe condensation*.[558] 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 olefin. In addition, intermediate lactones 37 have been isolated from the mixture:[559]

[553]For example, see Woodward; Singh *J. Am. Chem. Soc.* **1950**, *72*, 494.

[554]Stork; Ganem *J. Am. Chem. Soc.* **1973**, *95*, 6152; Stork; Singh *J. Am. Chem. Soc.* **1974**, *96*, 6181; Boeckman *J. Am. Chem. Soc.* **1974**, *96*, 6179.

[555]Eder; Sauer; Wiechert *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 496 [*Angew. Chem. 83*, 492]; Hajos; Parrish *J. Org. Chem.* **1974**, *39*, 1615. For a review of the mechanism, see Agami *Bull. Soc. Chim. Fr.* **1988**, 499-507.

[556]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 *Chimia* **1984**, *38*, 233-243.

[557]Because it was discovered by Claisen: *Ber.* **1890**, *23*, 977.

[558]For a review, see Johnson; Daub *Org. React.* **1951**, *6*, 1-73.

[559]Robinson; Seijo *J. Chem. Soc.* **1941**, 582.

37
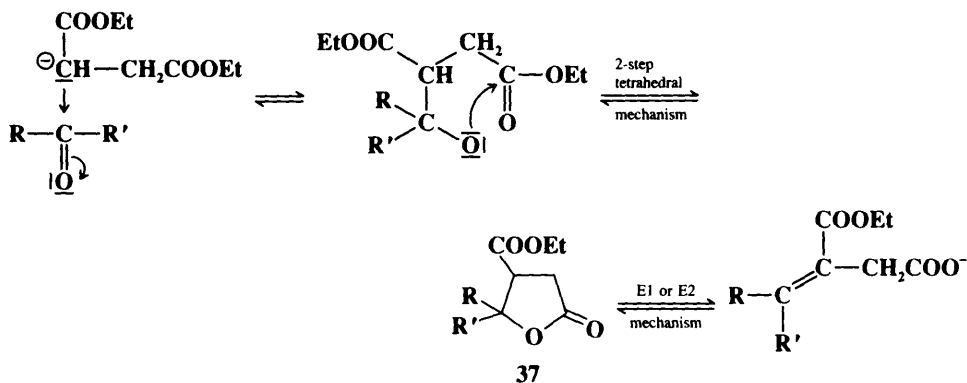
The Stobbe condensation has been extended to di-*t*-butyl esters of glutaric acid.[560]

This reaction is one step in an annulation sequence that also features two Michael (5-17) steps. An α,β-unsaturated ester is treated with a lithium enolate:
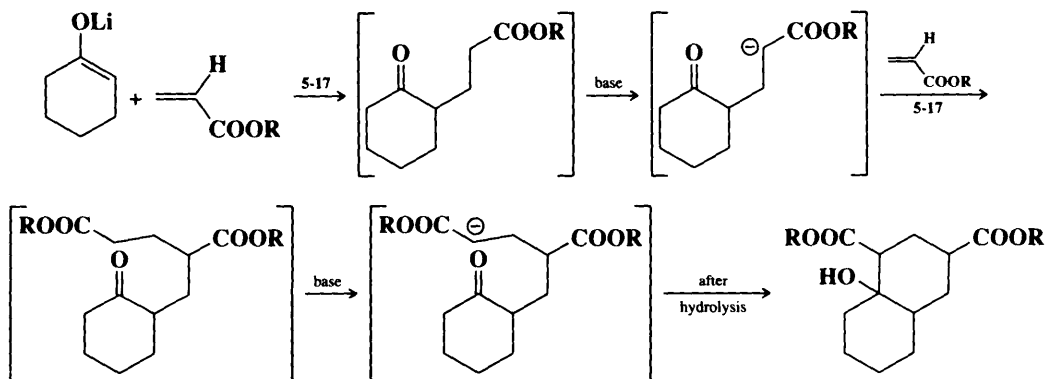
The entire sequence takes place in one laboratory step.[561]

OS **I**, 252; **III**, 132; **V**, 80, 564. Also see OS **IV**, 278, 478; **V**, 251.

6-41   The Knoevenagel Reaction
Bis(ethoxycarbonyl)methylene-de-oxo-bisubstitution, etc.
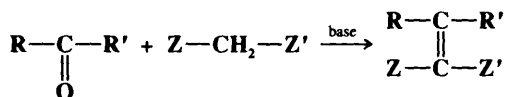
The condensation of aldehydes or ketones, usually not containing an α hydrogen, with compounds of the form Z—CH$_2$—Z' or Z—CHR—Z' is called the *Knoevenagel reaction*.[562]

[560]Puterbaugh *J. Org. Chem.* **1962**, *27*, 4010. See also El-Newaihy; Salem; Enayat; El-Bassiouny *J. Prakt. Chem.* **1982**, *324*, 379.

[561]Posner; Lu; Asirvatham; Silversmith; Shulman *J. Am. Chem. Soc.* **1986**, *108*, 511. For an extension of this work to the coupling of four components, see Posner; Webb; Asirvatham; Jew; Degl'Innocenti *J. Am. Chem. Soc.* **1988**, *110*, 4754.

[562]For a review, see Jones *Org. React.* **1967**, *15*, 204-599.

Z and Z' may be CHO, COR, COOH, COOR, CN, NO_2,[563] SOR, SO_2R, SO_2OR, or similar groups. When Z = COOH, decarboxylation of the product often takes place in situ.[564] 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, etc.; in fact any compound that contains a C—H bond the hydrogen of which can be removed by a base. The following examples illustrate the wide scope of the reaction:

$$PhCHO + CH_3COCH_2COOEt \xrightarrow[0°C]{Et_2NH} Ph{-}CH{=}C{-}COOEt$$
$$\underset{\textbf{38}}{\overset{COCH_3}{|}}$$

$$PhCHO + CH_3NO_2 \xrightarrow{n\text{-}C_5H_{11}NH_2} Ph{-}CH{=}CH{-}NO_2 \qquad \text{Ref. 563}$$

$$PhCH_2CH_2CHO + [Ph\overline{SOCHCOCH_2}]^{2-} \quad \underset{Na^+}{\overset{Li^+}{}} \quad \xrightarrow[\text{hydrol.}]{\text{(after}}$$

$$PhCH_2CH_2\underset{\underset{\textbf{39}}{OH}}{\overset{|}{CH}}CH_2COCH_2SOPh \qquad \text{Ref. 565}$$

$$PrCHO + HOOCCH_2COOH \xrightarrow[\text{piperidine}]{\text{pyridine-}} PrCH{=}CHCOOH$$

$$PhCOPh + CH_3CN \xrightarrow{KOH} Ph{-}\underset{\underset{O_\ominus}{\overset{|}{|}}}{\overset{\overset{CH_2CN}{|}}{C}}{-}Ph \qquad \text{Ref. 566}$$

cyclopentanone + $LiCH_2COOEt$ $\xrightarrow{\text{(after hydrol.)}}$ 1-hydroxy-1-(ethoxycarbonylmethyl)cyclopentane   Ref. 567

$$EtCOEt + Me_2\overset{\ominus}{C}{-}COO^\ominus \xrightarrow{\text{(after hydrol.)}} Et{-}\underset{\underset{OH}{\overset{|}{|}}}{\overset{\overset{Et}{|}}{C}}{-}\underset{\underset{Me}{\overset{|}{|}}}{\overset{\overset{Me}{|}}{C}}{-}COOH \qquad \text{Ref. 568}$$

[563]For a review of this reaction with respect to nitroalkanes (often called the *Henry reaction*), see Baer; Urbas, in Feuer, Ref. 180, pp. 76-117. See also Rosini; Ballini; Sorrenti *Synthesis* **1983**, 1014; Matsumoto *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 617 [*Angew. Chem.* **96**, 599]; Eyer; Seebach *J. Am. Chem. Soc.* **1985**, *107*, 3601. For reviews of the nitroalkenes that are the products of this reaction, see Barrett; Graboski *Chem. Rev.* **1986**, *86*, 751-762; Kabalka; Varma *Org. Prep. Proced. Int.* **1987**, *19*, 283-328.

[564]For a discussion of the mechanism when the reaction is accompanied by decarboxylation, see Tanaka; Oota; Hiramatsu; Fujiwara *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2473.

[565]Kuwajima; Iwasawa *Tetrahedron Lett.* **1974**, 107. See also Huckin; Weiler *Can. J. Chem.* **1974**, *52*, 2157.

[566]DiBiase; Lipisko; Haag; Wolak; Gokel *J. Org. Chem.* **1979**, *44*, 4640. For a review of addition of the conjugate bases of nitriles, see Arseniyadis; Kyler; Watt *Org. React.* **1984**, *31*, 1-364.

[567]Rathke *J. Am. Chem. Soc.* **1970**, *92*, 3222; van der Veen; Geenevasen; Cerfontain *Can. J. Chem.* **1984**, *62*, 2202.

[568]Moersch; Burkett *J. Org. Chem.* **1971**, *36*, 1149. See also Cainelli; Cardillo; Contento; Umani-Ronchi *Gazz. Chim. Ital.* **1974**, *104*, 625. When the nucleophile is $Ph\overset{\ominus}{C}HCOO^\ominus$, the reaction is known as the *Ivanov reaction*. For a discussion of the mechanism, see Toullec; Mladenova; Gaudemar-Bardone; Blagoev *J. Org. Chem.* **1985**, *50*, 2563.

$$\text{MeCHO} + \text{CH}_2\!\!=\!\!\text{CH}-\text{COO-}t\text{-Bu} \xrightarrow[\text{(DABCO)}]{\text{1,4-diazabicyclo[2.2.2]octane}} \underset{\underset{\text{OH}}{|}}{\text{Me}-\text{CH}}-\overset{\overset{\overset{\text{CH}_2}{\|}}{}}{\text{C}}-\text{COO-}t\text{-Bu}$$

Ref. 569

$$\text{Et}_2\text{CO} + \text{PhCH}\!\!=\!\!\text{NCH}_2\text{Ph} \xrightarrow[\text{(after hydrol.)}]{\text{NbCl}_3\text{-MeOCH}_2\text{CH}_2\text{OMe}} \underset{\underset{\underset{\text{Et}}{|}}{\overset{|}{\text{Et}-\text{C}-\text{OH}}}}{\text{Ph}-\text{CH}}-\text{NHCH}_2\text{Ph}$$ Ref. 570

Ref. 571

40

$$\underset{\underset{\text{Me}}{|}}{\text{Ph}-\text{CH}}-\text{CHO} + \underset{\underset{\text{OCMe}_2\text{OME}}{|}}{\overset{\overset{\text{CN}}{|}}{\text{Ph}-\text{C}}}\!^{\ominus} \xrightarrow[\text{(after hydrol.)}]{} \underset{\underset{\text{Me}}{|}}{\text{Ph}-\text{CH}}-\underset{\underset{\text{OH}}{|}}{\text{CH}}-\overset{\overset{\|}{\text{O}}}{\text{C}}-\text{Ph}$$ Ref. 572

$$\text{PhCHO} + \text{Li}-\overset{\overset{\|}{\text{O}}}{\text{C}}-\text{N(i-Pr)}_2 \longrightarrow \underset{\underset{\text{OH}}{|}}{\text{Ph}-\text{CH}}-\overset{\overset{\|}{\text{O}}}{\text{C}}-\text{N(i-Pr)}_2$$ Ref. 573

$$\text{iso-PrCHO} + \overset{\overset{\|}{\text{N}_2}}{\text{CHCOOEt}} \xrightarrow[\text{2. H}_2\text{O}]{\text{1. KOH–EtOH}} \text{iso-Pr}-\underset{\underset{\text{OH}}{|}}{\text{CH}}-\overset{\overset{\|}{\text{N}_2}}{\text{C}}-\text{COOEt}$$ Ref. 574

Ref. 575

41
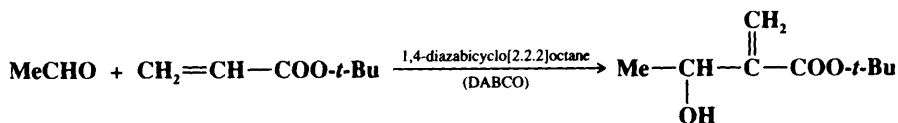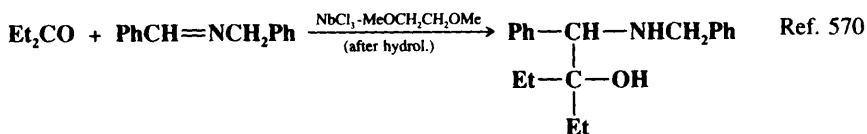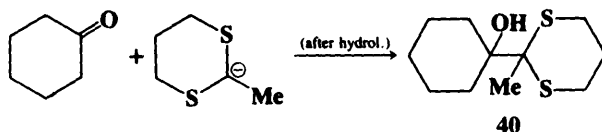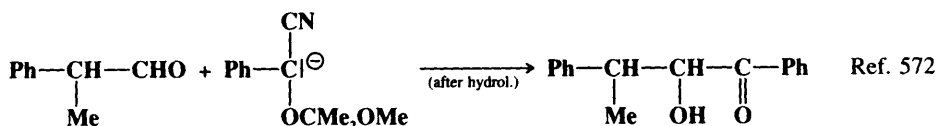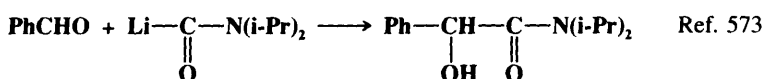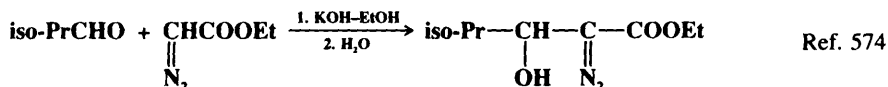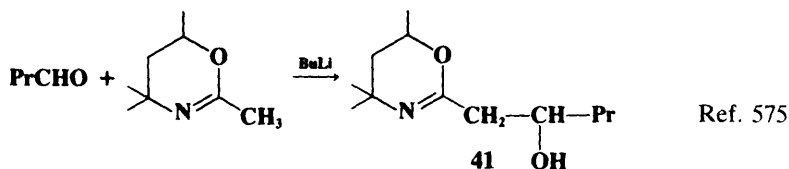
[569]Hoffmann; Rabe *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 795 [*Angew. Chem. 95*, 795]; Basavaiah; Gowriswari *Tetrahedron Lett.* **1986**, *27*, 2031. For a review of reactions of vinylic carbanions with aldehydes, see Drewes; Roos *Tetrahedron* **1988**, *44*, 4653-4670.

[570]Roskamp; Pedersen *J. Am. Chem. Soc.* **1987**, *109*, 6551.

[571]Corey; Seebach *Angew. Chem. Int. Ed. Engl.* **1965**, *4*, 1075 [*Angew. Chem. 77*, 1134]. For other examples of the addition of 1,3-dithianes and similar reagents to aldehydes, ketones, and compounds containing C=N bonds, see Seebach *Synthesis* **1969**, 17-36, pp. 27-29; Corey; Crouse *J. Org. Chem.* **1968**, *33*, 298; Duhamel; Duhamel; Mancelle *Bull. Soc. Chim. Fr.* **1974**, 331; Gröbel; Bürstinghaus; Seebach, *Synthesis* **1976**, 121; Meyers; Tait; Comins *Tetrahedron Lett.* **1978**, 4657; Blatcher; Warren *J. Chem. Soc., Perkin Trans. 1* **1979**, 1074; Ogura *Pure Appl. Chem.* **1987**, *59*, 1033.

[572]Hünig; Marschner *Chem. Ber.* **1989**, *122*, 1329.

[573]Smith; Swaminathan *J. Chem. Soc., Chem. Commun.* **1976**, 387.

[574]Wenkert; McPherson *J. Am. Chem. Soc.* **1972**, *94*, 8084. See also Schöllkopf; Bánhidai; Frasnelli; Meyer; Beckhaus *Liebigs Ann. Chem.* **1974**, 1767.

[575]Meyers; Nabeya; Adickes; Fitzpatrick; Malone; Politzer *J. Am. Chem. Soc.* **1969**, *91*, 764. For other examples, see Meyers; Temple *J. Am. Chem. Soc.* **1970**, *92*, 6644; Meyers; Nabeya; Adickes; Politzer; Malone; Kovelesky; Nolen; Portnoy *J. Org. Chem.* **1973**, *38*, 36.
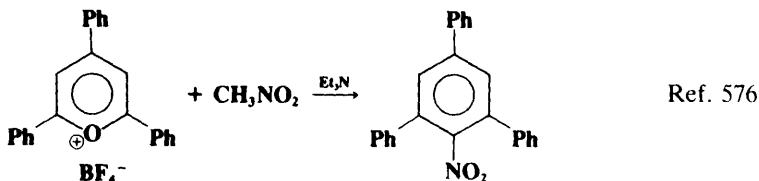
We see from these examples that many of the carbon nucleophiles we encountered in Chapter 10 are also nucleophiles toward aldehydes and ketones (compare reactions **0-94** through **0-98** and **0-100**). As we saw in Chapter 10, the initial products in many of these cases, e.g., **38** through **41,** can be converted by relatively simple procedures (hydrolysis, reduction, decarboxylation, etc.) to various other products. In the reaction with terminal acetylenes,[577] sodium acetylides are the most common reagents (when they are used, the reaction is often called the *Nef reaction*), but lithium,[578] magnesium, and other metallic acetylides have also been used. A particularly convenient reagent is lithium acetylide–ethylenediamine complex,[579] a stable, free-flowing powder that is commercially available. Alternatively, the substrate may be treated with the alkyne itself in the presence of 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 (**8-7**).[580] 1,4-Diols can be prepared by the treatment of aldehydes with dimetalloacetylenes $MC\equiv CM$.[581]

With most of these reagents the alcohol is not isolated (only the olefin) if the alcohol has a hydrogen in the proper position.[582] However, in some cases the alcohol is the major product. With suitable reactants, the Knoevenagel reaction, like the aldol (**6-39**), has been carried out diastereoselectively[583] and enantioselectively.[584] 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 olefin 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.[585] In reactions with ZCH_2Z', the catalyst is most often a secondary amine (piperdine is the most common), 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. Alkoxides are also common catalysts.

As with **6-39,** these reactions have sometimes been performed with acid catalysts.[586]

[576]Dimroth; Berndt; Reichardt *Org. Synth. V* 1128. See also Dimroth *Angew. Chem.* **1960,** *72,* 331-342; Dimroth; Wolf *Newer Methods Prep. Org. Chem.* **1964,** *3,* 357-423.

[577]For reviews, see Ziegenbein, in Viehe *Acetylenes;* Marcel Dekker: New York, 1969, pp. 207-241; Ried *Newer Methods Prep. Org. Chem.* **1968,** *4,* 95-138.

[578]See Midland *J. Org. Chem.* **1975,** *40,* 2250, for the use of amine-free monolithium acetylide.

[579]Beumel; Harris *J. Org. Chem.* **1963,** *28,* 2775.

[580]For a discussion of the mechanism of the Favorskii addition reaction, see Kondrat'eva; Potapova; Grigina; Glazunova; Nikitin *J. Org. Chem. USSR* **1976,** *12,* 948.

[581]Sudweeks; Broadbent *J. Org. Chem.* **1975,** *40,* 1131.

[582]For lists of reagents (with references) that condense with aldehydes and ketones to give olefin products, see Ref. 64, pp. 167-171, 180-184. For those that give the alcohol product, see Ref. 64, pp. 575, 773, 868-871, 875, 878-880, 901, 910-911.

[583]See, for example, Trost; Florez; Jebaratnam *J. Am. Chem. Soc.* **1987,** *109,* 613; Mahler; Devant; Braun *Chem. Ber.* **1988,** *121,* 2035; Ronan; Marchalin; Samuel; Kagan *Tetrahedron Lett.* **1988,** *29,* 6101; Barrett; Robyr; Spilling *J. Org. Chem.* **1989,** *54,* 1233; Pyne; Boche *J. Org. Chem.* **1989,** *54,* 2663.

[584]See, for example, Enders; Lotter; Maigrot; Mazaleyrat; Welvart *Nouv. J. Chim.* **1984,** *8,* 747; Ito; Sawamura; Hayashi *J. Am. Chem. Soc.* **1986,** *108,* 6405; Togni; Pastor *J. Org. Chem.* **1990,** *55,* 1649; Pastor; Togni *Tetrahedron Lett.* **1990,** *31,* 839; Sakuraba; Ushiki *Tetrahedron Lett.* **1990,** *31,* 5349; Niwa; Soai *J. Chem. Soc., Perkin Trans. 1* **1990,** 937.

[585]Lehnert *Tetrahedron Lett.* **1970,** 4723, *Tetrahedron* **1972,** *28,* 663, **1973,** *29,* 635, *Synthesis* **1974,** 667.

[586]For example, see Rappoport; Patai *J. Chem. Soc.* **1962,** 731.

Imines can be employed instead of aldehydes or ketones; the products are the same—an amine is lost instead of water.[587]

A number of special applications of the Knoevenagel reaction follow:

1. The dilithio derivative of N-methanesulfinyl-*p*-toluidine[588] (**42**) adds to aldehydes and ketones to give, after hydrolysis, the hydroxysulfinamides **43**, which, upon heating, undergo stereospecifically syn eliminations to give olefins.[589] The reaction is thus a method for achieving the conversion RR′CO → RR′C=CH$_2$ and represents an alternative to the Wittig reaction.[590]

$$\text{MeSONHAr} \xrightarrow{\text{2BuLi}} \underset{\underset{\text{Li}}{|}\ \underset{\text{Li}}{|}}{\text{CH}_2\text{SONAr}} \xrightarrow{\text{RCOR}'} \underset{\underset{\text{OLi}}{|}\ \ \ \underset{\text{Li}}{|}}{-\text{R}-\overset{\overset{\text{R}'}{|}}{\text{C}}-\text{CH}_2\text{SONAr}} \xrightarrow{\text{H}_2\text{O}}$$

$$\textbf{42}$$

$$\underset{\underset{\text{OH}}{|}}{\text{R}-\overset{\overset{\text{R}'}{|}}{\text{C}}-\text{CH}_2\text{SONAr}} \xrightarrow{\Delta} \underset{\underset{\text{R}'}{|}}{\text{R}-\text{C}}=\text{CH}_2 + \text{SO}_2 + \text{ArNH}_2 \quad \text{Ar} = p\text{-tolyl}$$

$$\textbf{43}$$

2. The reaction of ketones with tosylmethylisocyanide (**44**) gives different products,[591] depending on the reaction conditions.

[587]Charles *Bull. Soc. Chim. Fr.* **1963**, 1559, 1566, 1573, 1576; Siegrist; Liechti; Meyer; Weber *Helv. Chim. Acta* **1969**, *52*, 2521. For the use of iminium salts, see Nair; Jahnke *Synthesis* **1984**, 424. For a review as applied to heterocyclic compounds, see Fletcher; Siegrist *Adv. Heterocycl. Chem.* **1978**, *23*, 171-261.

[588]For a method of preparing **42**, see Bowlus; Katzenellenbogen *Synth. Commun.* **1974**, *4*, 137.

[589]Corey; Durst *J. Am. Chem. Soc.* **1968**, *90*, 5548, 5553.

[590]For similar reactions, see Jung; Sharma; Durst *J. Am. Chem. Soc.* **1973**, *95*, 3420; Kuwajima; Uchida *Tetrahedron Lett.* **1972**, 649; Johnson; Shanklin; Kirchhoff *J. Am. Chem. Soc.* **1973**, *95*, 6462; Lau; Chan *Tetrahedron Lett.* **1978**, 2383; Yamamoto; Tomo; Suzuki *Tetrahedron Lett.* **1980**, *21*, 2861; Martin; Phillips; Puckette; Colapret *J. Am. Chem. Soc.* **1980**, *102*, 5866; Arenz; Vostell; Frauenrath *Synlett* **1991**, 23.

[591]For reviews of α-metalated isocyanides, see Schöllkopf *Pure Appl. Chem.* **1979**, *51*, 1347-1355, *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 339-348 [*Angew. Chem. 89*, 351-360]; Hoppe *Angew. Chem. Int. Ed. Engl.* **1974**, *13*, 789-804 [*Angew. Chem. 86*, 878-893].

When the reaction is run with potassium *t*-butoxide in THF at $-5°C$, one obtains (after hydrolysis) the normal Knoevenagel product **45**, except that the isocyano group has been hydrated (**6-65**).[592] With the same base but with 1,2-dimethoxyethane (DME) as solvent the product is the nitrile **46**.[593] When the ketone is treated with **44** 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 **47**.[594] Since **46** can be hydrolyzed[595] to a carboxylic acid[592] and **47** to an α-hydroxy aldehyde,[594] 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[596] 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 $RR'C(OH)COMe$.[597] In this reaction, the $CH_2{=}C(Li)OMe$ is a synthon for the unavailable $CH_3{-}\overset{\ominus}{C}{=}O$ ion.[598] The reagent also reacts with esters RCOOR' to give $RC(OH)(COMe{=}CH_2)_2$. A synthon for the $Ph{-}\overset{\ominus}{C}{=}O$ ion is $Ph\overset{\ominus}{C}(CN)OSiMe_3$, which adds to aldehydes and ketones RCOR' to give, after hydrolysis, the α-hydroxy ketones $RR'C(OH)COPh$.[599]

4. Lithiated allylic carbamates (**48**) (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.[600] The reaction is called *the homoaldol reaction*, since the
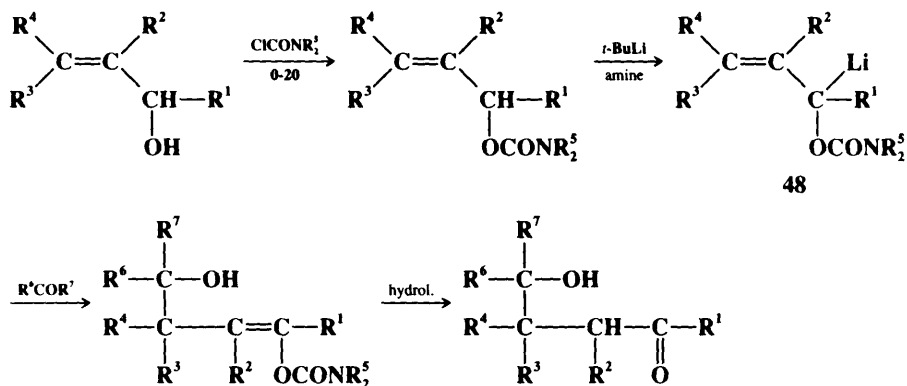
product is a homolog of the product of **6-39**. The reaction has been performed enantioselectively.[601]

[592]Schöllkopf; Schröder; Blume *Liebigs Ann. Chem.* **1972**, *766*, 130; Schöllkopf; Schröder *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 311 [*Angew. Chem. 84*, 289].
[593]Oldenziel; van Leusen; van Leusen *J. Org. Chem.* **1977**, *42*, 3114.
[594]Oldenziel; van Leusen *Tetrahedron Lett.* **1974**, 163, 167. For conversions to α,β-unsaturated ketones and diketones, see, respectively, Moskal; van Leusen *Tetrahedron Lett.* **1984**, *25*, 2585; van Leusen; Oosterwijk; van Echten; van Leusen *Recl. Trav. Chim. Pays-Bas* **1985**, *104*, 50.
[595]**45** can also be converted to a nitrile; see **7-38**.
[596]van Leusen; Oomkes *Synth. Commun.* **1980**, *10*, 399.
[597]Baldwin; Höfle; Lever *J. Am. Chem. Soc.* **1974**, *96*, 7125. For a similar reaction, see Tanaka; Nakai; Ishikawa *Tetrahedron Lett.* **1978**, 4809.
[598]For a synthon for the $^{\ominus}COCOOEt$ ion, see Reetz; Heimbach; Schwellnus *Tetrahedron Lett.* **1984**, *25*, 511.
[599]Hünig; Wehner *Synthesis* **1975**, 391.
[600]For a review, see Hoppe *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 932-948 [*Angew. Chem. 96*, 930-946].
[601]Krämer; Hoppe *Tetrahedron Lett.* **1987**, *28*, 5149.

5. A procedure for converting an aldehyde or ketone RR′CO to the homologous aldehyde RR′CHCHO consists of treating the substrate with lithium bis(ethylenedioxyboryl)methide, followed by oxidation with aqueous H_2O_2:[602]
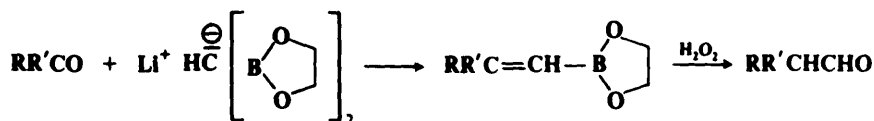
6. A method for the stereoselective synthesis of 1,2-diols consists of treating aromatic aldehydes with carbanions stabilized by an adjacent dimesitylboron group at −120°C, followed by oxidation with H_2O_2.[603]

erythro isomer
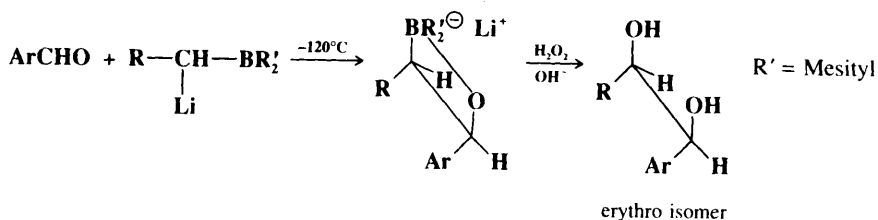
The erythro–threo ratio of the product was greater than 9:1.

7. The lithium salt of an active hydrogen compound adds to the lithium salt of the tosylhydrazone of an aldehyde to give product **49**. If X = CN, SPh, or SO_2R, **49** spontaneously loses N_2 and LiX to give the alkene **50**. The entire process is done in one reaction
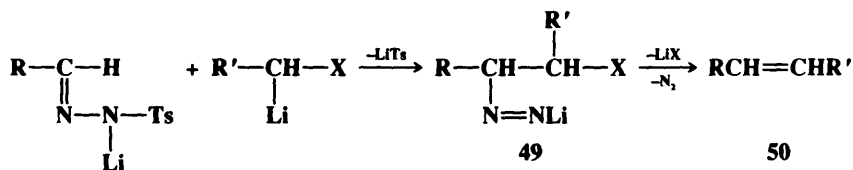
vessel: The active hydrogen compound is mixed with the tosylhydrazone and the mixture is treated with (i-Pr)$_2$NLi to form both salts at once.[604] This process is another alternative to the Wittig reaction for forming double bonds.

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; **66**, 220; **67**, 205; **68**, 14, 64; **69**, 19, 31. Also see OS **III**, 395; **V**, 450.

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[602]Matteson; Moody *J. Org. Chem.* **1980**, *45*, 1091. For other methods of achieving this conversion, see Corey; Tius *Tetrahedron Lett.* **1980**, *21*, 3535, 1980; Huang; Zhang *Synthesis* **1989**, 42.

[603]Pelter; Buss; Pitchford *Tetrahedron Lett.* **1985**, *26*, 5093.

[604]Vedejs; Dolphin; Stolle *J. Am. Chem. Soc.* **1979**, *101*, 249.

6-42   The Peterson Olefination Reaction
Alkylidene-de-oxo-bisubstitution

$$\underset{}{Me_3Si-CH-Li} + \underset{\underset{O}{\parallel}}{R'-C-R''} \xrightarrow[\text{hydrolysis}]{\text{after}} \underset{\underset{OH}{}}{R'-\overset{\overset{R''}{|}}{C}-\overset{\overset{R}{|}}{CH}-SiMe_3} \xrightarrow[\text{base}]{\text{acid or}} R'-\overset{\overset{R''}{|}}{C}=\overset{\overset{R}{|}}{C}-H$$
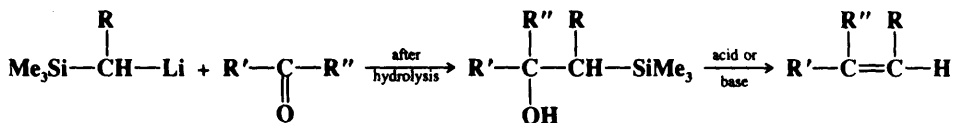
In the *Peterson olefination reaction*[605] the lithio (or sometimes magnesio) derivative of a trialkylsilane adds to an aldehyde or ketone to give a β-hydroxysilane, which spontaneously eliminates water, or can be made to do so by treatment with acid or base, to produce an olefin. This reaction is still another alternative to the Wittig reaction, and is sometimes called the *silyl-Wittig reaction*.[606] R can also be a COOR group, in which case the product is an α,β-unsaturated ester,[607] or an SO_2Ph group, in which case the product is a vinylic sulfone.[608] The stereochemistry of the product can often be controlled by whether an acid or a base is used to achieve elimination. Use of a base generally gives syn elimination (Ei mechanism, see p. 1006), while an acid usually results in anti elimination (E2 mechanism, see p. 983).[609]
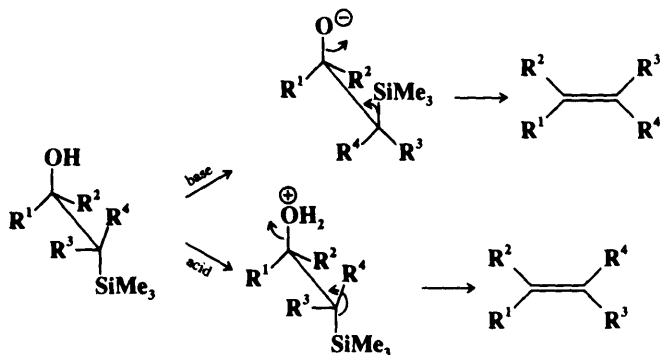
When aldehydes or ketones are treated with reagents of the form **51**, the product is an epoxy silane (**6-61**), which can be hydrolyzed to a methyl ketone.[610] For aldehydes, this is a method for converting RCHO to a methyl ketone RCH_2COMe.

$$\underset{\underset{Cl}{|}}{Me_3Si-\overset{\overset{Me}{|}}{C}-Li} + \underset{\underset{O}{\parallel}}{R-C-R'} \longrightarrow R-\overset{\overset{R'}{|}}{\underset{\underset{O}{\diagdown\diagup}}{C}}-\overset{\overset{Me}{|}}{C}-SiMe_3 \longrightarrow R-\overset{\overset{R'}{|}}{CH}-\underset{\underset{O}{\parallel}}{C}-Me$$

51
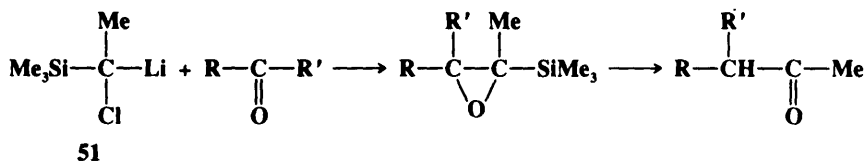
[605]Peterson *J. Org. Chem.* **1968**, *33*, 780. For reviews, see Ager *Org. React.* **1990**, *38*, 1-223, *Synthesis* **1984**, 384-398; Colvin *Silicon Reagents in Organic Synthesis*; Academic Press: New York, 1988, pp. 63-75; Weber *Silicon Reagents for Organic Synthesis*; Springer: New York, 1983, pp. 58-78; Magnus *Aldrichimica Acta* **1980**, *13*, 43-51; Chan *Acc. Chem. Res.* **1977**, *10*, 442-448. For a list of references, see Ref. 64, pp. 178-180. For books and reviews on silicon reagents in organic synthesis, see Chapter 12, Ref. 286.
[606]For discussions of the mechanism, see Bassindale; Ellis; Lau; Taylor *J. Chem. Soc., Perkin Trans. 2* **1986**, 593; Hudrlik; Agwaramgbo; Hudrlik *J. Org. Chem.* **1989**, *54*, 5613.
[607]Hartzell; Sullivan; Rathke *Tetrahedron Lett* **1974**, 1403; Shimoji; Taguchi; Oshima; Yamamoto; Nozaki *J. Am. Chem. Soc.* **1974**, *96*, 1620; Chan; Moreland *Tetrahedron Lett.* **1978**, 515; Strekowski; Visnick; Battiste *Tetrahedron Lett.* **1984**, *25*, 5603.
[608]Craig; Ley; Simpkins; Whitham; Prior *J. Chem. Soc., Perkin Trans. 1* **1985**, 1949.
[609]See Colvin, Ref. 605, pp. 65-69.
[610]Cooke; Roy; Magnus *Organometallics* **1982**, *1*, 893.

The reagents Me₃SiCHRM (M = Li or Mg) are often prepared from Me₃SiCHRCl[611] (by 2-38 or 2-39), but they have also been made by 2-21 and by other procedures.[612]

There are no references in *Organic Syntheses*, but see OS **69**, 89, for a related reaction.

6-43 The Addition of Active Hydrogen Compounds to CO_2 and CS_2
α-**Acylalkyl-de-methoxy-substitution** (overall reaction)

$$R-\underset{\underset{O}{\|}}{C}-CH_2R' + (MeO-\underset{\underset{O}{\|}}{C}-O)_2Mg \longrightarrow \quad [\text{chelate}] \quad \xrightarrow[\text{hydrol.}]{H^+} R-\underset{\underset{O}{\|}}{C}-\underset{\underset{COOH}{|}}{C}HR'$$

                    52   **53**
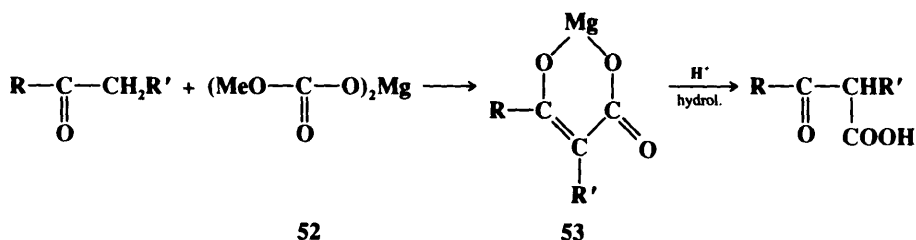
Ketones of the form $RCOCH_3$ and $RCOCH_2R'$ can be carboxylated indirectly by treatment with magnesium methyl carbonate **52**.[613] Because formation of the chelate **53** provides the driving force of the reaction, carboxylation cannot be achieved at a disubstituted α position. The reaction has also been performed on CH_3NO_2 and compounds of the form RCH_2NO_2[614] and on certain lactones.[615] Direct carboxylation has been reported in a number of instances. Ketones have been carboxylated in the α position to give β-keto acids.[616] The base here was lithium 4-methyl-2,6-di-*t*-butylphenoxide.

Ketones $RCOCH_2R'$ (as well as other active hydrogen compounds) undergo base-catalyzed addition to CS_2[617] to give a dianion intermediate $RCOCHR'CSS^-$, which can be dialkylated with a halide R″X to produce α-dithiomethylene ketones $RCOCR'{=}C(SR'')_2$.[618] Compounds of the form ZCH_2Z' also react with bases and CS_2 to give analogous dianions.[619]

OS **VII**, 476. See also OS **65**, 17.

6-44 The Perkin Reaction
α-**Carboxyalkylidene-de-oxo-bisubstitution**

$$Ar-\underset{\underset{O}{\|}}{C}-H + (RCH_2CO)_2O \xrightarrow{RCH_2COOK} Ar-\underset{\underset{H}{|}}{C}{=}\underset{\underset{R}{|}}{C}-COO^- + RCH_2COOH$$

[611]For a review of these reagents, see Anderson *Synthesis* **1985**, 717-734.

[612]See, for example, Ager *J. Chem. Soc., Perkin Trans. 1* **1986**, 183; Barrett; Flygare *J. Org. Chem.* **1991**, *56*, 638.

[613]Stiles *J. Am. Chem. Soc.* **1959**, *81*, 2598, *Ann. N.Y. Acad. Sci* **1960**, *88*, 332; Crombie; Hemesley; Pattenden *Tetrahedron Lett.* **1968**, 3021.

[614]Finkbeiner; Stiles *J. Am. Chem. Soc.* **1963**, *85*, 616; Finkbeiner; Wagner *J. Org. Chem.* **1963**, *28*, 215.

[615]Martin; Watts; Johnson *Chem. Commun.* **1970**, 27.

[616]Corey; Chen *J. Org. Chem.* **1973**, *38*, 4086; Tirpak; Olsen; Rathke *J. Org. Chem.* **1985**, *50*, 4877. For an enantioselective version, see Hogeveen; Menge *Tetrahedron Lett.* **1986**, *27*, 2767.

[617]For reviews of the reactions of CS_2 with carbon nucleophiles, see Ref. 106, pp. 120-225; Yokoyama; Imamoto *Synthesis* **1984**, 797-824, pp. 797-804.

[618]See, for example Corey; Chen *Tetrahedron Lett.* **1973**, 3817.

[619]Jensen; Dalgaard; Lawesson *Tetrahedron* **1974**, *30*, 2413; Konen; Pfeffer; Silbert *Tetrahedron* **1976**, *32*, 2507, and references cited in these papers.

The condensation of aromatic aldehydes with anhydrides is called the *Perkin reaction.*[620] When the anhydride has two α hydrogens (as shown), dehydration always occurs; the β-hydroxy acid salt is never isolated. In some cases, anhydr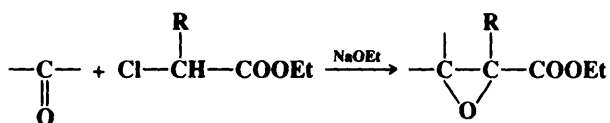ides of the form $(R_2CHCO)_2O$ have been used, and then the hydroxy compound is the product since dehydration cannot take place. The base in the Perkin reaction is nearly always the salt of the acid corresponding to the anhydride. Although the Na and K salts have been most frequently used, higher yields and shorter reaction times have been reported for the Cs salt.[621] Besides aromatic aldehydes, their vinylogs $ArCH=CHCHO$ also give the reaction. Otherwise, the reaction is not suitable for aliphatic aldehydes.[622]

OS **I**, 398; **II**, 61, 229; **III**, 426.

6-45 Darzens Glycidic Ester Condensation
(2 + 1)OC,CC-*cyclo*-α-Alkoxycarbonylmethylene-addition

$$\underset{O}{\overset{R}{\underset{\|}{-C-}}} + Cl-\underset{\underset{}{}}{\overset{R}{\underset{|}{CH}}}-COOEt \xrightarrow{\text{NaOEt}} -\overset{R}{\underset{}{C}}-\overset{R}{\underset{O}{C}}-COOEt$$

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.*[623] The reaction consists of an initial Knoevenagel-type reaction (**6-41**), followed by an internal SN2 reaction (**0-13**):[624]

$$\underset{O}{\overset{}{\underset{\|}{-C-}}} + Cl-\underset{R}{\overset{}{\underset{|}{CH}}}-COOEt \xrightarrow{OEt^-} -\overset{}{\underset{\underset{\ominus}{|O|}}{C}}-\overset{Cl}{\underset{R}{C}}-COOEt \longrightarrow -\overset{R}{\underset{O}{C}}-\overset{R}{\underset{}{C}}-COOEt$$
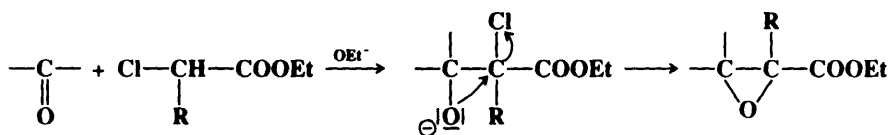
Although the intermediate halo alkoxide is generally not isolated, it has been done, not only with α-fluoro esters (since fluorine is such a poor leaving group in nucleophilic substitutions) but also with α-chloro esters.[625] This is only one of several types of evidence that rule out a carbene intermediate.[626] 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 (~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.[627] If a preformed dianion of an α-halo carboxylic

[620]For a review, see Johnson, *Org. React.* **1942**, *1*, 210-266.
[621]Koepp; Vögtle *Synthesis* **1987**, 177.
[622]Crawford; Little *J. Chem. Soc.* **1959**, 722.
[623]For a review, see Berti *Top. Stereochem.* **1973**, 7, 93-251, pp. 210-218.
[624]For discussions of the mechanism of the reaction, and especially of the stereochemistry, see Roux-Schmitt; Seyden-Penne; Wolfe *Tetrahedron* **1972**, 28, 4965; Bansal; Sethi *Bull. Chem. Soc. Jpn.* **1980**, 53, 1197.
[625]Ballester; Pérez-Blanco *J. Org. Chem.* **1958**, 23, 652; Martynov; Titov *J. Gen. Chem. USSR* **1960**, 30, 4072, **1962**, 32, 716, **1963**, 33, 1350, **1964**, 34, 2139; Elkik; Francesch *Bull. Soc. Chim. Fr.* **1973**, 1277, 1281.
[626]Another, based on the stereochemistry of the products, is described by Zimmerman; Ahramjian *J. Am. Chem. Soc.* **1960**, 82, 5459.
[627]Borch *Tetrahedron Lett.* **1972**, 3761.

acid Cl—$\overset{\ominus}{\text{C}}$R—COO$^{\ominus}$ is used instead, α,β-epoxy acids are produced directly.[628] The Darzens reaction has also been carried out on α-halo ketones, α-halo nitriles,[629] α-halo sulfoxides[630] and sulfones,[631] α-halo N,N-disubstituted amides,[632] α-halo ketimines,[633] and even on allylic[634] and benzylic halides. Phase transfer catalysis has been used.[635] The Darzens reaction has been performed enantioselectively, by coupling optically active α-bromo-β-hydroxy esters with aldehydes.[635a]

Glycidic esters can easily be converted to aldehydes (2-40). 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.[636] However, yields were not high. Acid-catalyzed Darzens reactions have also been reported.[637] See also 6-61.

OS III, 727; IV, 459, 649.

6-46 Tollens' Reaction
O-Hydro-C-(β-hydroxyalkyl)-addition

$$-\overset{|}{\underset{\text{R}}{\text{CH}}}-\overset{\text{O}}{\overset{\|}{\text{C}}}-\text{R} + 2\text{HCHO} \xrightarrow{\text{Ca(OH)}_2} -\overset{\text{CH}_2\text{OH}}{\underset{\text{OH}}{\overset{|}{\underset{|}{\text{C}}}}}-\overset{|}{\underset{|}{\text{CH}}}-\text{R} + \text{HCOOH}$$
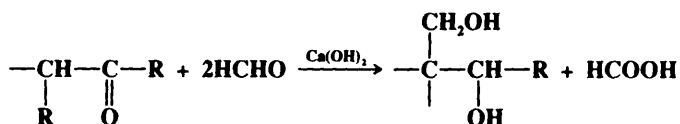
In *Tollens' reaction* an aldehyde or ketone containing an α hydrogen is treated with formaldehyde in the presence of Ca(OH)$_2$ or a similar base. The first step is a mixed aldol reaction (6-39).

$$-\overset{|}{\text{CH}}-\overset{\text{O}}{\overset{\|}{\text{C}}}-\text{R} + \text{H}-\overset{\text{O}}{\overset{\|}{\text{C}}}-\text{H} \xrightarrow{\text{base}} -\overset{\overset{\text{OH}}{\overset{|}{\text{H}-\text{C}-\text{H}}}}{\underset{}{\overset{|}{\text{C}}}}-\overset{\text{O}}{\overset{\|}{\text{C}}}-\text{R}$$
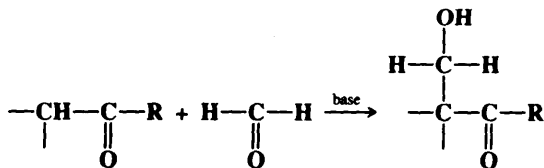
The reaction can be stopped at this point, but more often a second mole of formaldehyde is permitted to reduce the newly formed aldol to a 1,3-diol, in a crossed Cannizzaro reaction (9-69). If the aldehyde or ketone has several α hydrogens, they can all be replaced. An important use of the reaction is to prepare pentaerythritol from acetaldehyde:

$$\text{CH}_3\text{CHO} + 4\text{HCHO} \longrightarrow \text{C(CH}_2\text{OH)}_4 + \text{HCOOH}$$
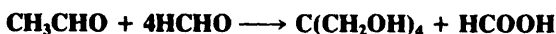
[628]Johnson; Bade *J. Org. Chem.* **1982**, *47*, 1205.
[629]See White; Wu *J. Chem. Soc., Chem. Commun.* **1974**, 988.
[630]Satoh; Sugimoto; Itoh; Yamakawa *Tetrahedron Lett.* **1989**, *30*, 1083.
[631]Vogt; Tavares *Can. J. Chem.* **1969**, *47*, 2875.
[632]Tung; Speziale; Frazier *J. Org. Chem.* **1963**, *28*, 1514.
[633]Mauzé *J. Organomet. Chem.* **1979**, *170*, 265.
[634]Sulmon; De Kimpe; Schamp; Declercq; Tinant *J. Org. Chem.* **1988**, *53*, 4457.
[635]See Jończyk; Kwast; Makosza *J. Chem. Soc., Chem. Commun.* **1977**, 902; Gladiali; Soccolini *Synth. Commun.* **1982**, *12*, 355; Starks; Liotta *Phase Transfer Catalysis*; Academic Press: New York, 1978, pp. 197-198.
[635a]Corey; Choi *Tetrahedron Lett.* **1991**, *32*, 2857.
[636]Deyrup *J. Org. Chem.* **1969**, *34*, 2724.
[637]Sipos; Schöbel; Baláspiri *J. Chem. Soc. C* **1970**, 1154; Sipos; Schöbel; Sirokmán *J. Chem. Soc., Perkin Trans. 2* **1975**, 805.

When aliphatic nitro compounds are used instead of aldehydes or ketones, no reduction occurs, and the reaction is essentially a Knoevenagel reaction, though it is usually also called a Tollens' reaction:

$$CH_3NO_2 + HCHO \xrightarrow{OH^-} HOCH_2CH_2NO_2$$

OS **I**, 425; **IV**, 907; **V**, 833.

6-47 The Wittig Reaction
Alkylidene-de-oxo-bisubstitution

In the *Wittig reaction* an aldehyde or ketone is treated with a *phosphorus ylide* (also called a *phosphorane*) to give an olefin.[638] Phosphorus ylides are usually prepared by treatment of a phosphonium salt with a base,[639] and phosphonium salts are usually prepared from the phosphine and an alkyl halide (0-43):

The overall sequence of three steps may be called the Wittig reaction, or only the final step. Phosphonium salts are also prepared by addition of phosphines to Michael olefins (like 5-7) and in other ways. The phosphonium salts are most often converted to the ylides by treatment with a strong base such as butyllithium, sodium amide,[640] sodium hydride, or a sodium alkoxide, though weaker bases can be used if the salt is acidic enough. For $(Ph_3P^+)_2CH_2$, sodium carbonate is a strong enough base.[641] When the base used does not contain lithium, the ylide is said to be prepared under "salt-free" conditions.[642]

[638]For a general treatise, see Cadogan *Organophosphorus Reagents in Organic Synthesis*; Academic Press: New York, 1979. For a monograph on the Wittig reaction, see Johnson *Ylid Chemistry*; Academic Press: New York, 1966. For reviews, see Maryanoff; Reitz *Chem. Rev.* **1989**, *89*, 863-927; Bestmann; Vostrowsky *Top. Curr. Chem.* **1983**, *109*, 85-164; Pommer; Thieme *Top. Curr. Chem.* **1983**, *109*, 165-188; Pommer *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 423-429 [*Angew. Chem. 89*, 437-443]; Maercker *Org. React.* **1965**, *14*, 270-490; House, Ref. 180, pp. 682-709; Lowe *Chem. Ind. (London)* **1970**, 1070-1079; Bergelson; Shemyakin, in Patai, Ref. 472, pp. 295-340, *Newer Methods Prep. Org. Chem.* **1968**, *5*, 154-175. For related reviews, see Tyuleneva; Rokhlin; Knunyants *Russ. Chem. Rev.* **1981**, *50*, 280-290; Starks; Liotta, Ref. 635, pp. 288-297; Weber; Gokel *Phase Transfer Catalysis in Organic Synthesis*; Springer: New York, 1977; pp. 234-241; Zbiral *Synthesis* **1974**, 775-797; Bestmann *Bull. Soc. Chim. Fr.* **1971**, 1619-1634, *Angew. Chem. Int. Ed. Engl.* **1965**, *4*, 583-587, 645-660, 830-838 [*Angew. Chem. 77*, 609-613, 651-666, 850-858], *Newer Methods Prep. Org. Chem.* **1968**, *5*, 1-60; Horner *Fortschr. Chem. Forsch.* **1966**, *7*, 1-61. For a historical background, see Wittig, *Pure Appl. Chem.* **1964**, *9*, 245-254. For a list of reagents and references for the Wittig and related reactions, see Ref. 64, pp. 173-178.

[639]When phosphonium *fluorides* are used, no base is necessary, as these react directly with the substrate to give the olefin: Schiemenz; Becker; Stöckigt *Chem. Ber.* **1970**, *103*, 2077.

[640]For a convenient method of doing this that results in high yields, see Schlosser; Schaub *Chimia* **1982**, *36*, 396.

[641]Ramirez; Pilot; Desai; Smith; Hansen; McKelvie *J. Am. Chem. Soc.* **1967**, *89*, 6273.

[642]Bestmann *Angew. Chem. Int. Ed. Engl.* **1965**, *4*, 586 [*Angew. Chem. 77*, 612].
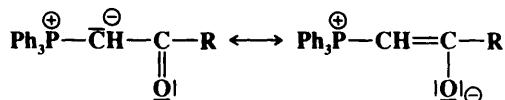
In the overall Wittig reaction, an olefin is formed from the aldehyde or ketone and an alkyl halide in which the halogen-bearing carbon contains at least one hydrogen:

$$\begin{array}{c} \text{H} \\ | \\ -\text{C}=\text{O} + \text{Br}-\text{C}-\text{R} \longrightarrow -\text{C}=\text{C}-\text{R} \\ | \qquad\qquad | \qquad\qquad | \quad | \\ \qquad\qquad\qquad \text{R}' \qquad\qquad\qquad \text{R}' \end{array}$$

This result is similar to that obtained in the Reformatsky reaction (**6-30**), but this is more general since no ester or other group is required to be α to the halogen. Another important advantage of the Wittig reaction is that the *position* of the new double bond is always certain, in contrast to the result in the Reformatsky reaction and in most of the base-catalyzed condensations (**6-39** to **6-46**). Examples of this are given below.

The reaction is very general. The aldehyde or ketone may be aliphatic, alicyclic, or aromatic (including diaryl ketones); it may contain double or triple bonds; it may contain various functional groups, such as OH, OR, NR_2, aromatic nitro or halo, acetal, or even ester groups.[643] Double or triple bonds *conjugated* with the carbonyl also do not interfere, the attack being at the C=O carbon.
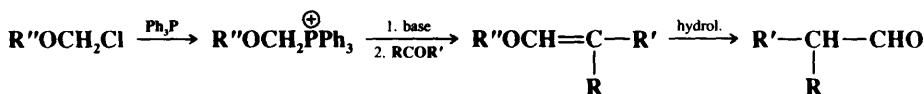
The phosphorus ylide may also contain double or triple bonds and certain functional groups. Simple ylides (R, R' = hydrogen or alkyl) are highly reactive, reacting with oxygen, water, hydrohalic acids, and alcohols, as well as carbonyl compounds and carboxylic esters, so the reaction must be run under conditions where these materials are absent. When an electron-withdrawing group, e.g., COR, CN, COOR, CHO, is present in the α position, the ylides are much more stable, because the charge on the carbon is spread by resonance:

$$\begin{array}{ccc} \overset{\oplus}{Ph_3}\overset{\ominus}{P}-\overset{}{\overset{\ominus}{C}H}-\overset{}{C}-R & \longleftrightarrow & \overset{\oplus}{Ph_3}P-CH=\overset{}{C}-R \\ \qquad\qquad || & & \qquad\qquad | \\ \qquad\qquad \overset{}{O}| & & \qquad\qquad |\overset{}{O}|\ominus \end{array}$$

These ylides react readily with aldehydes, but slowly or not at all with ketones.[644] In extreme cases, e.g., **54**, the ylide does not react with ketones *or* aldehydes. Besides these groups,

54
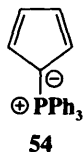
the ylide may contain one or two α halogens[645] or an α OR or OAr group. In the latter case the product is an enol ether, which can be hydrolyzed (**0-6**) to an aldehyde,[646] so that

$$R''OCH_2Cl \xrightarrow{Ph_3P} R''OCH_2\overset{\oplus}{P}Ph_3 \xrightarrow[\text{2. RCOR'}]{\text{1. base}} R''OCH=\overset{}{\underset{R}{C}}-R' \xrightarrow{\text{hydrol.}} R'-\overset{}{\underset{R}{C}H}-CHO$$

[643]Although phosphorus ylides also react with esters, that reaction is too slow to interfere: Greenwald; Chaykovsky; Corey *J. Org. Chem.* **1963**, *28*, 1128.

[644]For successful reactions of stabilized ylides with ketones, under high pressure, see Isaacs; El-Din *Tetrahedron Lett.* **1987**, *28*, 2191. See also Dauben; Takasugi *Tetrahedron Lett.* **1987**, 4377.

[645]Seyferth; Grim; Read *J. Am. Chem. Soc.* **1960**, *82*, 1510, **1961**, *83*, 1617; Seyferth; Heeren; Singh; Grim; Hughes *J. Organomet. Chem.* **1966**, *5*, 267; Schlosser; Zimmermann *Synthesis* **1969**, 75; Burton; Greenlimb *J. Fluorine Chem.* **1974**, *3*, 447; Smithers *J. Org. Chem.* **1978**, *43*, 2833; Miyano; Izumi; Fujii; Ohno; Hashimoto *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1197; Stork; Zhao *Tetrahedron Lett.* **1989**, *30*, 2173.

[646]For references to the use of the Wittig reaction to give enol ethers or enol thioethers, which are then hydrolyzed, see Ref. 64, pp. 715-716, 726.

this reaction is a means of achieving the conversion RCOR' → RR'CHCHO.[647] However, the ylide 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 ylide:

$$\overset{\oplus}{Ph_3P}CH_2CH_2Br \xrightarrow{\text{base}} \overset{\oplus}{Ph_3P}CH=CH_2$$
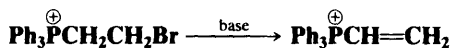
However, a β COO⁻ group may be present, and the product is a β,γ-unsaturated acid:[648]

$$Ph_3\overset{\oplus}{P}-\overset{\ominus}{C}HCH_2COO^- + -\overset{|}{C}=O \longrightarrow -\overset{|}{C}=CHCH_2COO^-$$
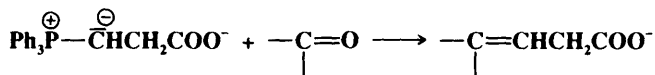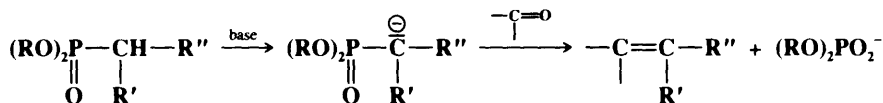
This is the only convenient way to make these compounds, since elimination by any other route gives the thermodynamically more stable α,β-unsaturated isomers. This is an illustration of the utility of the Wittig method for the specific location of a double bond. Another illustration is the conversion of cyclohexanones to olefins containing double bonds, e.g.,[649]
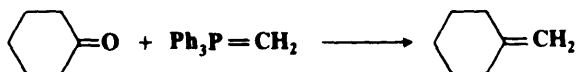
Still another example is the easy formation of anti-Bredt bicycloalkenones[650] (see p. 160). As indicated above, α,α'-dihalophosphoranes can be used to prepare 1,1-dihaloalkenes. Another way to prepare such compounds[651] is to treat the carbonyl compound with a mixture of CX₄ (X = Cl, Br, or I) and triphenylphosphine, either with or without the addition of zinc dust (which allows less Ph₃P to be used).[652]

The Wittig reaction has been carried out with polymer-supported ylides[653] (see p. 421).

Ylides are usually prepared from triphenylphosphine, but other triarylphosphines,[654] trialkylphosphines,[655] and triphenylarsine[656] have also been used. The Wittig reaction has also been carried out with other types of ylides, the most important being prepared from phosphonates:[657]

$$(RO)_2\overset{\|}{\underset{O}{P}}-\overset{R'}{\underset{|}{C}}H-R'' \xrightarrow{\text{base}} (RO)_2\overset{\|}{\underset{O}{P}}-\overset{\ominus}{\underset{R'}{C}}-R'' \xrightarrow{-\overset{|}{C}=O} -\overset{|}{C}=\overset{R''}{\underset{R'}{C}}-R'' + (RO)_2PO_2^-$$

[647]For other methods of achieving this conversion via Wittig-type reactions, see Ceruti; Degani; Fochi *Synthesis* **1987**, 79; Moskal; van Leusen *Recl. Trav. Chim. Pays-Bas* **1987**, *106*, 137; Doad *J. Chem. Res. (S)* **1987**, 370.

[648]Corey; McCormick; Swensen *J. Am. Chem. Soc.* **1964**, *86*, 1884.

[649]Wittig; Schöllkopf *Chem. Ber.* **1954**, *87*, 1318.

[650]Bestmann; Schade *Tetrahedron Lett.* **1982**, *23*, 3543.

[651]For a list of references to the preparation of haloalkenes by Wittig reactions, with references, see Ref. 64, pp. 376-377.

[652]See, for example, Rabinowitz; Marcus *J. Am. Chem. Soc.* **1962**, *84*, 1312; Ramirez; Desai; McKelvie *J. Am. Chem. Soc.* **1962**, *84*, 1745; Corey; Fuchs *Tetrahedron Lett.* **1972**, 3769; Posner; Loomis; Sawaya *Tetrahedron Lett.* **1975**, 1373; Suda; Fukushima *Tetrahedron Lett.* **1981**, *22*, 759; Gaviña; Luis; Ferrer; Costero; Marco *J. Chem. Soc., Chem. Commun.* **1985**, 296; Li; Alper *J. Org. Chem.* **1986**, *51*, 4354.

[653]Bernard; Ford; Nelson *J. Org. Chem.* **1983**, *48*, 3164.

[654]Schiemenz; Thobe *Chem. Ber.* **1966**, *99*, 2663.

[655]For example, see Johnson; LaCount *Tetrahedron* **1960**, *9*, 130; Bestmann; Kratzer *Chem. Ber.* **1962**, *95*, 1894.

[656]An arsenic ylide has been used in a catalytic version of the Wittig reaction; that is, the R₃AsO product is constantly regenerated to produce more arsenic ylide: Shi; Wang; Wang; Huang *J. Org. Chem.* **1989**, *54*, 2027.

[657]Horner; Hoffmann; Wippel *Chem. Ber.* **1958**, *91*, 61; Horner; Hoffmann; Wippel; Klahre *Chem. Ber.* **1959**, *92*, 2499; Wadsworth; Emmons *J. Am. Chem. Soc.* **1961**, *83*, 1733.

This method, sometimes called the *Horner–Emmons*, *Wadsworth–Emmons*, or *Wittig–Horner reaction*,[658] has several advantages over the use of phosphoranes.[659] These ylides are more reactive than the corresponding phosphoranes, and when R' is an electron-withdrawing group, these compounds often react with ketones that are inert to phosphoranes. 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 olefin product. Phosphonates are also cheaper than phosphonium salts and can easily be prepared by the *Arbuzov reaction*:[660]

$$(EtO)_3P + RCH_2X \longrightarrow (EtO)_2\overset{\displaystyle O}{\underset{\displaystyle \|}{P}}-CH_2R$$
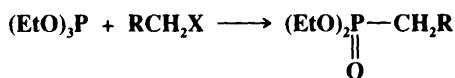
Ylides formed from phosphinoxides $Ar_2\overset{\displaystyle O}{\underset{\displaystyle \|}{P}}CHRR'$, phosphonic acid bisamides $(R_2''N)_2POCHRR'$,[661] and alkyl phosphonothionates $(MeO)_2PSCHRR'$[662] share some of these advantages. Phosphonates $Ph_2POCH_2NR_2'$ react with aldehydes or ketones R^2COR^3 to give good yields of enamines $R^2R^3C=CHNR_2'$.[663]

The mechanism[664] of the key step of the Wittig reaction is as follows:[665]
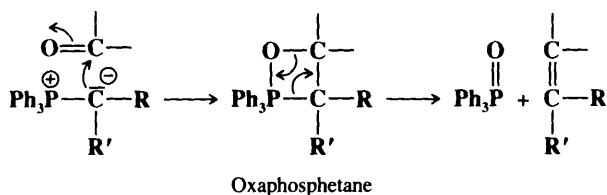
Oxaphosphetane

For many years it was assumed that a diionic compound, called a *betaine*, is an intermediate on the pathway from the starting compounds to the oxaphosphetane, and in fact it may be

Betaine
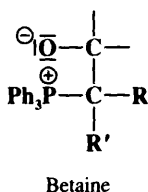
[658]For reviews, see Wadsworth *Org. React.* **1977**, *25*, 73-253; Stec *Acc. Chem. Res.* **1983**, *16*, 411-417; Walker, in Cadogan, Ref. 638, pp. 156-205; Dombrovskii; Dombrovskii *Russ. Chem. Rev.* **1966**, *35*, 733-741; Boutagy; Thomas *Chem. Rev.* **1974**, *74*, 87-99.

[659]For a convenient method of carrying out this reaction, see Seguineau; Villieras *Tetrahedron Lett.* **1988**, *29*, 477, and other papers in this series.

[660]Also known as the *Michaelis–Arbuzov rearrangement*. For reviews, see Petrov; Dogadina; Ionin; Garibina; Leonov *Russ. Chem. Rev.* **1983**, *52*, 1030-1035; Bhattacharya; Thyagarajan *Chem. Rev.* **1981**, *81*, 415-430. For related reviews, see Shokol; Kozhushko *Russ. Chem. Rev.* **1985**, *53*, 98-104; Brill; Landon *Chem. Rev.* **1984**, *84*, 577-585.

[661]Corey; Kwiatkowski *J. Am. Chem. Soc.* **1968**, *90*, 6816; Corey; Cane *J. Org. Chem.* **1969**, *34*, 3053.

[662]Corey; Kwiatkowski *J. Am. Chem. Soc.* **1966**, *88*, 5654.

[663]Broekhof; van der Gen *Recl. Trav. Chim. Pays-Bas* **1984**, *103*, 305; Broekhof; van Elburg; Hoff; van der Gen *Recl. Trav. Chim. Pays-Bas* **1984**, *103*, 317.

[664]For a review of the mechanism, see Cockerill; Harrison, Ref. 209, pp. 232-240. For a thorough discussion, see Vedejs; Marth *J. Am. Chem. Soc.* **1988**, *110*, 3948.

[665]It has been contended that another mechanism, involving single electron transfer, may be taking place in some cases: Olah; Krishnamurthy *J. Am. Chem. Soc.* **1982**, *104*, 3987; Yamataka; Nagareda; Hanafusa; Nagase *Tetrahedron Lett.* **1989**, *30*, 7187. A diradical mechanism has also been proposed for certain cases: Ward; McEwen *J. Org. Chem.* **1990**, *55*, 493.

so, but there is little or no evidence for it,[666] though many attempts have been made to find it. "Betaine" precipitates have been isolated in certain Wittig reactions,[667] but these are betaine–lithium halide adducts, and might just as well have been formed from the oxaphosphetane as from a true betaine.[668] In contrast, there is much evidence for the presence of the oxaphosphetane intermediates, at least with unstable ylides. For example,[31]P nmr spectra taken of the reaction mixtures at low temperatures[669] are compatible with an oxaphosphetane structure that persists for some time but not with a tetracoordinated phosphorus species. Since a betaine, an ylide, 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.[670] It has even been possible to detect cis and trans isomers of the intermediate oxaphosphetanes by nmr spectroscopy.[671] According to this mechanism, an optically active phosphonium salt $RR'R''\overset{\oplus}{P}CHR_2$ should retain its configuration all the way through the reaction, and it should be preserved in the phosphine oxide $RR'R''PO$. This has been shown to be the case.[672]

The proposed betaine intermediates can be formed, in a completely different manner, by nucleophilic substitution by a phosphine on an epoxide (0-49):
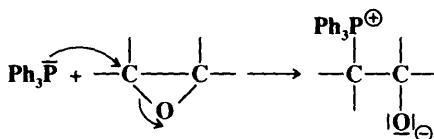
Betaines formed in this way can then be converted to the olefin, and this is one reason why betaine intermediates were long accepted in the Wittig reaction.

Some Wittig reactions give the Z olefin; some the E, and others give mixtures, and the question of which factors determine the stereoselectivity has been much studied.[673] It is generally found that ylides containing stabilizing groups or formed from trialkylphosphines give E olefins. However, ylides formed from triarylphosphines and not containing stabilizing groups often give Z or a mixture of Z and E olefins.[674] One explanation for this[669] is that the reaction of the ylide with the carbonyl compound is a 2 + 2 cycloaddition, which in order to be concerted must adopt the $[_\pi 2_s + {}_\pi 2_a]$ pathway. As we have seen earlier (p. 858), this pathway leads to the formation of the more sterically crowded product, in this case the Z olefin. If this explanation is correct, it is not easy to explain the predominant formation of E products from stable ylides, but E compounds are of course generally thermodynamically more stable than the Z isomers, and the stereochemistry seems to depend on many factors.

[666]See Vedejs; Marth *J. Am. Chem. Soc.* **1990**, *112*, 3905.

[667]Wittig; Weigmann; Schlosser *Chem. Ber.* **1961**, *94*, 676; Schlosser; Christmann *Liebigs Ann. Chem.* **1967**, *708*, 1.

[668]Maryanoff; Reitz, Ref. 638, p. 865.

[669]Vedejs; Snoble *J. Am. Chem. Soc.* **1973**, *95*, 5778; Vedejs; Meier; Snoble *J. Am. Chem. Soc.* **1981**, *103*, 2823. See also Nesmayanov; Binshtok; Reutov *Doklad. Chem.* **1973**, *210*, 499.

[670]Birum; Matthews *Chem. Commun.* **1967**, 137; Mazhar-Ul-Haque; Caughlan; Ramirez; Pilot; Smith *J. Am. Chem. Soc.* **1971**, *93*, 5229.

[671]Maryanoff; Reitz; Mutter; Inners; Almond; Whittle; Olofson *J. Am. Chem. Soc.* **1986**, *108*, 7664. See also Pískala; Rehan; Schlosser *Coll. Czech. Chem. Commun.* **1983**, *48*, 3539.

[672]McEwen; Kumli; Bladé-Font; Zanger; VanderWerf *J. Am. Chem. Soc.* **1964**, *86*, 2378.

[673]For reviews of the stereochemistry of the Wittig reactions, see Maryanoff; Reitz, Ref. 638; Gosney; Rowley, in Cadogan, Ref. 638, pp. 17-153; Reucroft; Sammes *Q. Rev., Chem. Soc.* **1971**, *25*, 135-169, pp. 137-148, 169; Schlosser *Top. Stereochem.* **1970**, *5*, 1-30.

[674]For cases where such an ylide gave E olefins, see Maryanoff; Reitz; Duhl-Emswiler *J. Am. Chem. Soc.* **1985**, *107*, 217; Le Bigot; El Gharbi; Delmas; Gaset *Tetrahedron* **1986**, *42*, 3813. For guidance in how to obtain the maximum yields of the Z product, see Schlosser; Schaub; de Oliveira-Neto; Jeganathan *Chimia* **1986**, *40*, 244.

The $E:Z$ ratio of the product can often be changed by a change in solvent or by the addition of salts.[675] Another way of controlling the stereochemistry of the product is by use of the aforementioned phosphonic acid bisamides. In this case the betaine (**55**) does form

$$R^1\!-\!\underset{\underset{O}{\|}}{C}\!-\!R^2 \;+\; R^3\!-\!\underset{\underset{R^4}{|}}{\overset{\ominus}{C}}\!-\!\underset{\underset{}{\overset{O}{\|}}}{P}(NR_2)_2 \;\longrightarrow\; R^1R^2C\!-\!\underset{\underset{R^4}{|}}{\overset{\overset{\ominus|\underline{O}|}{|}}{C}}\!-\!\underset{}{\overset{\overset{O}{\|}}{P}}(NR_2)_2 \;\xrightarrow{H_2O}\; R^1R^2C\!-\!\underset{\underset{OH\ R^4}{}}{\overset{\overset{R^3\ O}{|\ \ \|}}{C}}\!-\!P(NR_2)_2$$

<div align="center">

55   **56**

</div>

and when treated with water gives the β-hydroxyphosphonic acid bisamides **56**, 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.[661] **56** are generally formed as mixtures of diastereomers, and these mixtures can be separated by recrystallization. Cleavage of the two diastereomers gives the two isomeric olefins. Optically active phosphonic acid bisamides have been used to give optically active olefins.[676] Another method of controlling the stereochemistry of the olefin (to obtain either the Z or E isomer) starting with a phosphine oxide Ph_2POCH_2R, has been reported.[677]

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 ethylidenetriphenylphosphorane with heptanal at $-78°C$ gave **57**, which with butyllithium gave the ylide **58**. Treatment of this with an aldehyde $R'CHO$ gave the intermediate **59**,
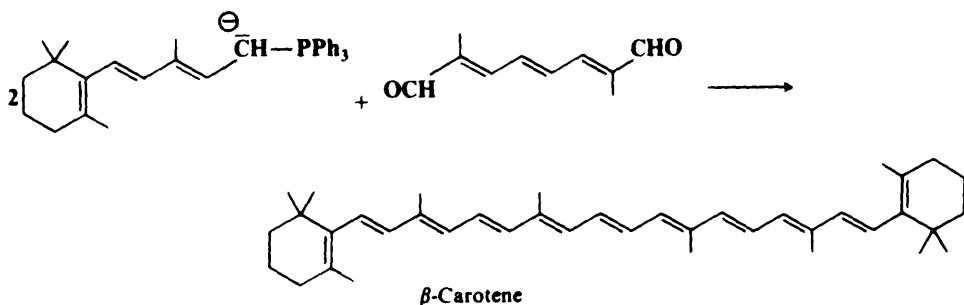
$$\underset{\underset{Me}{|}}{\overset{\overset{O^{\ominus}}{|}}{CH}}\!-\!\overset{\oplus}{CH}PPh_3 \;\xrightarrow{BuLi}\; \underset{\underset{Me}{|}}{\overset{\overset{O^{\ominus}Li^+}{|}}{RCH}}\!-\!C\!=\!PPh_3 \;\xrightarrow{R'CHO}\; \left[\underset{\underset{Me\ \ R'}{|\ \ |}}{\overset{\overset{O^{\ominus}\ \ PPh_3}{|\ \ \ |}}{RCH}}\!-\!C\!-\!CHO^{\ominus}Li^+\right] \;\longrightarrow\; \underset{R}{\overset{H}{>}}C\!=\!C\underset{\underset{R'}{\overset{CHOH}{|}}}{\overset{Me}{<}}$$

<div align="center">

57   **58**   **59**   **60**

$R = n\text{-}C_6H_{13}$

</div>

which after workup gave **60**.[678] This reaction gives the unsaturated alcohols **60** stereoselectively. **58** also reacts with other electrophiles. For example, treatment of **58** with N-chlorosuccinimide or $PhICl_2$ gives the vinylic chloride $RCH\!=\!CMeCl$ stereoselectively: NCS giving the cis and $PhICl_2$ the trans isomer.[679] The use of Br_2 and $FClO_3$ (see 2-4 for the explosive nature of this reagent) gives the corresponding bromides and fluorides, respectively.[680] Reactions of **58** with electrophiles have been called *scoopy* reactions (α substitution plus carbonyl *o*lefination via β-*o*xido *p*hosphorus ylides).[681]

[675]See, for example, Reitz; Nortey; Jordan; Mutter; Maryanoff *J. Org. Chem.* **1986**, *51*, 3302.

[676]Hanessian; Delorme; Beaudoin; Leblanc *J. Am. Chem. Soc.* **1984**, *106*, 5754.

[677]Buss; Warren *J. Chem. Soc., Perkin Trans. 1* **1985**, 2307; Ayrey; Warren *Tetrahedron Lett.* **1989**, *30*, 4581.

[678]Corey; Yamamoto *J. Am. Chem. Soc.* **1970**, *92*, 226; Schlosser; Christmann; Piskala; Coffinet *Synthesis* **1971**, 29; Schlosser; Coffinet *Synthesis* 380, **1971**, **1972**, 575; Corey; Ulrich; Venkateswarlu *Tetrahedron Lett.* **1977**, 3231; Schlosser; Tuong; Respondek; Schaub *Chimia* **1983**, *37*, 10.

[679]Schlosser; Christmann *Synthesis* **1969**, 38; Corey; Shulman; Yamamoto *Tetrahedron Lett.* **1970**, 447.

[680]Schlosser; Christmann, Ref. 679.

[681]Schlosser, Ref. 673, p. 22.

The Wittig reaction has been carried out intramolecularly, to prepare rings containing from 5 to 16 carbons,[682] both by single ring closure

$$R-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle (CH_2)_n}{\big\lfloor}}{C}}\quad\overset{\overset{\displaystyle R'}{\big|}}{\underset{}{\overset{\ominus}{C}}}-\overset{\oplus}{P}Ph_3\longrightarrow R-\overset{\underset{\underset{\displaystyle (CH_2)_n}{\big\lfloor}}{}}{C}\!\!=\!\!\overset{\overset{\displaystyle R'}{\big|}}{C}-R'$$

and double ring closure.[683]

The Wittig reaction has proved very useful in the synthesis of natural products, some of which are quite difficult to prepare in other ways.[684] One example out of many is the synthesis of β-carotene:[685]

β-Carotene

Phosphorus ylides also react in a similar manner with the C=O bonds of ketenes,[686] isocyanates,[687] and certain anhydrides[688] and imides,[689] the N=O of nitroso groups, and the C=N of imines.[690]

[682]For a review, see Becker *Tetrahedron* **1980**, *36*, 1717-1745.

[683]For a review of these double ring closures, see Vollhardt *Synthesis* **1975**, 765-780.

[684]For a review of applications of the Wittig reaction to the synthesis of natural products, see Bestmann; Vostrowsky, Ref. 638.

[685]Wittig; Pommer; German patent **1956**, 954,247, *CA* **1959**, *53*, 2279.

[686]For example, see Aksnes; Frøyen *Acta Chem. Scand.* **1968**, *22*, 2347.

[687]For example, see Frøyen *Acta Chem. Scand., Ser. B* **1974**, *28*, 586.

[688]See, for example, Abell; Massy-Westropp *Aust. J. Chem.* **1982**, *35*, 2077; Kayser; Breau *Can. J. Chem.* **1989**, *67*, 1401. For a study of the mechanism, see Abell; Clark; Robinson *Aust. J. Chem.* **1988**, *41*, 1243.

[689]For a review of the reactions with anhydrides and imides (and carboxylic esters, thiol esters, and amides), see Murphy; Brennan *Chem. Soc. Rev.* **1988**, *17*, 1-30. For a review with respect to imides, see Flitsch; Schindler *Synthesis* **1975**, 685-700.

[690]Bestmann; Seng *Tetrahedron* **1965**, *21*, 1373.
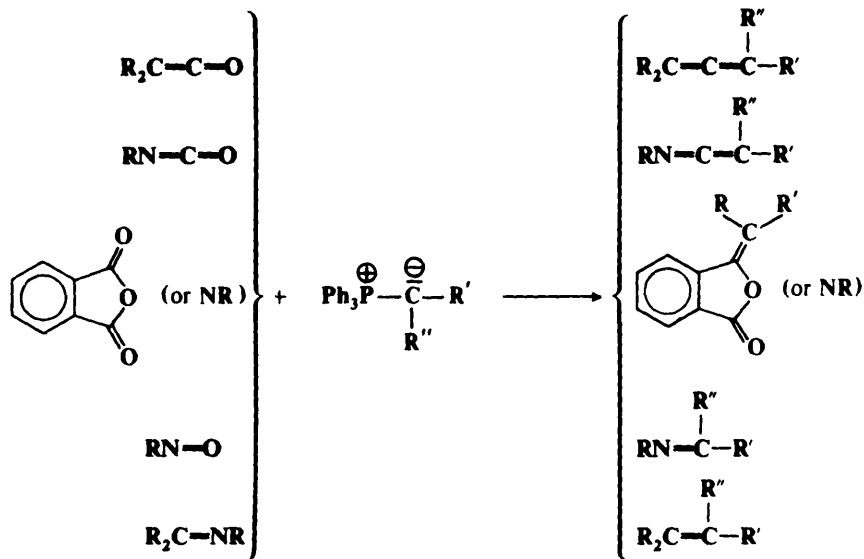
Phosphorus ylides react with carbon dioxide to give the isolable salts **61**,[691] which can be hydrolyzed to the carboxylic acids **62** (thus achieving the conversion $RR'CHX \rightarrow$
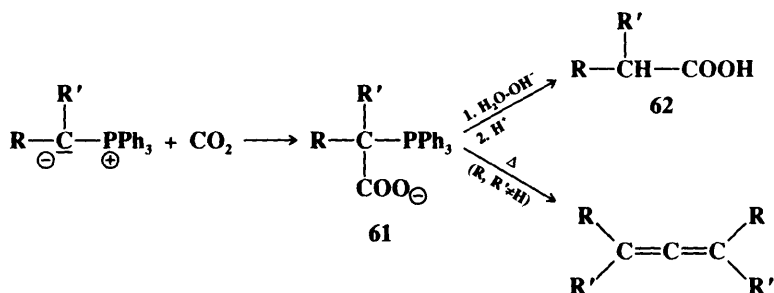
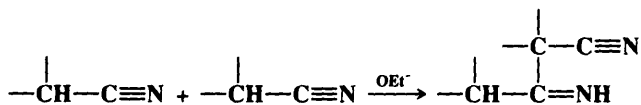$RR'CHCOOH$) or (if neither R nor R' is hydrogen) dimerized to allenes.

OS **V**, 361, 390, 499, 509, 547, 751, 949, 985; **VI**, 358; **VII**, 164, 232; **65**, 119; **66**, 220.
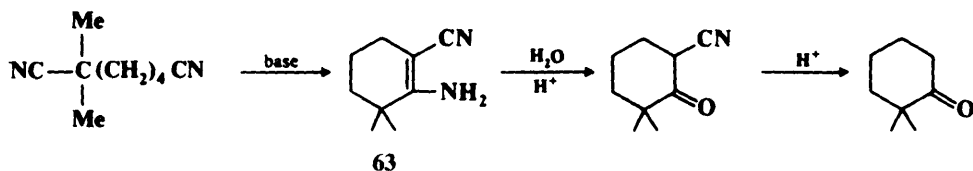
6-48 The Thorpe Reaction
_N_-Hydro-_C_-(α-cyanoalkyl)-addition

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 (**6-39**). The C=NH bond is, of

[691]Bestmann; Denzel; Salbaum *Tetrahedron Lett* **1974**, 1275.

course, hydrolyzable (**6-2**), so β-keto nitriles can be prepared in this manner. The Thorpe reaction can be done internally, in which case it is called the *Thorpe–Ziegler reaction*.[692] 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
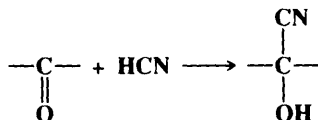

63

in the Thorpe–Ziegler reaction is not the imine, but the tautomeric enamine, e.g., **63**; if desired this can be hydrolyzed to an α-cyano ketone (**6-2**), which can in turn be hydrolyzed and decarboxylated (**6-5**, **2-40**). Other active-hydrogen compounds can also be added to nitriles.[693]

OS **VI**, 932.

J. Other Carbon Nucleophiles

6-49 The Formation of Cyanohydrins
O-Hydro-*C*-cyano-addition

The addition of HCN to aldehydes or ketones produces cyanohydrins.[694] This is an equilibrium reaction. 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 (**6-54**) competes. With α,β-unsaturated aldehydes and ketones, 1,4 addition competes (**5-25**). 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[695] in the presence of a Lewis acid or base,[695a] followed by hydrolysis of the resulting O-trimethylsilyl cyanohydrin **64**. When $TiCl_4$ is used,
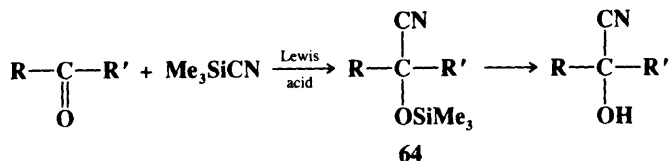
[692]For a monograph, see Taylor; McKillop *The Chemistry of Cyclic Enaminonitriles and ortho-Amino Nitriles*; Wiley: New York, 1970. For a review, see Schaefer; Bloomfield, *Org. React.* **1967**, *15*, 1-203.

[693]See for example, Josey *J. Org. Chem.* **1964**, *29*, 707; Barluenga; Fustero; Rubio; Gotor *Synthesis* **1977**, 780; Hiyama; Kobayashi *Tetrahedron Lett.* **1982**, *23*, 1597; Gewald; Bellmann; Jänsch *Liebigs Ann. Chem.* **1984**, 1702; Page; van Niel; Westwood *J. Chem. Soc., Perkin Trans. 1* **1988**, 269.

[694]For reviews, see Friedrich, in Patai; Rappoport *The Chemistry of Functional Groups, Supplement C*, pt. 2; Wiley: New York, 1983, pp. 1345-1390; Friedrich; Wallenfels, in Rappoport, Ref. 334, pp. 72-77.

[695]For reviews of Me_3SiCN and related compounds, see Rasmussen; Heilmann; Krepski *Adv. Silicon Chem.* **1991**, *1*, 65-187; Groutas; Felker *Synthesis* **1980**, 861-868. For procedures using Me_3SiCl and CN⁻ instead of Me_3SiCN, see Yoneda; Santo; Harusawa; Kurihara *Synthesis* **1986**, 1054; Sukata *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3820.

[695a]Kobayashi; Tsuchiya; Mukaiyama *Chem. Lett.* **1991**, 537.

$$\text{R—C—R' + Me}_3\text{SiCN} \xrightarrow[\text{acid}]{\text{Lewis}} \begin{array}{c} \text{CN} \\ | \\ \text{R—C—R'} \\ | \\ \text{OSiMe}_3 \end{array} \longrightarrow \begin{array}{c} \text{CN} \\ | \\ \text{R—C—R'} \\ | \\ \text{OH} \end{array}$$
$$\overset{\|}{\underset{\text{O}}{}}$$

64

the reaction between Me_3SiCN and aromatic aldehydes or ketones gives α-chloro nitriles Cl—CRR'—CN.[696]

Frequently it is the bisulfite addition product that is treated with CN^-. 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.
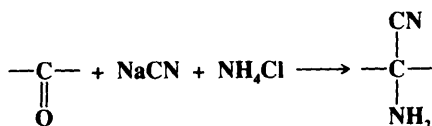
The addition is nucleophilic and the actual nucleophile is CN^-, so the reaction rate is increased by the addition of base.[697] This was demonstrated by Lapworth in 1903, and consequently this was one of the first organic mechanisms to be known.[698]

The reaction has been carried out enantioselectively: optically active cyanohydrins were prepared with the aid of optically active catalysts.[699]

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.

6-50 The Strecker Synthesis
Cyano,amino-de-oxo-bisubstitution

$$\begin{array}{c} \text{—C—} \\ \| \\ \text{O} \end{array} + \text{NaCN} + \text{NH}_4\text{Cl} \longrightarrow \begin{array}{c} \text{CN} \\ | \\ \text{—C—} \\ | \\ \text{NH}_2 \end{array}$$

α-Amino nitriles[700] 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*;[700a] it is a special case of the Mannich reaction (**6-16**). 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 **6-49**, the Strecker synthesis is useful for aromatic as well as aliphatic ketones. As in **6-49**, the Me_3SiCN method has been used; **64** is converted to the product with ammonia or an amine.[701]

OS **I**, 21, 355; **III**, 66, 84, 88, 275; **IV**, 274; **V**, 437; **VI**, 334.

[696]Kiyooka; Fujiyama; Kawaguchi *Chem. Lett.* **1984**, 1979.
[697]For a review, see Ogata; Kawasaki, in Zabicky *The Chemistry of the Carbonyl Group*, vol. 2, Wiley: New York, 1970, pp. 21-32. See also Okano; do Amaral; Cordes *J. Am. Chem. Soc.* **1976**, *98*, 4201; Ching; Kallen *J. Am. Chem. Soc.* **1978**, *100*, 6119.
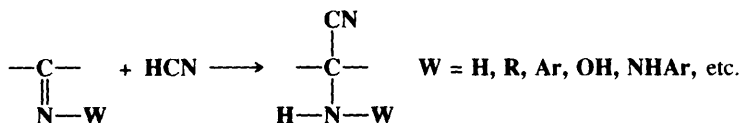[698]Lapworth *J. Chem. Soc.* **1903**, *83*, 998.
[699]See Minamikawa; Hayakawa; Yamada; Iwasawa; Narasaka *Bull. Chem. Soc. Jpn.* **1988**, *61*, 4379; Jackson; Jayatilake; Matthews; Wilshire *Aust. J. Chem.* **1988**, *41*, 203; Garner; Fernández; Gladysz *Tetrahedron Lett.* **1989**, *30*, 3931; Mori; Ikeda; Kinoshita; Inoue *Chem. Lett.* **1989**, 2119; Kobayashi; Tsuchiya; Mukaiyama *Chem. Lett.* **1991**, 541, and references cited in these papers.
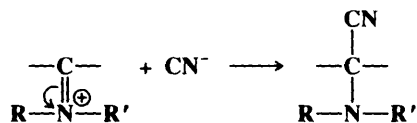[700]For a review of α-amino nitriles, see Shafran; Bakulev; Mokrushin *Russ. Chem. Rev.* **1989**, *58*, 148-162.
[700a]For a review of asymmetric Strecker syntheses, see Williams *Synthesis of Optically Active α-Amino Acids*; Pergamon: Elmsford, NY, 1989, pp. 208-229.
[701]See Mai; Patil *Tetrahedron Lett.* **1984**, *25*, 4583, *Synth. Commun.* **1985**, *15*, 157.

6-51 The Addition of HCN to C=N and C≡N Bonds
N-Hydro-C-cyano-addition

$$\underset{\underset{N-W}{\overset{\|}{\underset{|}{C}}}}{-\overset{|}{C}-} \quad + \quad HCN \quad \longrightarrow \quad \underset{\underset{H-N-W}{\overset{|}{\underset{|}{C}}}}{-\overset{\overset{CN}{|}}{C}-} \quad W = H, R, Ar, OH, NHAr, \text{ etc.}$$

HCN adds to imines, Schiff bases, hydrazones, oximes, and similar compounds. CN⁻ can be added to iminium ions:[330]

$$\underset{\underset{R-\overset{\oplus}{N}-R'}{\overset{\|}{\underset{|}{C}}}}{-\overset{|}{C}-} \quad + \quad CN^- \quad \longrightarrow \quad \underset{R-\overset{|}{N}-R'}{-\overset{\overset{CN}{|}}{C}-}$$
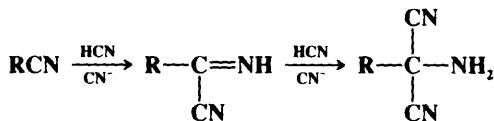
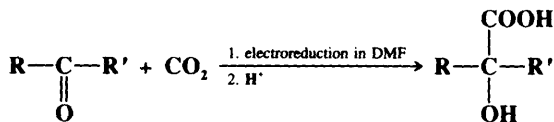As in **6-48**, the addition to imines has been carried out enantioselectively.[702]

The addition of KCN to triisopropylbenzenesulfonyl hydrazones **65** provides an indirect method for achieving the conversion RR′CO → RR′CHCN.[703] The reaction is successful for hydrazones of aliphatic aldehydes and ketones.

$$\underset{\textbf{65}}{RR'C=NNHSO_2Ar} + KCN \xrightarrow{\text{MeOH}} RR'CHCN \qquad Ar = 2,4,6-(i-Pr)_3C_6H_2$$
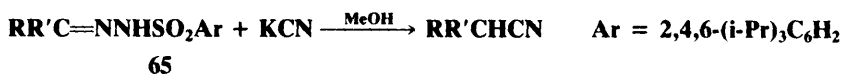
HCN can also be added to the C≡N bond to give iminonitriles or α-aminomalononitriles.[704]

$$RCN \xrightarrow[\text{CN}^-]{\text{HCN}} \underset{\underset{CN}{|}}{R-\overset{|}{C}=NH} \xrightarrow[\text{CN}^-]{\text{HCN}} \underset{\underset{CN}{|}}{R-\overset{\overset{CN}{|}}{C}-NH_2}$$

OS **V**, 344. See also OS **V**, 269.

6-52 The Addition of CO₂ to Aldehydes and Ketones
O-Hydro-C-carboxyl-addition

$$\underset{\underset{O}{\overset{\|}{\underset{|}{C}}}}{R-\overset{|}{C}-R'} + CO_2 \xrightarrow[\text{2. H}^\bullet]{\text{1. electroreduction in DMF}} \underset{\underset{OH}{|}}{R-\overset{\overset{COOH}{|}}{C}-R'}$$

[702]Saito; Harada *Tetrahedron Lett.* **1989**, *30*, 4535.

[703]Jiricny; Orere; Reese *J. Chem. Soc., Perkin Trans. 1* **1980**, 1487. For other methods of achieving this conversion, see Ziegler; Wender *J. Org. Chem.* **1977**, *42*, 2001; Cacchi; Caglioti; Paolucci *Synthesis* **1975**, 120; Yoneda; Harusawa; Kurihara *Tetrahedron Lett.* **1989**, *30*, 3681; Okimoto; Chiba *J. Org. Chem.* **1990**, *55*, 1070.

[704]For an example, see Ferris; Sanchez *Org. Synth. V.* 344.

Aromatic aldehydes and ketones have been converted to α-hydroxy acids by electrolysis carried out in the presence of CO_2 in DMF, followed by hydrolysis.[705] Yields were moderate to high.

Addition of ArH to C=O, C=N, and C≡N bonds is discussed under aromatic substitution: **1-16, 1-20** to **1-25, 1-27,** and **1-28.**
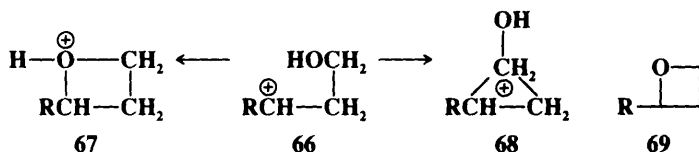
6-53   The Prins Reaction
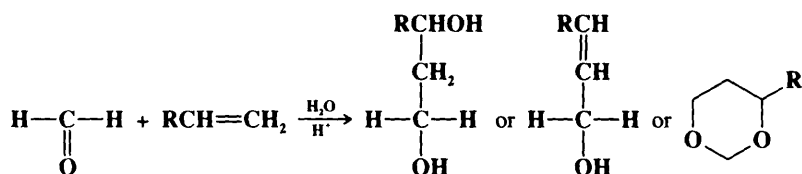
The addition of an olefin to formaldehyde in the presence of an acid[706] catalyst is called the *Prins reaction.*[707] Three main products are possible; which one predominates depends on the olefin and the conditions. When the product is the 1,3-diol or the dioxane,[708] the reaction involves addition 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 attacks the C=C:
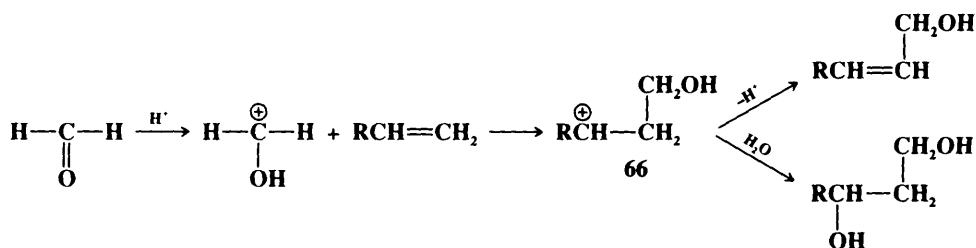
66 can undergo loss of H^+ to give the olefin or add water to give the diol.[709] It has been proposed that **66** is stabilized by neighboring-group attraction, with either the oxygen[710] or

[705]Mcharek; Heintz; Troupel; Perichon *Bull. Soc. Chim. Fr.* **1989,** 95.

[706]The Prins reaction has also been carried out with basic catalysts: Griengl; Sieber *Monastsh. Chem.* **1973,** *104,* 1008, 1027.

[707]For reviews, see Adams; Bhatnagar *Synthesis* **1977,** 661-672; Isagulyants; Khaimova; Melikyan; Pokrovskaya *Russ. Chem. Rev.* **1968,** *37,* 17-25. For a list of references, see Ref. 64, p. 125.

[708]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; Nigmatullin; Ibatullin; Rafikov *Doklad. Chem.* **1977,** *236,* 507.

[709]Hellin; Davidson; Coussemant *Bull. Soc. Chim. Fr.* **1966,** 1890, 3217.

[710]Blomquist; Wolinsky *J. Am. Chem. Soc.* **1957,** *79,* 6025; Schowen; Smissman; Schowen *J. Org. Chem.* **1968,** *33,* 1873.

a carbon[711] stabilizing the charge (**67** and **68**, respectively). This stabilization is postulated to explain the fact that with 2-butenes[712] 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 **67** or **68**.[710,711] Additional evidence for the intermediacy of **67** is the finding that oxetanes (**69**) subjected to the reaction conditions (which would protonate **69** to give **67**) give essentially the same product ratios as the corresponding alkenes.[713] An argument against the intermediacy of **67** and **68** 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.[714] Since addition to the C=C bond is electrophilic, the reactivity of the olefin 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[715] (**6-6**) or between **66** and formaldehyde.

Lewis acids such as $SnCl_4$ also catalyze the reaction, in which case the species that adds to the olefins is $H_2\overset{\oplus}{C}\!\!-\!\!O\!\!-\!\!\overset{\ominus}{S}nCl_4$.[716] The reaction can also be catalyzed by peroxides, in which case the mechanism is probably a free-radical one.

A closely related reaction has been performed with other aldehydes and even with ketones; without a catalyst, but with heat.[717] The aldehydes and ketones here are active ones, such as chloral and acetoacetic ester. The product in these cases is a β-hydroxy olefin, and the mechanism is pericyclic:[718]
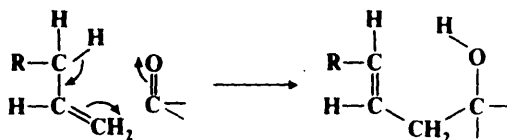
This reaction is reversible and suitable β-hydroxy olefins can be cleaved by heat (**7-43**). There is evidence that the cleavage reaction occurs by a cyclic mechanism (p. 1043), and, by the principle of microscopic reversibility, the addition mechanism should be cyclic too.[719] Note that this reaction is an oxygen analog of the ene synthesis (**5-16**). This reaction can also be done with unactivated aldehydes[720] and ketones[721] if Lewis-acid catalysts such as

[711]Dolby; Lieske; Rosencrantz; Schwarz *J. Am. Chem. Soc.* **1963**, *85*, 47; Dolby; Schwarz *J. Org. Chem.* **1963**, *28*, 1456; Safarov; Isagulyants; Nigmatullin *J. Org. Chem. USSR* **1974**, *10*, 1378.

[712]Fremaux; Davidson; Hellin; Coussemant *Bull. Soc. Chim. Fr.* **1967**, 4250.

[713]Meresz; Leung; Denes *Tetrahedron Lett.* **1972**, 2797.

[714]For example, see LeBel, Liesemer; Mehmedbasich *J. Org. Chem.* **1963**, *28*, 615; Portoghese; Smissman *J. Org. Chem.* **1962**, *27*, 719; Wilkins; Marianelli *Tetrahedron* **1970**, *26*, 4131; Karpaty; Hellin; Davidson; Coussemant *Bull. Soc. Chim. Fr.* **1971**, 1736; Coryn; Anteunis *Bull. Soc. Chim. Belg.* **1974**, *83*, 83.

[715]Ref. 709; Isagulyants; Isagulyants; Khairudinov; Rakhmankulov *Bull. Acad. Sci. USSR. Div. Chem. Sci* **1973**, *22*, 1810; Sharf; Kheifets; Freidlin *Bull. Acad. Sci. USSR, Div. Chem. Sci* **1974**, *23*, 1681.

[716]Yang; Yang; Ross *J. Am. Chem. Soc.* **1959**, *81*, 133.

[717]Arnold; Veeravagu *J. Am. Chem. Soc.* **1960**, *82*, 5411; Klimova; Abramov; Antonova; Arbuzov *J. Org. Chem. USSR* **1969**, *5*, 1308; Klimova; Antonova; Arbuzov *J. Org. Chem. USSR* **1969**, *5*, 1312, 1315.

[718]See for example, Achmatowicz; Szymoniak *J. Org. Chem.* **1980**, *45*, 1228; Ben Salem; Jenner *Tetrahedron Lett.* **1986**, *27*, 1575. There is evidence that the mechanism is somewhat more complicated than shown here: Kwart; Brechbiel *J. Org. Chem.* **1982**, *47*, 3353.
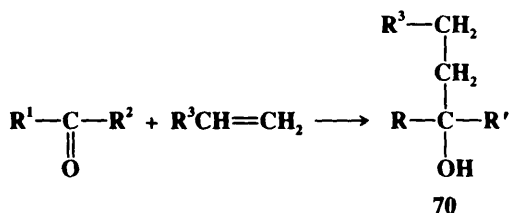
[719]For other evidence, see Ref. 718; Papadopoulos; Jenner *Tetrahedron Lett.* **1981**, *22*, 2773.

[720]Snider *Acc. Chem. Res.* **1980**, *13*, 426-432; Snider; Phillips *J. Org. Chem.* **1983**, *48*, 464; Cartaya-Marin; Jackson; Snider *J. Org. Chem.* **1984**, *49*, 2443.

[721]Jackson; Goldman; Snider *J. Org. Chem.* **1984**, *49*, 3988.

dimethylaluminum chloride Me_2AlCl or ethylaluminum dichloride $EtAlCl_2$ are used.[722] Lewis acid catalysts also increase rates with activated aldehydes.[723] The use of optically active catalysts has given optically active products with high enantiomeric excesses.[724]

In a related reaction, alkenes can be added to aldehydes and ketones to give reduced alcohols **70**. This has been accomplished by several methods,[725] including treatment with

$$
R^1{-}\underset{\underset{O}{\|}}{C}{-}R^2 \;+\; R^3CH{=}CH_2 \;\longrightarrow\;
R{-}\underset{\underset{OH}{|}}{\overset{\overset{R^3{-}CH_2}{|}}{\overset{CH_2}{|}}{C}}{-}R'
$$

70

SmI_2[726] or Zn and Me_3SiCl,[727] and by electrochemical[728] and photochemical[729] 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.

6-54   The Benzoin Condensation
Benzoin aldehyde condensation

$$
2ArCHO \;+\; KCN \;\longrightarrow\; Ar{-}\underset{\underset{OH}{|}}{CH}{-}\underset{\underset{O}{\|}}{C}{-}Ar
$$
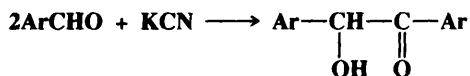
When certain aldehydes are treated with cyanide ion, *benzoins* are produced in a reaction called the *benzoin condensation*. The condensation can be regarded as involving the addition of one molecule of aldehyde to the C=O group of another. The reaction can be accomplished only for aromatic aldehydes, though not for all of them,[730] 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.

[722]For discussions of the mechanism with Lewis-acid catalysts, see Stephenson; Orfanopoulos *J. Org. Chem.* **1981,** *46,* 2200; Kwart; Brechbiel *J. Org. Chem.* **1982,** *47,* 5409; Song; Beak *J. Org. Chem.* **1990,** *112,* 8126.
[723]Benner; Gill; Parrott; Wallace *J. Chem. Soc., Perkin Trans. 1* **1984,** 291, 315, 331.
[724]Maruoka; Hoshino; Shirasaka; Yamamoto *Tetrahedron Lett.* **1988,** *29,* 3967; Mikami; Terada; Nakai *J. Am. Chem. Soc.* **1990,** *112,* 3949.
[725]For references, see Ujikawa; Inanaga; Yamaguchi *Tetrahedron Lett.* **1989,** *30,* 2837; Ref. 64, pp. 575-576.
[726]Ujikawa et al., Ref. 725.
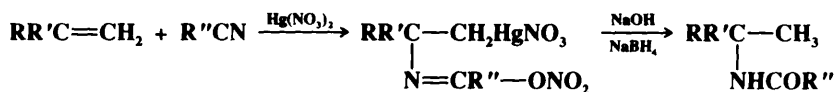[727]Corey; Pyne *Tetrahedron Lett.* **1983,** *24,* 2821.
[728]See Shono; Kashimura; Mori; Hayashi; Soejima; Yamaguchi *J. Org. Chem.* **1989,** *54,* 6001.
[729]See Belotti; Cossy; Pete; Portella *J. Org. Chem.* **1986,** *51,* 4196.
[730]For a review, see Ide; Buck *Org. React.* **1948,** *4,* 269-304.

The following is the accepted mechanism,[731] which was originally proposed by Lapworth in 1903:[732]

The reaction is reversible. 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, CN⁻ 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.[733] In this case aliphatic aldehydes can also be used[734] (the products are called *acyloins*), and mixtures of aliphatic and aromatic aldehydes give mixed α-hydroxy ketones.[735] The reaction has also been carried out without CN⁻, 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.[736]

OS **I**, 94; **VII**, 95.

Reactions in Which Carbon Adds to the Hetero Atom

A. Oxygen Adding to the Carbon

6-55 The Ritter Reaction
N-Hydro,*N*-alkyl-*C*-oxo-biaddition

$$R—C\equiv N + R'OH \xrightarrow{H^+} R—\underset{\underset{O}{\|}}{C}—\underset{\underset{H}{|}}{N}—R'$$

Alcohols can be added to nitriles in an entirely different manner from that of reaction **6-9**. In this reaction, the alcohol is converted by a strong acid to a carbocation, which adds to the negative nitrogen, water adding to the carbon:

$$R'OH \xrightarrow{H^+} R'^+ + R—C\equiv N \longrightarrow R—\overset{\oplus}{C}=N—R' \xrightarrow{H_2O} R—\underset{\underset{OH}{|}}{C}=N—R'$$

[731]For a discussion, See Kuebrich; Schowen; Wang; Lupes *J. Am. Chem. Soc.* **1971**, *93*, 1214.

[732]Lapworth *J. Chem. Soc.* **1903**, *83*, 995, **1904**, *85*, 1206.

[733]See Ugai; Tanaka; Dokawa *J. Pharm. Soc. Jpn.* **1943**, *63*, 296 [*CA 45*, 5148]; Breslow *J. Am. Chem. Soc.* **1958**, *80*, 3719; Breslow; Kool *Tetrahedron Lett.* **1988**, *29*, 1635; Castells; López-Calahorra; Domingo *J. Org. Chem.* **1988**, *53*, 4433; Diederich; Lutter *J. Am. Chem. Soc.* **1989**, *111*, 8438. For another catalyst, see Lappert; Maskell *J. Chem. Soc., Chem. Commun.* **1982**, 580.

[734]Stetter; Rämsch; Kuhlmann *Synthesis* **1976**, 733; Stetter; Kuhlmann *Org. Synth. VII*, 95; Matsumoto; Ohishi; Inoue *J. Org. Chem.* **1985**, *50*, 603.

[735]Stetter; Dämbkes *Synthesis* **1977**, 403.

[736]Rozwadowska *Tetrahedron* **1985**, *41*, 3135.

The immediate product tautomerizes to the N-alkyl amide. Only alcohols that give rise to fairly stable carbocations react (secondary, tertiary, benzylic, etc.); primary alcohols do not give the reaction. The carbocation need not be generated from an alcohol but may come from protonation of an olefin or from other sources. In any case, the reaction is called the *Ritter reaction*.[737] HCN also gives the reaction, the product being a formamide. Since the amides (especially the formamides) are easily hydrolyzable to amines, the Ritter reaction provides a method for achieving the conversions R'OH → R'NH$_2$ (see **0-46**) and alkene → R'NH$_2$ (see **5-7**) 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[738] or Ph$_2$CCl$^+$ SbCl$_6^-$ or a similar salt[739] in the presence of the nitrile.

Olefins 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.[740] This method has the advantage of avoiding strong acids.
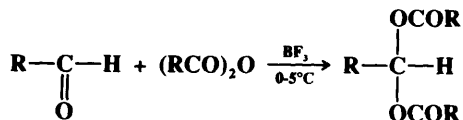
$$RR'C{=}CH_2 + R''CN \xrightarrow{Hg(NO_3)_2} \underset{\underset{N{=}CR''{-}ONO_2}{|}}{RR'C{-}CH_2HgNO_3} \xrightarrow[NaBH_4]{NaOH} \underset{\underset{NHCOR''}{|}}{RR'C{-}CH_3}$$

The Ritter reaction can be applied to cyanamides RNHCN to give ureas RNHCONHR'.[741]

OS **V**, 73, 471.

6-56 Acylation of Aldehydes and Ketones
O-Acyl-C-acyloxy-addition

$$R{-}\underset{\underset{O}{\|}}{C}{-}H + (RCO)_2O \xrightarrow[0\text{-}5°C]{BF_3} R{-}\underset{\underset{OCOR}{|}}{\overset{\overset{OCOR}{|}}{C}}{-}H$$

Aldehydes can be converted to *acylals* by treatment with an anhydride in the presence of BF$_3$, other Lewis acids,[742] proton acids,[743] or PCl$_3$.[744] 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.[745]

OS **IV**, 489.

[737]Ritter; Minieri *J. Am. Chem. Soc.* **1948**, 70, 4045. For reviews, see Krimen; Cota *Org. React.* **1969**, 17, 213-325; Beckwith, in Zabicky, Ref. 65, pp. 125-130; Johnson; Madroñero *Adv. Heterocycl. Chem.* **1966**, 6, 95-146.

[738]Martinez; Alvarez; Vilar; Fraile; Hanack; Subramanian *Tetrahedron Lett.* **1989**, 30, 581.

[739]Barton; Magnus; Garbarino; Young *J. Chem. Soc., Perkin Trans. 1* **1974**, 2101. See also Top; Jaouen *J. Org. Chem.* **1981**, 46, 78.

[740]Sokolov; Reutov *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1968**, 225; Brown; Kurek *J. Am. Chem. Soc.* **1969**, 91, 5647; Chow; Robson; Wright *Can. J. Chem.* **1965**, 43, 312; Fry; Simon *J. Org. Chem.* **1982**, 47, 5032.

[741]Anatol; Berecoechea *Bull. Soc. Chim. Fr.* **1975**, 395, *Synthesis* **1975**, 111.

[742]For example, FeCl$_3$: Kochhar; Bal; Deshpande; Rajadhyaksha; Pinnick *J. Org. Chem.* **1983**, 48, 1765.

[743]For example, see Olah; Mehrotra *Synthesis* **1982**, 962.

[744]See Michie; Miller *Synthesis* **1981**, 824.

[745]Libman; Sprecher; Mazur *Tetrahedron* **1969**, 25, 1679.

6-57   The Addition of Aldehydes to Aldehydes

$$3RCHO \xrightarrow{H^+}$$

When catalyzed by acids, low-molecular-weight aldehydes add to each other to give cyclic acetals, the most common product being the trimer.[746] The cyclic trimer of formaldehyde is called *trioxane*, and that of acetaldehyde is known as *paraldehyde*. Under certain conditions, it is possible to get tetramers[747] 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 formadehyde and acetaldehyde have low boiling points, it is often convenient to use them in the form of their trimers or polymers.

B.   Nitrogen Adding to the Carbon

6-58   The Addition of Isocyanates to Isocyanates
Alkylimino-de-oxo-bisubstitution

71

$$2R-N=C=O \longrightarrow R-N=C=N-R$$

The treatment of isocyanates with 3-methyl-1-ethyl-3-phospholene-1-oxide (**71**) is a useful method for the synthesis of carbodiimides[748] in good yields.[749] 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 $R_3\overset{\oplus}{P}-\overset{\ominus}{O}$):[750]

[746]For a review, see Bevington *Q. Rev., Chem. Soc.* **1952**, *6*, 141-156.
[747]Barón; Manderola; Westerkamp *Can. J. Chem.* **1963**, *41*, 1893.
[748]For reviews of the chemistry of carbodiimides, see Williams; Ibrahim *Chem. Rev.* **1981**, *81*, 589-636; Mikołajczyk; Kiełbasiński *Tetrahedron* **1981**, *37*, 233-284; Kurzer; Douraghi-Zadeh *Chem. Rev.* **1967**, *67*, 107-152.
[749]Campbell; Monagle; Foldi *J. Am. Chem. Soc.* **1962**, *84*, 3673.
[750]Monagle; Campbell; McShane *J. Am. Chem. Soc.* **1962**, *84*, 4288.

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 71,[751] precisely what is predicted by this mechanism. Certain other catalysts are also effective.[752]

OS V, 501.

6-59   The Conversion of Carboxylic Acid Salts to Nitriles
Nitrilo-de-oxido,oxo-tersubstitution

$$RCOO^- + BrCN \xrightarrow{250-300^\circ C} RCN + CO_2$$
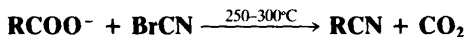
Salts of aliphatic or aromatic carboxylic acids can be converted to the corresponding nitriles by heating with BrCN or ClCN. Despite appearances, this is not a substitution reaction. When $R^{14}COO^-$ was used, the label appeared in the nitrile, not in the CO_2,[753] and optical activity in R was retained.[754] The acyl isocyanate $RCON=C=O$ could be isolated from the reaction mixture; hence the following mechanism was proposed:[753]
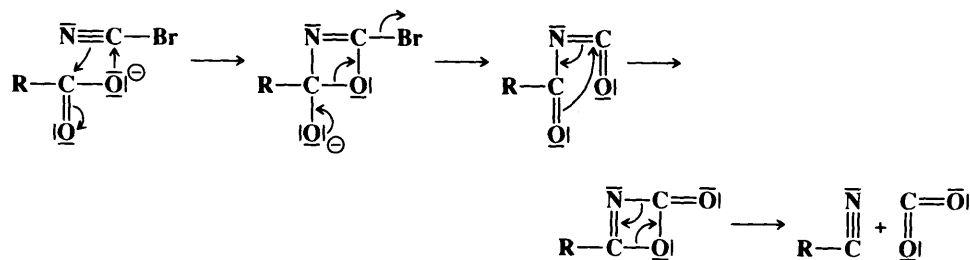
6-60   The Trimerization of Nitriles
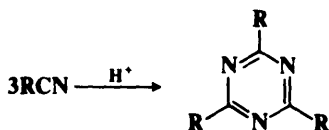
Nitriles can be trimerized with various acids, bases, or other catalysts to give triazines.[755] HCl is most often used, and then the reaction is similar to reaction 6-57. However, most nitriles with an α hydrogen do not give the reaction.

OS III, 71.

C.   Carbon Adding to the Carbon.   The reactions in this group (6-61 to 6-64) are cycloadditions.

[751]Monagle; Mengenhauser J. Org. Chem. 1966, 31, 2321.
[752]Monagle J. Org. Chem. 1962, 27, 3851; Appleman; DeCarlo J. Org. Chem. 1967, 32, 1505; Ulrich; Tucker; Sayigh J. Org. Chem. 1967, 32, 1360, Tetrahedron Lett. 1967, 1731; Ostrogovich; Kerek; Buzás; Doca Tetrahedron 1969, 25, 1875.
[753]Douglas; Eccles; Almond Can. J. Chem. 1953, 31, 1127; Douglas; Burditt Can. J. Chem. 1958, 36, 1256.
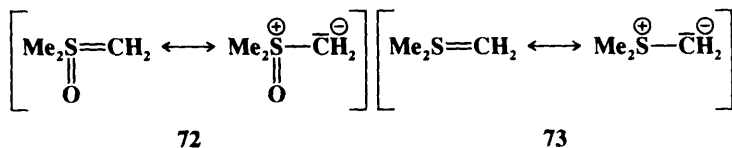[754]Barltrop; Day; Bigley J. Chem. Soc. 1961, 3185.
[755]For a review, see Martin; Bauer; Pankratov Russ. Chem. Rev. 1978, 47, 975-990. For a review with respect to cyanamides RNH—CN, see Pankratov; Chesnokova Russ. Chem. Rev. 1989, 58, 879-890.

6-61   The Formation of Epoxides from Aldehydes and Ketones
(1 + 2)*OC,CC-cyclo*-Methylene-addition

$$-\overset{|}{\underset{\underset{O}{\|}}{C}} + Me_2\overset{\oplus}{S}-\overset{\ominus}{\underset{\underset{O}{\|}}{CH_2}} \longrightarrow -\overset{|}{\underset{\underset{CH_2}{\diagdown\diagup}}{C}}-O$$

72
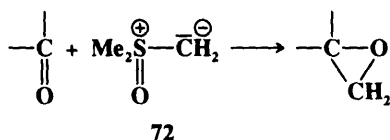
Aldehydes and ketones can be converted to epoxides[756] in good yields with the sulfur ylides dimethyloxosulfonium methylide (**72**) and dimethylsulfonium methylide (**73**).[757] For most purposes, **72** is the reagent of choice, because **73** is much less stable and ordinarily must be

$$\left[Me_2\underset{\underset{O}{\|}}{S}{=}CH_2 \longleftrightarrow Me_2\overset{\oplus}{\underset{\underset{O}{\|}}{S}}-\overset{\ominus}{CH_2} \right] \quad \left[Me_2S{=}CH_2 \longleftrightarrow Me_2\overset{\oplus}{S}-\overset{\ominus}{CH_2} \right]$$

72   **73**

used as soon as it is formed, while **72** can be stored several days at room temperature. However, when diastereomeric epoxides can be formed, **73** usually attacks from the more hindered and **72** from the less-hindered side. Thus, 4-*t*-butylcyclohexanone, treated with **72** gave exclusively **75** while **73** gave mostly **74**.[758] Another difference in behavior between the

74   **75**

New bond is axial   New bond is equatorial
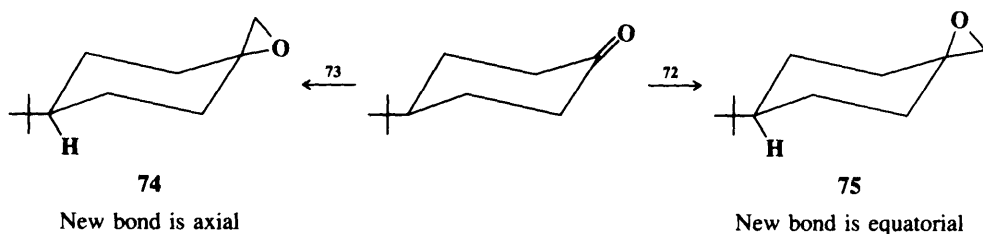
two reagents is that with α,β-unsaturated ketones, **72** gives only cyclopropanes (reaction 5-50), while **73** gives oxirane formation. Other sulfur ylides have been used in an analogous manner, to transfer CHR or CR₂. Among these are $Me_2S{=}CHCOO^-$,[759] $Me_2S{=}CHPh$,[760] $Me_2S{=}CH$—vinyl,[761] and **111** on p. 872,[762] which transfer $CHCOO^-$, CHPh, CH—vinyl, and CPh₂, respectively. Nitrogen-containing sulfur ylides, such as **112** on p. 872 and $Ph(Me_2N)SO{=}CH_2$, as well as carbanions like **114** on p. 872 and sulfonium salts such as trimethylsulfonium bromide Me_3S^+ Br^- (with a phase-transfer catalyst)[763] have also been

[756]For reviews, see Block *Reactions of Organosulfur Compounds*; Academic Press: New York, 1978, pp. 101-105; Berti *Top. Stereochem.* **1973**, 7, 93-251, pp. 218-232. For a list of reagents, with references, see Ref. 64, pp. 468-470.

[757]For reviews, see House, Ref. 180, pp. 709-733; Durst *Adv. Org. Chem.* **1969**, 6, 285-388, pp. 321-330; Johnson, Ref. 638, pp. 328-351. For a monograph on sulfur ylides, see Trost; Melvin *Sulfur Ylides*; Academic Press: New York, 1975.

[758]Corey; Chaykovsky *J. Am. Chem. Soc.* **1965**, 87, 1353.

[759]Adams; Hoffman; Trost *J. Org. Chem.* **1970**, 35, 1600.

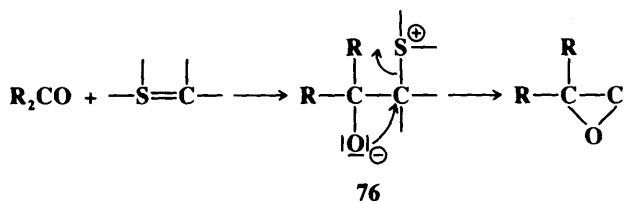[760]Yoshimine; Hatch *J. Am. Chem. Soc.* **1967**, 89, 5831.

[761]Braun; Huber; Kresze *Tetrahedron Lett.* **1973**, 4033.

[762]Corey; Jautelat; Oppolzer *Tetrahedron Lett.* **1967**, 2325.

[763]Borredon; Delmas; Gaset *Tetrahedron Lett.* **1982**, 23, 5283, *Tetrahedron* **1987**, 43, 3945, **1988**, 44, 1073; Mosset; Grée *Synth. Commun.* **1985**, 15, 749; Bouda; Borredon; Delmas; Gaset *Synth. Commun.* **1987**, 17, 503.

used.[764] High yields have been achieved by the use of sulfonium ylides anchored to insoluble polymers under phase transfer conditions.[765]
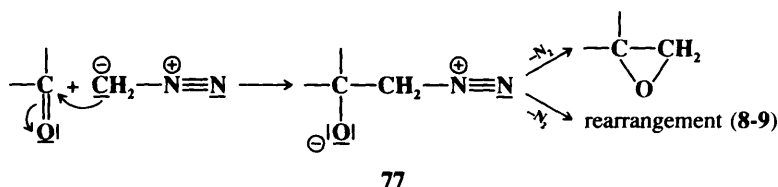
The generally accepted mechanism for the reaction between sulfur ylides and aldehydes or ketone is

$$R_2CO \; + \; -\overset{|}{\underset{|}{S}}=\overset{|}{\underset{|}{C}}- \longrightarrow R-\overset{R}{\underset{\underset{|\underset{\ominus}{\overset{..}{\underset{..}{O}}|}}{|}}{\overset{S^{\oplus}}{\underset{|}{C}}}-\overset{|}{\underset{|}{C}}- \longrightarrow R-\overset{R}{\underset{|}{\underset{O}{C}}}\overset{}{\diagdown}\overset{}{C}$$

76

which is similar to that of the reaction of sulfur ylides with C=C double bonds (**5-50**).[766] 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.[767]

Phosphorus ylides do not give this reaction, but give **6-47** instead.

Aldehydes and ketones can also be converted to epoxides by treatment with a diazoalkane,[768] 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 **8-9**). The reaction can be carried out with many aldehydes, ketones, and quinones. A mechanism that accounts for both products is

$$-\overset{|}{\underset{\underset{O|}{\overset{||}{C}}}{C}} + \; \overset{\ominus}{C}H_2-\overset{\oplus}{N}\equiv\underline{N} \longrightarrow -\overset{|}{\underset{\ominus\underline{O}|}{C}}-CH_2-\overset{\oplus}{N}\equiv\underline{N} \quad \begin{array}{l} \nearrow \; -\overset{|}{\underset{O}{C}}-CH_2 \\ \\ \searrow \; \text{rearrangement (8-9)} \end{array}$$

77

Compound **77** or nitrogen-containing derivatives of it have sometimes been isolated.

Dihalocarbenes and carbenoids, which readily add to C=C bonds (**5-50**), do not generally add to the C=O bonds of ordinary aldehydes and ketones.[769]

Symmetrical epoxides can be prepared by treatment of aromatic aldehydes with hexamethylphosphorus triamide.[770]

$$2ArCHO \; + \; (Me_2N)_3P \longrightarrow \overset{Ar\diagdown\diagup Ar}{\underset{O}{\bigtriangledown}}$$
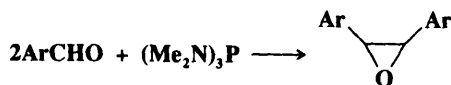
See also **6-45**.
OS **V**, 358, 755.

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[764]Johnson; Haake; Schroeck *J. Am. Chem. Soc.* **1970**, *92*, 6594; Johnson; Janiga *J. Am. Chem. Soc.* **1973**, *95*, 7692; Johnson *Acc. Chem. Res.* **1973**, *6*, 341-347; Tamura; Matsushima; Ikeda; Sumoto *Synthesis* **1976**, 35.

[765]Farrall; Furst; Fréchet *Tetrahedron Lett.* **1979**, 203.

[766]See, for example, Townsend; Sharpless *Tetrahedron Lett.* **1972**, 3313; Johnson; Schroeck; Shanklin *J. Am. Chem. Soc.* **1973**, *95*, 7424.

[767]Johnson et al., Ref. 766.

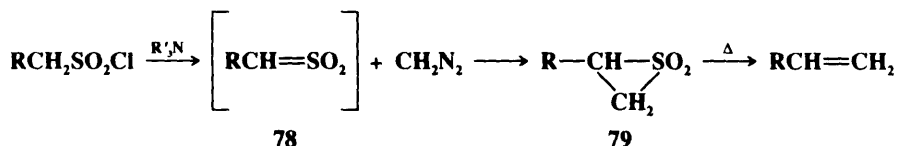[768]For a review, see Gutsche, *Org. React.* **1954**, *8*, 364-429.

[769]For exceptions, see Greuter; Winkler; Belluš *Helv. Chim. Acta* **1979**, *62*, 1275; Sadhu; Matteson *Tetrahedron Lett.* **1986**, *27*, 795; Araki; Butsugan *J. Chem. Soc., Chem. Commun.* **1989**, 1286.

[770]Mark *J. Am. Chem. Soc.* **1963**, *85*, 1884; *Org. Synth. V*, 358; Newman; Blum *J. Am. Chem. Soc.* **1964**, *86*, 5598.

6-62   The Formation of Episulfides and Episulfones[771]

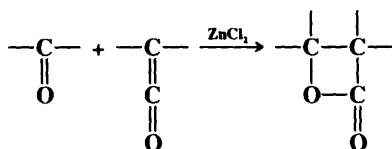$$2R_2CN_2 + S \longrightarrow R_2C\underset{S}{\overset{}{\diagdown\diagup}}CR_2$$
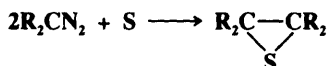
Diazoalkanes, treated with sulfur, give episulfides.[772] It is likely that $R_2C{=}S$ is an intermediate, which is attacked by another molecule of diazoalkane, in a process similar to that shown in **6-61**. Thioketones *do* react with diazoalkanes to give episulfides.[773] Thioketones have also been converted to episulfides with sulfur ylides.[758]

Alkanesulfonyl chlorides, when treated with diazomethane in the presence of a base (usually a tertiary amine), give episulfones (**79**).[774] The base removes HCl from the sulfonyl

$$RCH_2SO_2Cl \xrightarrow{R'_3N} \left[RCH{=}SO_2 \right] + CH_2N_2 \longrightarrow R{-}\underset{CH_2}{\overset{}{\underset{\diagdown\diagup}{CH{-}SO_2}}} \xrightarrow{\Delta} RCH{=}CH_2$$

$$\qquad\qquad\qquad\quad \textbf{78} \qquad\qquad\qquad\qquad\qquad\qquad \textbf{79}$$

halide to produce the highly reactive sulfene (**78**) (**7-14**), which then adds CH_2. The episulfone can then be heated to give off SO_2 (**7-25**), making the entire process a method for achieving the conversion $RCH_2SO_2Cl \rightarrow RCH{=}CH_2$.[775]

OS **V**, 231, 877.

6-63   The Formation of β-Lactones and Oxetanes
         (2 + 2)*OC,CC-cyclo*-[oxoethylene]-1/2/addition

$$\overset{|}{\underset{O}{\overset{\|}{C}}} + \underset{\underset{O}{\overset{\|}{C}}}{\overset{|}{\underset{\overset{\|}{O}}{C}}} \xrightarrow{ZnCl_2} \overset{|}{\underset{\underset{O}{\overset{\|}{O{-}C}}}{C}}{-}\overset{|}{C}{-}$$

Aldehydes, ketones, and quinones react with ketenes to give β-lactones, diphenylketene being used most often.[776] 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 in 98% enantiomeric excess.[777] Other di- and trihalo aldehydes and ketones also give the reaction enantioselectively, with somewhat lower ee values.[778] Ketene adds to another molecule of itself:

$$2CH_2{=}C{=}O \longrightarrow \underset{H_2C{-}C{=}O}{\overset{CH_2{=}C{-}O}{|\qquad\ \ |}} + \underset{HC{-}C{=}O}{\overset{CH_3{-}C{-}O}{\|\qquad\ \ |}}$$
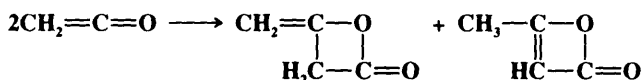
[771]For a review, see Muller; Hamer *1,2-Cycloaddition Reactions*; Wiley: New York, 1967, pp. 57-86.
[772]Schönberg; Frese *Chem. Ber.* **1962**, 95, 2810.
[773]For example, see Beiner; Lecadet; Paquer; Thuillier *Bull. Soc. Chim. Fr.* **1973**, 1983.
[774]Opitz; Fischer *Angew. Chem. Int. Ed. Engl.* **1965**, 4, 70 [*Angew. Chem.* 77, 41].
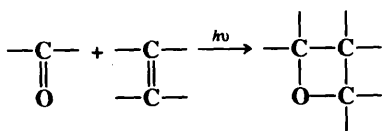[775]For a review of this process, see Fischer *Synthesis* **1970**, 393-404.
[776]For reviews, see Ref. 771, pp. 139-168; Ulrich *Cycloaddition Reactions of Heterocumulenes*; Academic Press: New York, 1967, pp. 39-45, 64-74.
[777]Wynberg; Staring *J. Am. Chem. Soc.* **1982**, 104, 166, *J. Chem. Soc., Chem. Commun.* **1984**, 1181.
[778]Wynberg; Staring *J. Org. Chem.* **1985**, 50, 1977.

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 these cases the major dimerization product is not the β-lactone, but a cyclobutenone (see **5-49**). However, the proportion of ketene that dimerizes to β-lactone can be increased by the addition of catalysts such as triethylamine or triethyl phosphite.[779] Ketene acetals $R_2C\!=\!C(OR')_2$ add to aldehydes and ketones in the presence of $ZnCl_2$ to give the corresponding oxetanes.[780]

Ordinary aldehydes and ketones can add to olefins, under the influence of uv light, to give oxetanes. This reaction, called the *Paterno–Büchi reaction*,[781] is similar to the photochemical dimerization of olefins discussed at **5-49**. In general, the mechanism consists of the

$$-\underset{\underset{O}{\|}}{C}- \;+\; -\underset{\underset{-C-}{\|}}{C}- \;\xrightarrow{h\upsilon}\; -\underset{\underset{O-C-}{|}}{\overset{|}{C}}-\overset{|}{\underset{|}{C}}-$$

addition of an excited state of the carbonyl compound to the ground state of the olefin. Both singlet (S_1)[782] and n,π^* triplet[783] states have been shown to add to olefins to give

oxetanes. A diradical intermediate[784] $\overset{\bullet}{O}-\overset{|}{C}-\overset{|}{C}-\overset{\bullet}{C}-$ has been detected spectrally.[785] Yields

in the Paterno-Büchi reaction are variable, ranging from very low to fairly high (90%). 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. 241). In most cases quinones react normally with alkenes, giving oxetane products, but other α,β-unsaturated ketones usually give preferential cyclobutane formation (**5-49**). Aldehydes and ketones also add photochemically to allenes to give the corresponding alkylideneoxetanes and dioxaspiro compounds:[786]

$$C\!=\!O \;+\; C\!=\!C\!=\!C \;\xrightarrow{h\nu}\; \square\!\!<_O + \; \text{(diagram)} + \text{(diagram)}$$
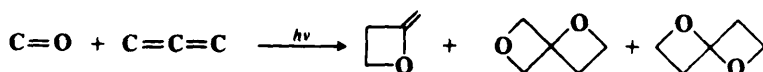
OS **III**, 508; **V**, 456. For the reverse reaction, see OS **V**, 679.

[779]Farnum; Johnson; Hess; Marshall; Webster *J. Am. Chem. Soc.* **1965**, *87*, 5191; Elam; *J. Org. Chem.* **1967**, *32*, 215.
[780]Aben; Hofstraat; Scheeren *Recl. Trav. Chim. Pays-Bas* **1981**, *100*, 355.
[781]For reviews, see Ninomiya; Naito *Photochemical Synthesis*; Academic Press: New York, 1989, pp. 138-152; Carless, in Coyle *Photochemistry in Organic Synthesis*; Royal Society of Chemistry: London, 1986, pp. 95-117; Carless, in Horspool *Synthetic Organic Photochemistry*; Plenum: New York, 1984, pp. 425-487; Jones *Org. Photochem.* **1981**, *5*, 1-122; Arnold *Adv. Photochem.* **1968**, *6*, 301-423; Chapman; Lenz *Org. Photochem.* **1967**, *1*, 283-321, pp. 283-294; Ref. 771, pp. 111-139.
[782]See, for example, Turro *Pure Appl. Chem.* **1971**, *27*, 679-705; Yang; Kimura; Eisenhardt *J. Am. Chem. Soc.* **1973**, *95*, 5058; Singer; Davis; Muralidharan *J. Am. Chem. Soc.* **1969**, *91*, 897; Barltrop; Carless *J. Am. Chem. Soc.* **1972**, *94*, 1951, 8761.
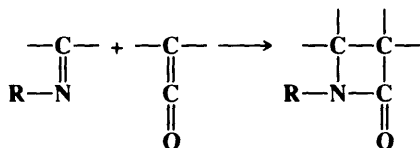[783]Arnold; Hinman; Glick *Tetrahedron Lett.* **1964**, 1425; Yang; Nussim; Jorgenson; Murov *Tetrahedron Lett.* **1964**, 3657.
[784]For other evidence for these diradical intermediates, see references cited in Griesbeck; Stadtmüller *J. Am. Chem. Soc.* **1990**, *112*, 1281.
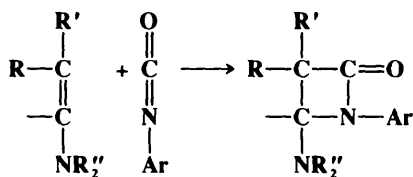[785]Freilich; Peters *J. Am. Chem. Soc.* **1981**, *103*, 6255, **1985**, *107*, 3819.
[786]Arnold; Glick *Chem. Commun.* **1966**, 813; Gotthardt; Steinmetz; Hammond *Chem. Commun.* **1967**, 480, *J. Org. Chem.* **1968**, *33*, 2774. For a review of the formation of heterocycles by cycloadditions of allenes, see Schuster; Coppola *Allenes in Organic Synthesis*; Wiley: New York, 1984, pp. 317-326.

6-64   The Formation of β-Lactams
(2 + 2)NC,CC-cyclo-[oxoethylene]-1/2/addition

$$-\overset{\|}{\underset{R-N}{C}}- \;+\; -\overset{\|}{\underset{\overset{\|}{O}}{\underset{C}{C}}}- \;\longrightarrow\; -\overset{|}{\underset{R-N-C}{C}}-\overset{|}{\underset{\overset{\|}{O}}{C}}-$$

Ketenes add to imines to give β-lactams.[787] The reaction is generally carried out with ketenes of the form $R_2C=C=O$. It has not been successfully applied to $RCH=C=O$, except when these are generated is situ by decomposition of a diazo ketone (the Wolff rearrangement, **8-8**) 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[788] $R_2C=C=S$ give β-thiolactams.[789] Imines also form β-lactams when treated with (1) zinc (or another metal) and an α-bromo ester (Reformatsky conditions—**6-30**),[790] or (2) the chromium carbene complexes $(CO)_5Cr=C(Me)OMe$.[791] The latter method has been used to prepare optically active β-lactams.[792] Ketenes have also been added to certain hydrazones (e.g., $PhCH=NNMe_2$) to give N-amino β-lactams.[793]

Like the similar cycloaddition of ketenes to olefins (**5-49**), most of these reactions probably take place by the diionic mechanism c (p. 857).[794] β-Lactams have also been prepared in the opposite manner: by the addition of enamines to isocyanates:[795]

$$R-\overset{R'}{\underset{-\overset{|}{\underset{NR_2''}{C}}}{\overset{|}{C}}} \;+\; \overset{O}{\underset{\overset{\|}{\underset{Ar}{N}}}{\overset{\|}{C}}} \;\longrightarrow\; R-\overset{R'}{\underset{-\overset{|}{\underset{NR_2''}{C}}-N-Ar}{\overset{|}{C}-C=O}}$$

The reactive compound chlorosulfonyl isocyanate[796] $ClSO_2NCO$ forms β-lactams even with unactivated alkenes,[797] as well as with allenes,[798] conjugated dienes,[799] and cyclopropenes.[800] OS V, 673; **65**, 135, 140.

[787]For a list of references, see Ref. 64, pp. 961-962. For reviews of the formation of β-lactams, see Brown *Heterocycles* **1989**, *29*, 2225-2294; Isaacs *Chem. Soc. Rev.* **1976**, *5*, 181-202; Mukerjee; Srivastava *Synthesis* **1973**, 327-346; Ref. 771, pp. 173-206; Ulrich, Ref. 776, pp. 75-83, 135-152; Anselme, in Patai *The Chemistry of the Carbon–Nitrogen Double Bond*, Ref. 40, pp. 305-309. For a review of cycloaddition reactions of imines, see Sandhu; Sain *Heterocycles* **1987**, *26*, 777-818.

[788]For a review of thioketenes, see Schaumann *Tetrahedron* **1988**, *44*, 1827-1871.

[789]Schaumann *Chem. Ber.* **1976**, *109*, 906.

[790]For a review, see Hart; Ha *Chem. Rev.* **1989**, *89*, 1447-1465.

[791]Hegedus; McGuire; Schultze; Yijun; Anderson *J. Am. Chem. Soc.* **1984**, *106*, 2680; Hegedus; McGuire; Schultze *Org. Synth.* **65**, 140.

[792]Hegedus; Imwinkelried; Alarid-Sargent; Dvorak; Satoh *J. Am. Chem. Soc.* **1990**, *112*, 1109.

[793]Sharma; Pandhi *J. Org. Chem.* **1990**, *55*, 2196.

[794]See Moore; Hernandez; Chambers *J. Am. Chem. Soc.* **1978**, *100*, 2245; Pacansky; Chang; Brown; Schwarz *J. Org. Chem.* **1982**, *47*, 2233; Brady; Shieh *J. Org. Chem.* **1983**, *48*, 2499.

[795]For example, see Perelman; Mizsak *J. Am. Chem. Soc.* **1962**, *84*, 4988; Opitz; Koch *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 152 [*Angew. Chem.* **75**, 167].

[796]For reviews of this compound, see Kamal; Sattur *Heterocycles* **1987**, *26*, 1051-1076; Szabo *Aldrichimica Acta* **1977**, *10*, 23-29; Rasmussen; Hassner *Chem. Rev.* **1976**, *76*, 389-408; Graf *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 172-182 [*Angew. Chem.* **80**, 179-189].

[797]Graf *Liebigs Ann. Chem.* **1963**, *661*, 111; Bestian *Pure Appl. Chem.* **1971**, *27*, 611-634. See also Barrett; Betts; Fenwick *J. Org. Chem.* **1985**, *50*, 169.
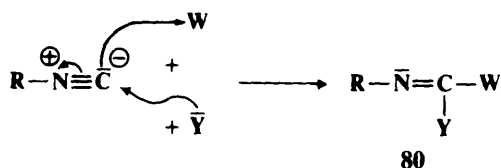
[798]Moriconi; Kelly *J. Am. Chem. Soc.* **1966**, *88*, 3657. *J. Org. Chem.* **1968**, *33*, 3036. See also Martin; Carter; Chitwood *J. Org. Chem.* **1971**, *36*, 2225.

[799]Moriconi; Meyer *J. Org. Chem.* **1971**, *36*, 2841; Malpass; Tweddle *J. Chem. Soc. Perkin Trans. 1* **1977**, 874.

[800]Moriconi; Kelly; Salomone *J. Org. Chem.* **1968**, *33*, 3448.
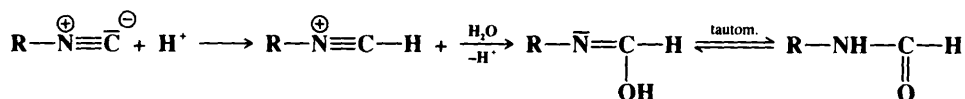
Addition to Isocyanides[801]

Addition to R—N≡C (with charges ⊕ on N and ⊖ on 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 add to the nitrogen, which, however, loses its positive charge by obtaining as an unshared pair one of the triple-bond pairs of electrons:

$$R-\overset{\oplus}{N}\equiv\overset{\ominus}{C} \quad \overset{W}{\underset{+\ \bar{Y}}{\longrightarrow}} \quad R-\bar{N}=C-W \atop \qquad\qquad | \atop \qquad\qquad Y$$

80

In most of the reactions considered below, **80** undergoes a further reaction, so the product

is of the form $R-\bar{N}H-\overset{|}{\underset{|}{C}}-$. See also **9-30**.

6-65   The Addition of Water to Isocyanides
           1/N,2/C-Dihydro-2/C-oxo-biaddition

$$R-\overset{\oplus}{N}\equiv\overset{\ominus}{C} + H_2O \xrightarrow{H^+} R-\bar{N}H-\underset{\underset{O}{\parallel}}{C}-H$$
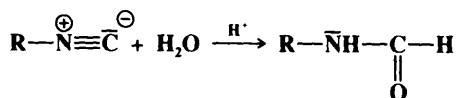
Formamides can be prepared by the acid-catalyzed addition of water to isocyanides. The mechanism is probably[802]

$$R-\overset{\oplus}{N}\equiv\overset{\ominus}{C} + H^+ \longrightarrow R-\overset{\oplus}{N}\equiv C-H + \xrightarrow[-H^+]{H_2O} R-\bar{N}=\underset{\underset{OH}{|}}{C}-H \xrightleftharpoons{tautom.} R-NH-\underset{\underset{O}{\parallel}}{C}-H$$

The reaction has also been carried out under alkaline conditions, with OH⁻ in aqueous dioxane.[803] The mechanism here involves nucleophilic attack by OH⁻ at the carbon atom.
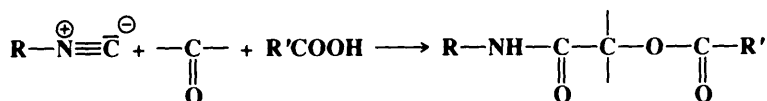
6-66   The Reduction of Isocyanides
           1/N,2,2,2/C-Tetrahydro-biaddition

$$R-\overset{\oplus}{N}\equiv\overset{\ominus}{C} + LiAlH_4 \longrightarrow R-NH-CH_3$$

Isocyanides have been reduced to N-methylamines with lithium aluminum hydride as well as with other reducing agents.

[801]For a monograph, see Ugi *Isonitrile Chemistry*; Academic Press: New York, 1971. For reviews, see Walborsky; Periasamy, in Patai; Rappoport, Ref. 694, pt. 2, pp. 835-887; Hoffmann; Marquarding; Kliimann; Ugi, in Rappoport, Ref. 334, pp. 853-883.
[802]Drenth; *Recl. Trav. Chim. Pays-Bas* **1962**, *81*, 319; Lim; Stein *Can. J. Chem.* **1971**, *49*, 2455.
[803]Cunningham; Buist; Arkle *J. Chem. Soc., Perkin Trans. 2* **1991**, 589.

6-67 The Passerini and Ugi Reactions[804]
1/ N-Hydro-2/ C-(α-acyloxyalkyl),2/ C-oxo-biaddition

$$R—\overset{\oplus}{N}{\equiv}\overset{\ominus}{C} + \underset{O}{\overset{|}{—\overset{||}{C}—}} + R'COOH \longrightarrow R—NH—\overset{||}{\underset{O}{C}}—\overset{|}{\underset{|}{C}}—O—\overset{||}{\underset{O}{C}}—R'$$

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*. The following mechanism has been postulated:
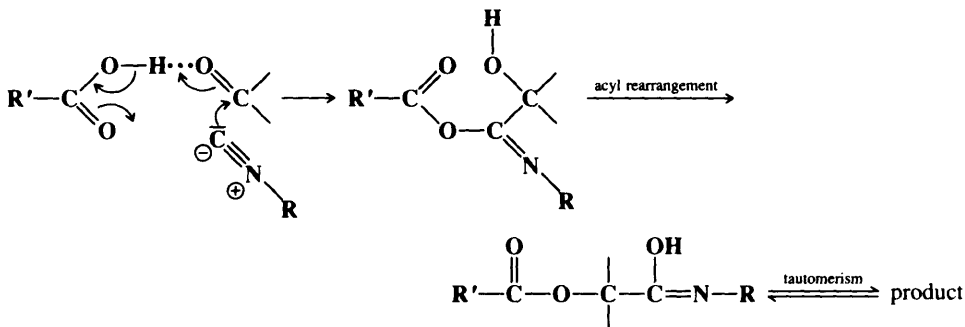
If ammonia or an amine is also added to the mixture (in which case the reaction is known as the *Ugi reaction*, or the *Ugi four-component condensation*, abbreviated 4 CC),

the product is the corresponding bisamide $R'—\overset{||}{\underset{O}{C}}—NH—\overset{|}{\underset{|}{C}}—\overset{||}{\underset{O}{C}}—NH—R$ (from NH_3) or

$R'—\overset{||}{\underset{O}{C}}—NR''—\overset{|}{\underset{|}{C}}—\overset{||}{\underset{O}{C}}—NH—R$ (from a primary amine $R''NH_2$). 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 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.[805]

6-68 The Addition of O- and N-Halides to Isocyanides

$$R—\overset{\oplus}{N}{\equiv}\overset{\ominus}{C} + t\text{-BuOCl} \xrightarrow{ZnCl_2} R—\overset{—}{N}{=}\underset{Cl}{\overset{|}{C}}—O—t\text{-Bu} \xrightarrow{H_2O} R—NH—\overset{||}{\underset{O}{C}}—O—t\text{-Bu}$$
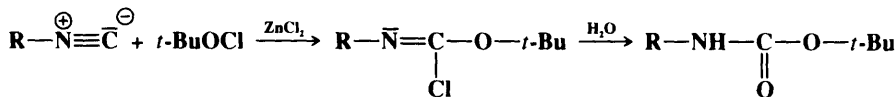
1/ N-Hydro-2/ C-butoxy,2/ C-oxo-biaddition

$$R—\overset{\oplus}{N}{\equiv}\overset{\ominus}{C} + MeCONHBr \longrightarrow R—\overset{—}{N}{=}\underset{Br}{\overset{|}{C}}—NHCOMe \xrightarrow{H_2O} R—NH—\overset{||}{\underset{O}{C}}—NHCOMe$$
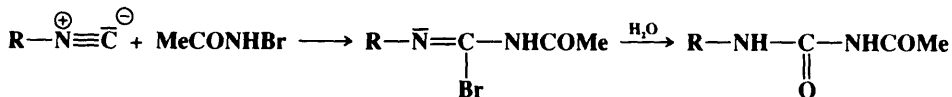
1/ N-Hydro-2/ C-acylamino,2/C-oxo-biaddition

[804]For reviews, see Ugi *Angew. Chem. Int. Ed. Engl.* **1982**, 21, 810-819 [*Angew. Chem. 94*, 826-836]; Marquarding; Gokel; Hoffmann; Ugi, in Ugi, Ref. 801, pp. 133-143, Gokel; Lüdke; Ugi, in Ugi, Ref. 801, pp. 145-199, 252-254.
[805]For reviews, see Ugi, in Gross; Meienhofer *The Peptides*, vol. 2; Academic Press: New York, 1980, pp. 365-381, *Intra-Sci. Chem. Rep.* **1971**, 5, 229-261, *Rec. Chem. Prog.* **1969**, 30, 289-311; Gokel; Hoffmann; Kleimann; Klusacek; Lüdke; Marquarding; Ugi, in Ugi, Ref. 801, pp. 201-215. See also Kunz; Pfrengle *J. Am. Chem. Soc.* **1988**, 110, 651.

Alkyl hypochlorites and N-halo amides add to isocyanides to give, after hydrolysis, carbamates and N-acylureas (ureides), respectively.[806]

6-69   The Formation of Metalated Aldimines
   1/1/Lithio-alkyl-addition

$$R-\overset{\oplus}{N}\equiv\overset{\ominus}{C} + R'Li \longrightarrow R-N=\underset{\underset{Li}{|}}{C}-R'$$
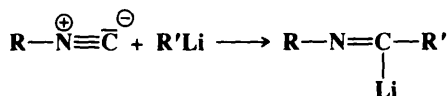
Isocyanides that do not contain an α hydrogen react with alkyllithium compounds,[807] as well as with Grignard reagents, to give lithium (or magnesium) aldimines.[808] These metalated aldimines are versatile nucleophiles and react with various substrates as follows (see also **8-25**):
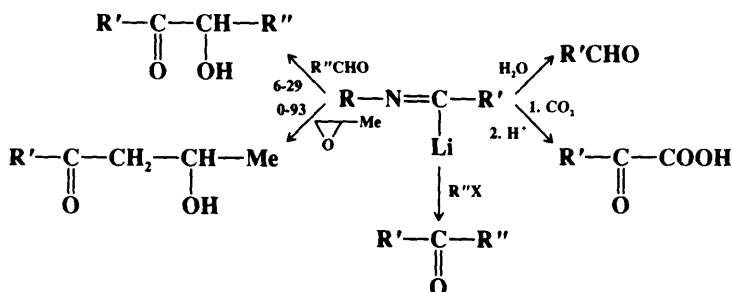
The reaction therefore constitutes a method for converting an organometallic compound R'M to an aldehyde R'CHO (see also **2-32**), an α-keto acid,[809] a ketone R'COR (see also **2-32**), an α-hydroxy ketone, or a β-hydroxy ketone. In each case the C=N bond is hydrolyzed to a C=O bond (**6-2**).

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 → PhCH=NR.[810]

OS **VI**, 751.

[806]Okano; Ito; Shono; Oda *Bull Chem. Soc. Jpn.* **1963**, *36*, 1314. See also Yamada; Wada; Tanimoto; Okano *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2480.

[807]For a review of other metallation reactions of isocyanides, see Ito; Murakami *Synlett* **1990**, 245-250.

[808]Niznik; Morrison; Walborsky *J. Org. Chem.* **1974**, *39*, 600; Marks; Walborsky *J. Org. Chem.* **1981**, *46*, 5405, **1982**, *47*, 52. See also Walborsky; Ronman *J. Org. Chem.* **1978**, *43*, 731. For the formation of zinc aldimines, see Murakami; Ito; Ito *J. Org. Chem.* **1988**, *53*, 4158.

[809]For a review of the synthesis and properties of α-keto acids, see Cooper; Ginos; Meister *Chem. Rev.* **1983**, *83*, 321-358.

[810]Jones; Foster; Putinas *J. Am. Chem. Soc.* **1987**, *109*, 5047.