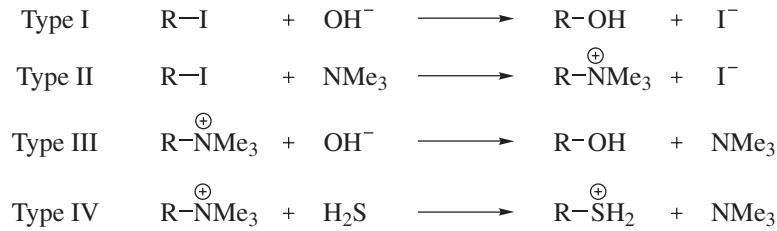
CHAPTER 10

Aliphatic Substitution: Nucleophilic and Organometallic

In nucleophilic aliphatic substitution the attacking (electron donating) reagent (the nucleophile) brings an electron pair to the substrate, using this pair to form the new bond, and the leaving group (the nucleofuge) comes away with an electron pair:

This equation says nothing about charges. Nuclephile Y may be neutral or negatively charged; RX may be neutral or positively charged; so there are four charge types, examples of which are



In all cases, Y must have an unshared pair of electrons, so that all nucleophiles are Lewis bases. When Y is the solvent, the reaction is called *solvolysis*. Nucleophilic substitution at an aromatic carbon is considered in Chapter 13.

Nucleophilic substitution at an alkyl carbon is said to *alkylate* the nucleophile. For example, the above reaction between RI and NMe_3 is an *alkylation* of trimethylamine. Similarly, nucleophilic substitution at an acyl carbon is an *acylation* of the nucleophile.

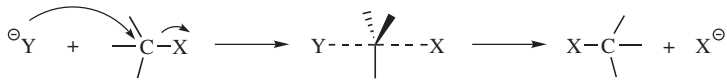
March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Sixth Edition, by Michael B. Smith and Jerry March

MECHANISMS

Several distinct mechanisms are possible for aliphatic nucleophilic substitution reactions, depending on the substrate, nucleophile, leaving group, and reaction conditions. In all of them, however, the attacking reagent carries the electron pair with it, so that the similarities are greater than the differences. Mechanisms that occur at a saturated carbon atom are considered first.[1] By far the most common are the S_N1 and S_N2 mechanisms.

The S_N2 Mechanism

The designation S_N2 stands for *substitution nucleophilic bimolecular*. The IUPAC designation (p. 420) is A_ND_N. In this mechanism, there is *backside attack*:[2] the nucleophile approaches the substrate from a position 180° away from the leaving group. The reaction is a one-step process with no intermediate (see, however, pp. 428–431 and 440). The C—Y bond is formed as the C—X bond is broken to generate transition state **1**.



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The energy necessary to break the C—X bond is supplied by simultaneous formation of the C—Y bond. The position of the atoms at the top of the curve of free energy of activation is represented as transition state **1**. Of course, the reaction does not stop here since this is the transition state. The group X must leave as the group Y comes in, because at no time can the carbon have more than eight electrons in its outer shell. When the transition state is reached, the central carbon atom has gone from its initial sp^3 hybridization to an sp^2 state with an approximately perpendicular *p* orbital. One lobe of this *p* orbital overlaps with the nucleophile and the other with the leaving group. This is why a frontside S_N2 mechanism has never been observed. In a hypothetical frontside transition state, both the nucleophile and the leaving group would have to overlap with the same lobe of the *p* orbital. The backside mechanism involves the maximum amount of overlap throughout the course of the reaction. During the transition state the three nonreacting substituents and the central carbon are approximately coplanar. They will be exactly coplanar if both the entering and the leaving group are the same.

[1]For a monograph on this subject, see Hartshorn, S.R. *Aliphatic Nucleophilic Substitution*, Cambridge University Press, Cambridge, ***1973***. For reviews, see Katritzky, A.R.; Brycki, B.E. *Chem. Soc. Rev.* ***1990***, *19*, 83; Richard, J.P. *Adv. Carbocation Chem.* ***1989***, *1*, 121; de la Mare, P.B.D.; Swedlund, B.E., in Patai, S. *The Chemistry of the Carbon–Halogen Bond*, pt. 1, Wiley, NY, ***1973***, pp. 409–490. Streitwieser, A. *Solvolytic Displacement Reactions*, McGraw-Hill, NY, ***1962***.

[2]See Sun, L.; Hase, W.L.; Song, K. *J. Am. Chem. Soc.* ***2001***, *123*, 5753.

There is a large amount of evidence for the S_N2 mechanism. First, there is the kinetic evidence. Since both the nucleophile and the substrate are involved in the rate-determining step (the only step, in this case), the reaction should be first order in each component, second order overall, and satisfy the rate expression, Eq. (10.1).

$$\text{Rate} = k[\text{RX}][\text{Y}] \tag{10.1}$$

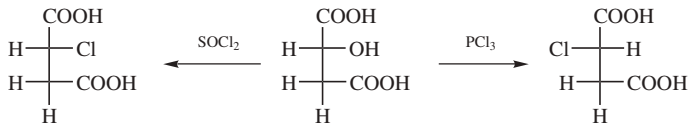
This rate law has been found to apply. Note that the 2 in S_N2 stands for bimolecular. It must be remembered that this is not always the same as second order (see p. 315). If a large excess of nucleophile is present (for example, if it is the solvent) the mechanism may still be bimolecular, although the experimentally determined kinetics will be first order, Eq. (10.2).

$$\text{Rate} = k[\text{RX}] \tag{10.2}$$

As previously mentioned (p. 318), such kinetics are called *pseudo-first order.*

The kinetic evidence is a necessary but not a sufficient condition; we will meet other mechanisms that are also consistent with these data. Much more convincing evidence is obtained from the fact that the mechanism predicts inversion of configuration when substitution occurs at a chiral carbon and this has been observed many times. This inversion of configuration (see p. 158) that proceeds through transition state **1** is called the *Walden inversion* and was observed long before the S_N2 mechanism was formulated by Hughes and Ingold.[3]

At this point it is desirable for us to see just how it was originally proved that a given substitution reaction proceeds with inversion of configuration, even before the mechanism was known. Walden presented a number of examples[4] in which inversion *must* have taken place. For example, (+)-malic acid (**2**) could be converted to (+)-chlorosuccinic acid by thionyl chloride and to (−)-chlorosuccinic acid by phosphorus pentachloride.



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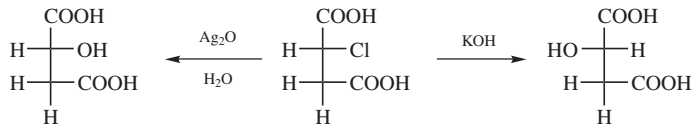
[3]Cowdrey, W.A.; Hughes, E.D.; Ingold, C.K.; Masterman, S.; Scott, A.D. *J. Chem. Soc.* ***1937***, 1252. The idea that the addition of one group and removal of the other are simultaneous was first suggested by Lewis, G.N., in *Valence and the Structure of Atoms and Molecules*, Chemical Catalog Company, NY, ***1923***, p. 113. The idea that a one-step substitution leads to inversion was proposed by Olsen, A.R. *J. Chem. Phys.* ***1933***, *1*, 418.

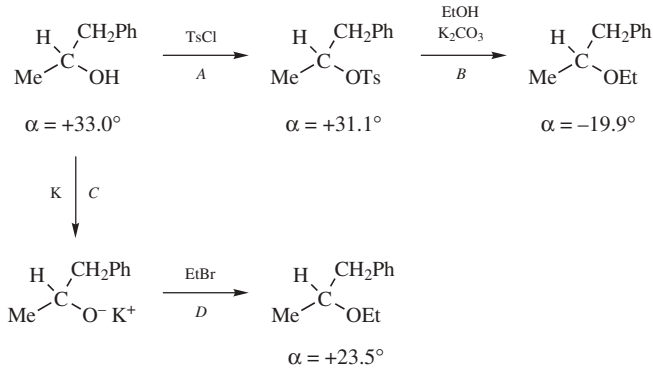
[4]Walden, P. *Berichte* ***1893***, *26*, 210; ***1896***, *29*, 133; ***1899***, *32*, 1855.

One of these must be an inversion and the other a retention of configuration, but the question is which is which? The signs of rotation are of no help in answering this question since, as we have seen (p. 154), rotation need not be related to configuration. Another example discovered by Walden is formation of **3** from **4**.[5]



3 **4**

A series of experiments designed to settle the matter of exactly where inversion takes place was performed by Phillips, Kenyon, and co-workers. In 1923, Phillips carried out the following cycle based on (+)-1-phenyl-2-propanol.[6]



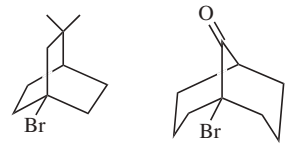
In this cycle, (+)-1-phenyl-2-propanol is converted to its ethyl ether by two routes, path *AB* giving the (−) ether, and path *CD* giving the (+) ether. Therefore, at least one of the four steps must be an inversion. It is extremely unlikely that there is inversion in step *A*, *C*, or *D*, since in all these steps the C—O bond is unbroken, and in none of them could the oxygen of the bond have come from the reagent. There is therefore a high probability that *A*, *C*, and *D* proceeded with retention, leaving *B* as the inversion. A number of other such cycles were carried out, always with nonconflicting results.[7] These experiments not only definitely showed that certain specific reactions proceed with inversion, but also established the configurations of many compounds.

Walden inversion has been found at a primary carbon atom by the use of a chiral substrate containing a deuterium and a hydrogen atom at the carbon bearing the

[5]For a discussion of these cycles, see Kryger, L.; Rasmussen, S.E. *Acta Chem. Scand.* ***1972***, *26*, 2349.
[6]Phillips, H. *J. Chem. Soc.* ***1923***, *123*, 44. For analyses of such cycles and general descriptions of more complex ones, see Garwood, D.C.; Cram, D.J. *J. Am. Chem. Soc.* ***1970***, *92*, 4575; Cram, D.J.; Cram, J.M. *Fortschr. Chem. Forsch.* ***1972***, *31*, 1.
[7]See Kenyon, J.; Phillips, H.; Shutt, G.R. *J. Chem. Soc.* ***1935***, 1663 and references cited therein.

leaving group.[8] Inversion of configuration has also been found for S_N2 reactions proceeding in the gas phase.[9] High-pressure mass spectrometry has been used to probe the energy surface for gas-phase S_N2 reactions, which have two transition states (a "loose" transitions state and a "tight" transition state).[10]

Another kind of evidence for the S_N2 mechanism comes from compounds with potential leaving groups at bridgehead carbons. If the S_N2 mechanism is correct, these compounds should not be able to react by this mechanism, since



5 **6**

the nucleophile cannot approach from the rear. Among the many known examples of unsuccessful reaction attempts at bridgeheads under S_N2 conditions[11] are treatment of the [2.2.2] system **5** with ethoxide ion[12] and treatment of the [3.3.1] system **6** with sodium iodide in acetone.[13] In these cases, open-chain analogs underwent the reactions readily. As a final example of evidence for the S_N2 mechanism, the reaction between optically active 2-octyl iodide and radioactive iodide ion may be mentioned:

$$C_6H_{13}CHMeI + {}^*I^- \longrightarrow C_6H_{13}CHMe{}^*I + I^-$$

We expect racemization in this reaction, since if we start with the pure *R* isomer, at first each exchange will produce an *S* isomer, but with increasing concentration of *S* isomer, *it* will begin to compete for I^- with the (*R*) isomer, until at the end a racemic mixture is left. The point investigated was a comparison of the rate of inversion with the rate of uptake of radioactive ${}^*I^-$. It was found[14] that the rates were identical within experimental error:

Rate of inversion	$2.88 \pm 0.03 \times 10^{-5}$
Rate of exchange	$3.00 \pm 0.25 \times 10^{-5}$

[8]Streitwieser, Jr., A. *J. Am. Chem. Soc.* ***1953***, *75*, 5014.

[9]Speranza, M.; Angelini, G. *J. Am. Chem. Soc.* ***1980***, *102*, 3115 and references cited therein; Sauers, R.R. *J. Org. Chem.* ***2002***, *67*, 1221; Kempf, B.; Hampel, N.; Ofial, A.R.; Mayr, H. *Chem. Eur. J.* ***2003***, *9*, 2209. For a review of nucleophilic displacements in the gas phase, see Riveros, J.M.; José, S.M.; Takashima, K. *Adv. Phys. Org. Chem.* ***1985***, *21*, 197.

[10]Li, C.; Ross, P.; Szulejko, J.E.; McMahon, T.B. *J. Am. Chem. Soc.* ***1996***, *118*, 9360.

[11]For a review of bridgehead reactivity in nucleophilic substitution reactions, see Müller, P.; Mareda, J., in Olah, G.A. *Cage Hydrocarbons*, Wiley, NY, ***1990***, pp. 189–217. For a review of reactions at bridgehead carbons, see Fort, Jr., R.C.; Schleyer, P.v.R. *Adv. Alicyclic Chem.* ***1966***, *1*, 283.

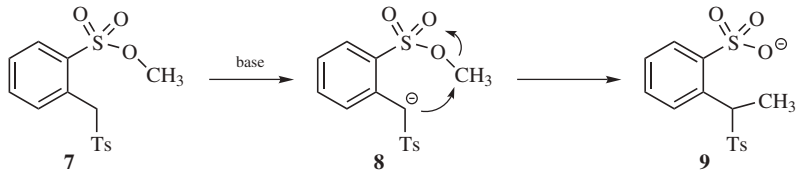
[12]Doering, W. von E.; Levitz, M.; Sayigh, A.; Sprecher, M.; Whelan, Jr., W.P. *J. Am. Chem. Soc.* ***1953***, *75*, 1008. Actually, a slow substitution was observed in this case, but not by an S_N2 mechanism.

[13]Cope, A.C.; Synerholm, M.E. *J. Am. Chem. Soc.* ***1950***, *72*, 5228.

[14]Hughes, E.D.; Juliusburger, F.; Masterman, S.; Topley, B.; Weiss, J. *J. Chem. Soc.* ***1935***, 1525.

What was actually measured was the rate of racemization, which is twice the rate of inversion, since each inversion creates, in effect, two racemic molecules. The significance of this result is that it shows that every act of exchange is an act of inversion.

Eschenmoser and co-workers have provided strong evidence that the transition state in an S_N2 reaction must be linear.[15] Base treatment of methyl α-tosyl-*o*-toluenesulfonate (**7**) gives the *o*-(l-tosylethyl)benzenesulfonate ion (**9**). The role of



the base is to remove the a proton to give the ion **8**. It might be supposed that the negatively charged carbon of **8** attacks the methyl group in an internal S_N2 process, but this is not the case. Cross-over experiments[15] (p. 736) have shown that the negatively charged carbon attacks the methyl group of another molecule rather than the nearby one in the same molecule, that is, the reaction is intermolecular and not intramolecular, despite the more favorable entropy of the latter pathway (p. 302). The obvious conclusion is that intramolecular attack does not take place because complete linearity cannot be attained. This behavior is in sharp contrast to that in cases in which the leaving group is not constrained (p. 446), where intramolecular S_N2 mechanisms operate freely.

There is evidence, both experimental and theoretical, that there are intermediates in at least some S_N2 reactions in the gas phase, in charge type I reactions, where a negative ion nucleophile attacks a neutral substrate.[16] Two energy minima, one before and one after the transition state appear in the reaction coordinate (Fig. 10.1).[17] The energy surface for the S_N2 Menshutkin reaction (p. 555) has been examined and it was shown that charge separation was promoted by the solvent.[18] An *ab initio* study of the S_N2 reaction at primary and secondary carbon centers has looked at the energy barrier (at the transition state) to the reaction.[19] These minima correspond to unsymmetrical ion–dipole complexes.[20] Theoretical calculations also show such minima in certain solvents (e.g., DMF), but not in water.[21] The

[15]Tenud, L.; Farooq, S.; Seibl, J.; Eschenmoser, A. *Helv. Chim. Acta* ***1970***, *53*, 2059. See also, King, J.F.; McGarrity, M.J. *J. Chem. Soc., Chem. Commun.* ***1979***, 1140.
[16]See Angel, L.A; Ervin, K.M. *J. Am. Chem. Soc.* ***2003***, *125*, 1014.
[17]Taken from Chandrasekhar, J.; Smith, S.F.; Jorgensen, W.L. *J. Am. Chem. Soc.* ***1985***, *107*, 154.
[18]Gao, J.; Xia, X. *J. Am. Chem. Soc.* ***1993***, *115*, 9667.
[19]Lee, I.; Kim, C.K.; Chung, D.S.; Lee, B.-S. *J. Org. Chem.* ***1994***, *59*, 4490.
[20]Pellerite, M.J.; Brauman, J.I. *J. Am. Chem. Soc.* ***1980***, *102*, 5993; Wolfe, S.; Mitchell, D.J.; Schlegel, H.B. *J. Am. Chem. Soc.* ***1981***, *103*, 7692; Evanseck, J.D.; Blake, J.F.; Jorgensen, W.L. *J. Am. Chem. Soc.* ***1987***, *109*, 2349; Kozaki, T.; Morihashi, K.; Kikuchi, O. *J. Am. Chem. Soc.* ***1989***, *111*, 1547; Jorgensen, W.L. *Acc. Chem. Res.* ***1989***, *22*, 184.
[21]Chandrasekhar, J.; Jorgensen, W.L. *J. Am. Chem. Soc.* ***1985***, *107*, 2974.

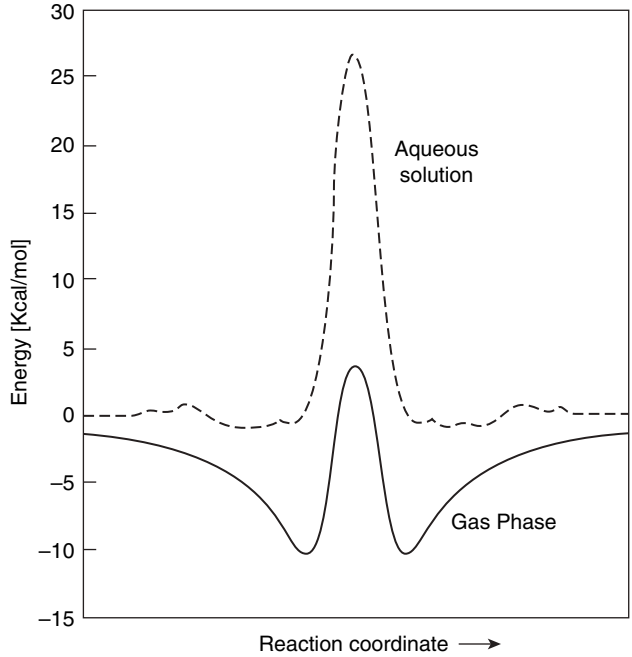


Fig. 10.1. Free-energy profile for the gas-phase (solid line) and aqueous solution (dashed line) S_N2 reaction between CH_3Cl and Cl^-, from molecular orbital calculations.[17]

S_N2 reactions can occur at atoms other than carbon, X (e.g., nitrogen or sulfur[22]), and analogous to the phenomenon observed for S_N2 reactions at carbon.[23] The valence of the element X, controls the intrinsic barrier for the reaction in accord with the properties seen in the Periodic table.[24]

For a list of some of the more important reactions that operate by the S_N2 mechanism, see Table 10.7.

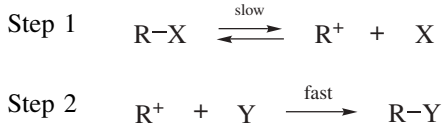
Note that in some reactions, such as bromine transfer between carbanions via nucleophilic attack on bromine, anomalous kinetic behavior is observed. The largest rate constants are associated with bromine transfer between cyano-activated carbanions and the smallest relate to the removal of bromine from the nitromethane and nitroethane moieties.[25] The Brønsted plot ($\log k$ vs. ΔpK_a) for this reaction shows that unlike any normal Brønsted plot, which by definition displays a positive slope, the plot for $MeNO_2$ and $EtNO_2$ is negative. In deprotonation reactions of carbon compounds, the reactivity of nitroethane and nitromethane were shown to be anomalous.[26] In the series nitromethane, ethane, and isopropane, contrary

[22]See reactions **10-60–10-68** and Bachrach, S.M.; Gailbreath, B.D. *J. Org. Chem.* ***2001***, *66*, 2005.
[23]Hoz, S.; Basch, H.; Wolk, J.L.; Hoz, T.; Rozental, E. *J. Am. Chem. Soc.* ***1999***, *121*, 7724.
[24]Yi, R.; Basch, H.; Hoz, S. *J. Org. Chem.* ***2002***, *67*, 5891.
[25]Grinblat, J.; Ben-Zion, M.; Hoz, S. *J. Am. Chem. Soc.* ***2001***, *123*, 10738.
[26]Pearson, R.G.; Dillon, R.L. *J. Am. Chem. Soc.* ***1953***, *75*, 2439.

to expectations, compounds with higher acidity undergo slower deprotonation (i.e., the Brønsted plot displays a negative slope).[27]

The S_N1 Mechanism

The most ideal version of the S_N1 mechanism (*substitutional nucleophilic unimolecular*) consists of two steps[28] (once again, possible charges on the substrate and nucleophile are not shown):



The first step is a slow ionization of the substrate and is the rate-determining step. The second is a rapid reaction between the intermediate carbocation and the nucleophile. The reactive nature of the carbocation can be expressed by its electrophilic character, or electrophlicity. A theoretical discussion concerning the origin of the electrophilicity concept was proposed by Parr et al.[29] In general, a good electrophile was characterized by having a high value of electronegativity (or a high value of electronic chemical potential), and a low value of the chemical hardness. The effect of substitution has been studied[30] in the context of superelectrophilicity (where carbocations are generated in super acidic media). Solvent effects have also been studied.[31] Electrophlicity scales have been proposed using other carbocations.[32]

Returning to the S_N1 mechanism, ionization of a leaving group to form the carbocation is always assisted by the solvent,[33] since the energy necessary to break the bond is largely recovered by solvation of R^+ and of X. For example, the ionization of *t*-BuCl to *t*-Bu^+ and Cl^- in the gas phase without a solvent requires 150 kcal mol^{-1} (630 kJ mol^{-1}). In the absence of a solvent, such a process simply would not take place, except at very high temperatures. In water, this ionization requires only 20 kcal mol^{-1} (84 kJ mol^{-1}). The difference is solvation energy. In

[27]Kresge, A.J. *Can. J. Chem.* ***1974***, *52*, 1897; Yamataka, H.; Mustanir; Mishima, M. *J. Am. Chem. Soc.* ***1999***, *121*, 10223.

[28]For a direct observation of the two steps see Mayr, H.; Minegishi, S. *Angew. Chem. Int. Ed.* ***2002***, *41*, 4493.

[29]Parr, R. G.; Szentpály, L.V.; Liu, S. *J. Am. Chem. Soc.* ***1999***, *121*, 1922.

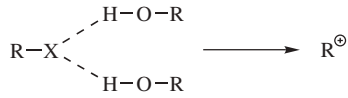
[30]See Pérez, P. *J. Org. Chem.* ***2004***, *69*, 5048.

[31]Pérez, P.; Toro-Labbé, A.; Contreras, R. *J. Am. Chem. Soc.* ***2001***, *123*, 5527.

[32]Pérez, P.; Toro-Labbé, A.; Aizman, A.; Contreras, R. *J. Org. Chem.* ***2002***, *67*, 4747; Parr, R.G.; Szentpály, L.-v.; Liu, S. *J. Am. Chem. Soc.* ***1999***, *121*, 1922.

[33]For reviews of solvolysis, see Okamoto, K. *Adv. Carbocation Chem.* ***1989***, *1*, 171; Blandamer, M.J.; Scott, J.M.W.; Robertson, R.E. *Prog. Phys. Org. Chem.* ***1985***, *15*, 149; Robertson, R.E. *Prog. Phys. Org. Chem.* ***1967***, *4*, 213. For a review of the solvolytic cleavage of *tert*-butyl substrates, see Dvorko, G.F.; Ponomareva, E.A.; Kulik, N.I. *Russ. Chem. Rev.* ***1984***, *53*, 547.

cases where the role of the solvent is solely to assist in departure of the leaving group from the frontside, that is, where there is a complete absence of backside (S_N2) participation by solvent molecules, the mechanism is called *limiting* S_N1. There is kinetic and other evidence[34] that in pulling the leaving group X away from RX, two molecules of a protic solvent form weak hydrogen bonds with X.



In the IUPAC system, the S_N1 mechanism is $D_N + A_N$ or $D_N^{\ddagger} + A_N$ (where ‡ denotes the rate-determining step). The IUPAC designations for the S_N1 and S_N2 mechanisms thus clearly show the essential differences between them: A_ND_N indicates that bond breaking is concurrent with bond formation; $D_N + A_N$ shows that the former happens first.

In looking for evidence for the S_N1 mechanism, the first thought is that it should be a first-order reaction following the rate law:

$$\text{Rate} = k[\text{RX}] \tag{10.3}$$

Since the slow step involves only the substrate, the rate should be dependent only on the concentration of that. Although the solvent is necessary to assist in the process of ionization, it does not enter the rate expression, because it is present in large excess. However, the simple rate law given in Eq. (10.3) is not sufficient to account for all the data. Many cases are known where pure first-order kinetics are followed, but in many other cases more complicated kinetics are found. We can explain this by taking into account the reversibility of the first step. The X formed in this step competes with Y for the cation and the rate law must be modified as shown (see Chapter 6).

$$\begin{gathered}
\mathbf{RX} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathbf{R^+ + X} \\
\mathbf{R^+ + Y} \xrightarrow{k_2} \mathbf{RY} \\
\mathbf{Rate} = \frac{k_1 k_2\,[\mathbf{RX}][\mathbf{Y}]}{k_{-1}\,[\mathbf{X}] + k_2\,[\mathbf{Y}]}
\end{gathered} \tag{10.4}$$

At the beginning of the reaction, when the concentration of X is very small, $k_{-1}[X]$ is negligible compared with $k_2[Y]$ and the rate law is reduced to Eq. (10.3). Indeed, S_N1 reactions generally do display simple first-order kinetics in their initial stages. Most kinetic studies of S_N1 reactions fall into this category. In the later stages of S_N1 solvolyses, [X] becomes large and Eq. (10.4) predicts that the rate should

[34]Blandamer, M.J.; Burgess, J.; Duce, P.P.; Symons, M.C.R.; Robertson, R.E.; Scott, J.M.W. *J. Chem. Res. (S)* ***1982***, 130.

decrease. This is found to be the case for diarylmethyl halides,[35] although not for *tert*-butylhalides, which follow Eq. (10.3) for the entire reaction.[36] An explanation for this difference is that *tert*-butylcations are less selective than the relatively stable diarylmethyl type (p. 240). Although halide ion is a much more powerful nucleophile than water, there is much more water available since it is the solvent.[37] The selective diphenylmethyl cation survives many collisions with solvent molecules before combining with a reactive halide, but the less selective *tert*-butylion cannot wait for a reactive but relatively rare halide ion and combines with the solvent.

If the X formed during the reaction can decrease the rate, at least in some cases, it should be possible to *add* X from the outside and further decrease the rate in that way. This retardation of rate by addition of X is called *common-ion effect* or the *mass-law effect*. Once again, addition of halide ions decreases the rate for diphenylmethyl but not for *tert*-butylhalides.

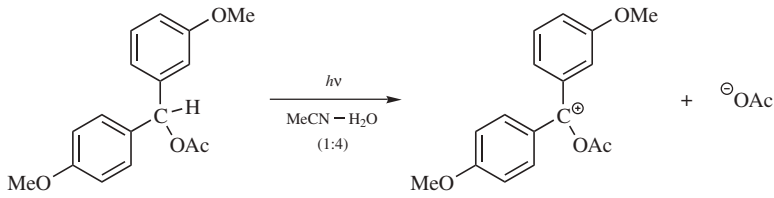
One factor that complicates the kinetic picture is the *salt effect*. An increase in ionic strength of the solution usually increases the rate of an S_N1 reaction (p. 501). But when the reaction is of charge type II, where both Y and RX are neutral, so that X is negatively charged (and most solvolyses are of this charge type), the ionic strength increases as the reaction proceeds and this increases the rate. This effect must be taken into account in studying the kinetics. Incidentally, the fact that the addition of outside ions *increases* the rate of most S_N1 reactions makes especially impressive the *decrease* in rate caused by the common ion.

Note that the pseudo-first-order rate law for an S_N2 reaction in the presence of a large excess of Y [Eq. (10.1)] is the same as that for an ordinary S_N1 reaction [Eq. (10.3)]. It is thus not possible to tell these cases apart by simple kinetic measurements. However, we can often distinguish between them by the common-ion effect mentioned above. Addition of a common ion will not markedly affect the rate of an S_N2 reaction beyond the effect caused by other ions. Unfortunately, as we have seen, not all S_N1 reactions show the common-ion effect, and this test fails for *tert*-butyl and similar cases.

Kinetic studies also provide other evidence for the S_N1 mechanism. One technique used ^{19}F NMR to follow the solvolysis of trifluoroacetyl esters.[38] If this mechanism operates essentially as shown on p. 432, the rate should be the same for a given substrate under a given set of conditions, *regardless of the identity of the nucleophile or its concentration*. In one experiment that demonstrates this, benzhydryl chloride (Ph_2CHCl) was treated in SO_2 with the nucleophiles fluoride ion, pyridine, and triethylamine at several concentrations of each nucleophile.[39] In each case the initial rate of the reaction was approximately the same when

[35]Benfey, O.T.; Hughes, E.D.; Ingold, C.K. *J. Chem. Soc.* ***1952***, 2488.
[36]Bateman, L.C.; Hughes, E.D.; Ingold, C.K. *J. Chem. Soc.* ***1940***, 960.
[37]In the experiments mentioned, the solvent was actually "70%" or "80%" aqueous acetone. The "80%" aqueous acetone consists of 4 vol of dry acetone and 1 vol of water.
[38]Creary, X.; Wang, Y.-X. *J. Org. Chem.* ***1992***, *57*, 4761. Also see, Fărcaşiu, D.; Marino, G.; Harris, J.M.; Hovanes, B.A.; Hsu, C.S. *J. Org. Chem.* ***1994***, *59*, 154.
[39]Bateman, L.C.; Hughes, E.D.; Ingold, C.K. *J. Chem. Soc.* ***1940***, 1011.

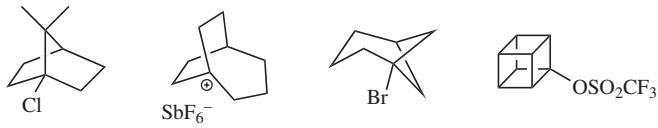
corrections were made for the salt effect. The same type of behavior has been shown in a number of other cases, even when the reagents are as different in their nucleophilicities (see p. 490) as H_2O and HO^-.



10

It is normally not possible to detect the carbocation intermediate of an S_N1 reaction directly, because its lifetime is very short. However, in the case of 3,4-dimethoxydiphenylmethyl acetate (**10**) and certain other substrates in polar solvents it was possible to initiate the reaction photolytically, and under these conditions the UV spectra of the intermediate carbocations could be obtained,[40] providing additional evidence for the S_N1 mechanism.

Further evidence for the S_N1 mechanism is that reactions run under S_N1 conditions fail or proceed very slowly at the bridgehead positions[10] of [2.2.1] (norbornyl) systems[41] (e.g., 1-chloroapocamphane, **8**). If S_N1 reactions require carbocations



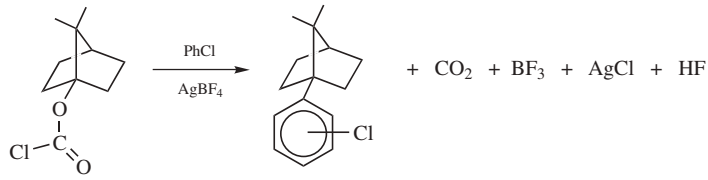
11 **12** **13** **14**

and if carbocations must be planar or nearly planar, then it is no surprise that bridgehead 1-norbornyl carbon atoms, which cannot assume planarity, do not become the seat of carbocations. As an example, **11**, boiled 21 h with 30% KOH in 80% ethanol or 48 h with aqueous ethanolic silver nitrate, gave no reaction in either case,[42] although analogous open-chain systems reacted readily. According to this theory, S_N1 reactions should be possible with larger rings, since near-planar carbocations might be expected there. This turns out to be the case. For example, [2.2.2] bicyclic systems undergo S_N1 reactions much faster than smaller bicyclic systems, although the reaction is still slower than with open-chain systems.[43] Proceeding to a still larger system, the bridgehead [3.2.2] cation **12** is actually stable enough to be kept in solution in SbF_5–SO_2ClF at temperatures below $-50°C$[44] (see also, p. 486). Other small bridgehead systems that undergo S_N1 reactions are the

[40]McClelland, R.A.; Kanagasabapathy, V.M.; Steenken, S. *J. Am. Chem. Soc.* ***1988***, *110*, 6913.
[41]For a review, see Fort, Jr., R.C., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 4; Wiley, NY, ***1973***, pp. 1783–1835.
[42]Bartlett, P.D.; Knox, L.H. *J. Am. Chem. Soc.* ***1939***, *61*, 3184.
[43]For synthetic examples, see Kraus, G.A.; Hon, Y. *J. Org. Chem.* ***1985***, *50*, 4605.
[44]Olah, G.A.; Liang, G.; Wiseman, J.R.; Chong, J.A. *J. Am. Chem. Soc.* ***1972***, *74*, 4927.

[3.1.1] (e.g., **13**)[45] and the cubyl (e.g., **14**)[46] systems. *Ab initio* calculations show that the cubyl cation, although it cannot be planar, requires less energy to form than the 1-norbornyl cation.[47] There are reactions where the cationic carbon is not coplanar with conjugating substituents (such as phenyl), and formation of the carbocation is more difficult but the reaction proceeds.[48]

Certain nucleophilic substitution reactions that normally involve carbocations can take place at norbornyl bridgeheads[49] (though it is not certain that carbocations are actually involved in all cases) if the leaving group used is of the type that cannot function as a nucleophile (and thus come back) once it has gone, and in the displacement of $ClCO_2$ in **15**. In this example,[50] chlorobenzene is the nucleophile (see **11-10**).



15

Additional evidence for the S_N1 mechanism, in particular, for the intermediacy of carbocations, is that solvolysis rates of alkyl chlorides in ethanol parallel carbocation stabilities as determined by heats of ionization measured in superacid solutions (p. 236).[51] It is important to note that some solvolysis reactions proceed by an S_N2 mechanism.[52]

Ion Pairs in the S_N1 Mechanism[53]

Like the kinetic evidence, the stereochemical evidence for the S_N1 mechanism is less clear-cut than it is for the S_N2 mechanism.[54] If there is a free carbocation, it is planar (p. 245), and the nucleophile should attack with equal facility from either

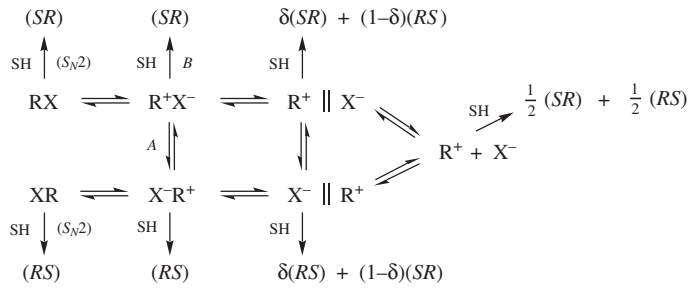
[45]Della, E.W.; Pigou, P.E.; Tsanaktsidis, J. *J. Chem. Soc., Chem. Commun.* ***1987***, 833.
[46]Eaton, P.E.; Yang, C.; Xiong, Y. *J. Am. Chem. Soc.* ***1990***, *112*, 3225; Moriarty, R.M.; Tuladhar, S.M.; Penmasta, R.; Awasthi, A.K. *J. Am. Chem. Soc.* ***1990***, *112*, 3228.
[47]Hrovat, D.A.; Borden, W.T. *J. Am. Chem. Soc.* ***1990***, *112*, 3227.
[48]Lee, I.; Kim, N.D.; Kim, C.K. *Tetrahedron Lett.* ***1992***, *33*, 7881.
[49]Bartlett, P.D.; Knox, L.H. *J. Am. Chem. Soc.* ***1939***, *61*, 3184; Clive, D.L.J.; Denyer, C.V. *Chem. Commun.* ***1971***, 1112; White, E.H.; McGirk, R.H.; Aufdermarsh, Jr., C.A.; Tiwari, H.P.; Todd, M.J. *J. Am. Chem. Soc.* ***1973***, *95*, 8107; Beak, P.; Harris, B.R. *J. Am. Chem. Soc.* ***1974***, *96*, 6363.
[50]For a review of reactions with the OCOCl leaving group, see Beak, P. *Acc. Chem. Res.* ***1976***, *9*, 230.
[51]Arnett, E.M.; Petro, C.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1979***, *101*, 522; Arnett, E.M.; Pienta, N.J. *J. Am. Chem. Soc.* ***1980***, *102*, 3329; Arnett, E.M.; Molter, K.E. *Acc. Chem. Res.* ***1985***, *18*, 339.
[52]Lee, I.; Lee, Y.S.; Lee, B.-S.; Lee, H.W. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 1441.
[53]For reviews of ion pairs in S_N reactions, see Beletskaya, I.P. *Russ. Chem. Rev.* ***1975***, *44*, 1067; Harris, J.M. *Prog. Phys. Org. Chem.* ***1974***, *11*, 89; Raber, D.J.; Harris, J.M.; Schleyer, P.v.R., in Szwarc, M. *Ions and Ion Pairs in Organic Reactions*, Vol. 2; Wiley, NY, ***1974***, pp. 247–374.
[54]For an alternative view of the S_N1/S_N2 mechanism see Uggerud, E. *J. Org. Chem.* ***2001***, *66*, 7084.

side of the plane, resulting in complete racemization. Although many first-order substitutions do give complete racemization, many others do not. Typically there is 5–20% inversion, although in a few cases, a small amount of retention of configuration has been found. These and other results have led to the conclusion that in many S_N1 reactions at least some of the products are not formed from free carbocations but rather from *ion pairs*. According to this concept,[55] S_N1 reactions proceed in this manner:

$$\mathrm{R{-}X} \rightleftharpoons \underset{\mathbf{16}}{\mathrm{R^+\,X^-}} \rightleftharpoons \underset{\mathbf{17}}{\mathrm{R^+\|\,X^-}} \rightleftharpoons \underset{\mathbf{18}}{\mathrm{R^+ + X^-}}$$

where **16** is an *intimate*, *contact*, or *tight* ion pair, **17** a *loose*, or *solvent-separated* ion pair, and **18** the dissociated ions (each surrounded by molecules of solvent).[56] The reaction in which the intimate ion pair recombines to give the original substrate is referred to as *internal return*. The reaction products can result from attack by the nucleophile at any stage. In the intimate ion pair **16**, R^+ does not behave like the free cation of **18**. There is probably significant bonding between R^+ and X^- and asymmetry may well be maintained.[57] Here, X^- ''solvates'' the cation on the side from which it departed, while solvent molecules near **16** can only solvate it from the opposite side. Nucleophilic attack by a solvent molecule on **16** thus leads to inversion.

Ignoring the possibilities of elimination or rearrangement (see Chapters 17 and 18), a complete picture of the possibilities for solvolysis reactions[58] in a solvent SH is represented by following diagram,[59] although in any particular case it is unlikely that all these reactions occur:



[55]Proposed by Winstein, S.; Clippinger, E.; Fainberg, A.H.; Heck, R.; Robinson, G.C. *J. Am. Chem. Soc.* ***1956***, *78*, 328.

[56]For a review of the energy factors involved in the recombination of ion pairs, see Kessler, H.; Feigel, M. *Acc. Chem. Res.* ***1982***, *15*, 2.

[57]Fry, J.L.; Lancelot, C.J.; Lam, L.K.M.; Harris, J.M.; Bingham, R.C.; Raber, D.J.; Hall, R.E.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1970***, *92*, 2538.

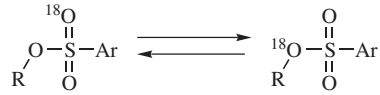
[58]For solvolysis of tertiary derivatives with a discussion of solvent participation versus solvation see Richard, J.P.; Toteva, M.M.; Amyes, T.L. *Org. Lett.* ***2001***, *3*, 2225.

[59]Shiner, Jr., V.J.; Fisher, R.D. *J. Am. Chem. Soc.* ***1971***, *93*, 2553.

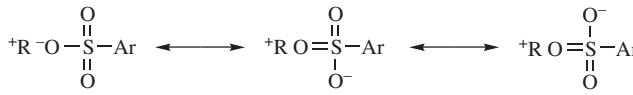
In this scheme RS and SR represent enantiomers, and so on, and δ represents some fraction. The following are the possibilities: (*1*) Direct attack by SH on RX gives SR (complete inversion) in a straight S_N2 process. (*2*) If the intimate ion pair $R^+ X^-$ is formed, the solvent can attack at this stage. This can lead to total inversion if reaction A does not take place or to a combination of inversion and racemization if there is competition between A and B. (*3*) If the solvent-separated ion pair is formed, SH can attack here. The stereochemistry is not maintained as tightly and more racemization (perhaps total) is expected. (*4*) Finally, if free R^+ is formed, it is planar, and attack by SH gives complete racemization.

The ion-pair concept thus predicts that S_N1 reactions can display either complete racemization or partial inversion. The fact that this behavior is generally found is evidence that ion pairs are involved in many S_N1 reactions. There is much other evidence for the intervention of ion pairs,[60] includng ion-molecule pairs.[61]

1. The compound 2-octyl brosylate was labeled at the sulfone oxygen with ^{18}O and solvolyzed. The unreacted brosylate recovered at various stages of solvolysis had the ^{18}O considerably, although not completely, scrambled:[62]



In an intimate ion pair, the three oxygens become equivalent:



Similar results were obtained with several other sulfonate esters.[63] The possibility must be considered that the scrambling resulted from ionization

[60]For further evidence beyond that given here, see Winstein, S.; Baker, R.; Smith, S. *J. Am. Chem. Soc.* ***1964***, *86*, 2072; Streitwieser, Jr., A.; Walsh, T.D. *J. Am. Chem. Soc.* ***1965***, *87*, 3686; Sommer, L.H.; Carey, F.A. *J. Org. Chem.* ***1967***, *32*, 800, 2473; Kwart, H.; Irvine, J.L. *J. Am. Chem. Soc.* ***1969***, *91*, 5541; Harris, J.M.; Becker, A.; Fagan, J.F.; Walden, F.A. *J. Am. Chem. Soc.* ***1974***, *96*, 4484; Bunton, C.A.; Huang, S.K.; Paik, C.H. *J. Am. Chem. Soc.* ***1975***, *97*, 6262; Humski, K.; Sendijarević, V.; Shiner, Jr., V.J. *J. Am. Chem. Soc.* ***1976***, *98*, 2865; Maskill, H.; Thompson, J.T.; Wilson, A.A. *J. Chem. Soc., Chem. Commun.* ***1981***, 1239; McManus, S.P.; Safavy, K.K.; Roberts, F.E. *J. Org. Chem.* ***1982***, *47*, 4388; McLennan, D.J.; Stein, A.R.; Dobson, B. *Can. J. Chem.* ***1986***, *64*, 1201; Kinoshita, T.; Komatsu, K.; Ikai, K.; Kashimura, K.; Tanikawa, S.; Hatanaka, A.; Okamoto, K. *J. Chem. Soc. Perkin Trans. 2* ***1988***, 1875; Ronco, G.; Petit, J.; Guyon, R.; Villa, P. *Helv. Chim. Acta* ***1988***, *71*, 648; Kevill, D.N.; Kyong, J.B.; Weitl, F.L. *J. Org. Chem.* ***1990***, *55*, 4304.

[61]Jia, Z.S.; Ottosson, H.; Zeng, X.; Thibblin, A. *J. Org. Chem.* ***2002***, *67*, 182.

[62]Diaz, A.F.; Lazdins, I.; Winstein, S. *J. Am. Chem. Soc.* ***1968***, *90*, 1904.

[63]Goering, H.L.; Jones, B.E. *J. Am. Chem. Soc.* ***1980***, *102*, 1628; Yukawa, Y.; Morisaki, H.; Tsuji, K.; Kim, S.; Ando, T. *Tetrahedron Lett.* ***1981***, *22*, 5187; Chang, S.; le Noble, W.J. *J. Am. Chem. Soc.* ***1983***, *105*, 3708; Paradisi, C.; Bunnett, J.F. *J. Am. Chem. Soc.* ***1985***, *107*, 8223; Fujio, M.; Sanematsu, F.; Tsuno, Y.; Sawada, M.; Takai, Y. *Tetrahedron Lett.* ***1988***, *29*, 93.

of one molecule of $ROSO_2Ar$ to R^+ and $ArSO_2O^-$ followed by attack by the $ArSO_2O^-$ ion on *another* carbocation or perhaps on a molecule of $ROSO_2Ar$ in an S_N2 process. However, this was ruled out by solvolyzing unlabeled substrate in the presence of labeled $HOSO_2Ar$. These experiments showed that there was some intermolecular exchange (3–20%), but not nearly enough to account for the amount of scrambling found in the original experiments. Similar scrambling was found in solvolysis of labeled carboxylic esters $R—^{18}O—COR'$, where the leaving group is $R'COO^-$.[64] In this case also, the external addition of $RCOO^-$ did not result in significant exchange. However, it has been proposed that the scrambling could result from a concerted process, not involving ion-pair intermediates, and there is some evidence for this view.[65]

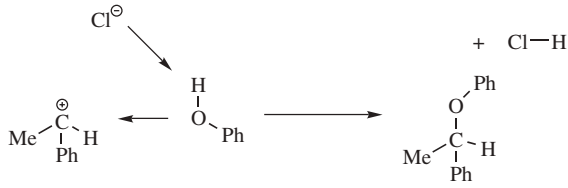
2. The *special salt effect*. The addition of $LiClO_4$ or LiBr in the acetolysis of certain tosylates produced an initial steep rate acceleration that then decreased to the normal linear acceleration (caused by the ordinary salt effect).[66] This is interpreted as follows: the ClO_4^- (or Br^-) traps the solvent-separated ion pair to give $R^+ \parallel ClO_4^-$ which, being unstable under these conditions, goes to product. Hence, the amount of solvent-separated ion pair that would have returned to the starting material is reduced, and the rate of the overall reaction is increased. The special salt effect has been directly observed by the use of picosecond absorption spectroscopy.[67]

3. We have previously discussed the possibilities of racemization or inversion of the *product* RS of a solvolysis reaction. However, the formation of an ion pair followed by internal return can also affect the stereochemistry of the *substrate* molecule RX. Cases have been found where internal return racemizes an original optically active RX, an example being solvolysis in aqueous acetone of α-*p*-anisylethyl *p*-nitrobenzoate,[68] while in other cases partial or complete retention is found, for example, solvolysis in aqueous acetone of *p*-chlorobenzhydryl *p*-nitrobenzoate.[69] Racemization of RX is presumably caused by the equilibrium pathway: $RX \rightleftharpoons R^+X^- \rightleftharpoons X^-R^+ \rightleftharpoons XR$. Evidence for ion pairs is that, in some cases where internal return involves racemization, it has been shown that such racemization is *faster* than solvolysis. For example, optically active *p*-chlorobenzhydryl chloride racemizes ~30 times faster than it solvolyzes in acetic acid.[70]

[64]Goering, H.L.; Hopf, H. *J. Am. Chem. Soc.* ***1971***, *93*, 1224, and references cited therein.
[65]Dietze, P.E.; Wojciechowski, M. *J. Am. Chem. Soc.* ***1990***, *112*, 5240.
[66]Winstein, S.; Clippinger, E.; Fainberg, A.H.; Heck, R.; Robinson, G.C. *J. Am. Chem. Soc.* ***1956***, *78*, 328; Winstein, S.; Klinedinst, Jr., P.E.; Clippinger, E. *J. Am. Chem. Soc.* ***1961***, *83*, 4986; Cristol, S.J.; Noreen, A.L.; Nachtigall, G.W. *J. Am. Chem. Soc.* ***1972***, *94*, 2187.
[67]Simon, J.D.; Peters, K.S. *J. Am. Chem. Soc.* ***1982***, *104*, 6142.
[68]Goering, H.L.; Briody, R.G.; Sandrock, G. *J. Am. Chem. Soc.* ***1970***, *92*, 7401.
[69]Goering, H.L.; Briody, R.G.; Levy, J.F. *J. Am. Chem. Soc.* ***1963***, *85*, 3059.
[70]Winstein, S.; Gall, J.S.; Hojo, M.; Smith, S. *J. Am. Chem. Soc.* ***1960***, *82*, 1010. See also, Shiner, Jr., V.J.; Hartshorn, S.R.; Vogel, P.C. *J. Org. Chem.* ***1973***, *38*, 3604.

Molecular orbital calculations[71] made on *t*-BuCl show that the C—Cl distance in the intimate ion pair is 2.9 Å and the onset of the solvent-separated ion pair takes place at about 5.5 Å (cf. the C—Cl bond length of 1.8 Å).

In a few cases, S_N1 reactions have been found to proceed with partial retention (20–50%) of configuration. Ion pairs have been invoked to explain some of these.[72] For example, it has been proposed that the phenolysis of optically active α-phenylethyl chloride, in which the ether of net retained configuration is obtained, involves a four-center mechanism:



This conclusion is strengthened by the fact that partial retention was obtained in this system only with chloride or other neutral leaving groups; with leaving groups bearing a positive charge, which are much less likely to form hydrogen bonds with the solvent, no retention was found.[73] Partial retention can also arise when the ion pair is shielded at the backside by an additive such as acetonitrile, acetone, or aniline.[74]

The difference between the S_N1 and S_N2 mechanisms is in the timing of the steps. In the S_N1 mechanism, first X leaves, then Y attacks. In the S_N2 case, the two things happen simultaneously. One could imagine a third possibility: first the attack of Y and then the removal of X. This is not possible at a saturated carbon, since it would mean more than eight electrons in the outer shell of carbon. However, this type of mechanism is possible and indeed occurs at other types of substrate (p. 473; Chapter 13).

Mixed S_N1 and S_N2 Mechanisms

Some reactions of a given substrate under a given set of conditions display all the characteristics of S_N2 mechanisms; other reactions seem to proceed by S_N1 mechanisms, but cases are found that cannot be characterized so easily. There seems to be something in between, a mechanistic "borderline" region.[75] At least two broad

[71]Jorgensen, W.L.; Buckner, J.K.; Huston, S.E.; Rossky, P.J. *J. Am. Chem. Soc.* ***1987***, *109*, 1891.
[72]Okamoto, K. *Pure Appl. Chem.* ***1984***, *56*, 1797. For a similar mechanism with amine nucleophiles, see Lee, I.; Kim, H.Y.; Kang, H.K.; Lee, H.W. *J. Org. Chem.* ***1988***, *53*, 2678; Lee, I.; Kim, H.Y.; Lee, H.W.; Kim, I.C. *J. Phys. Org. Chem.* ***1989***, *2*, 35.
[73]Okamoto, K.; Kinoshita, T.; Shingu, H. *Bull. Chem. Soc. Jpn.* ***1970***, *43*, 1545.
[74]Okamoto, K.; Nitta, I.; Dohi, M.; Shingu, H. *Bull. Chem. Soc. Jpn.* ***1971***, *44*, 3220; Kinoshita, T.; Ueno, T.; Ikai, K.; Fujiwara, M.; Okamoto, K. *Bull. Chem. Soc. Jpn.* ***1988***, *61*, 3273; Kinoshita, T.; Komatsu, K.; Ikai, K.; Kashimura, K.; Tanikawa, S.; Hatanaka, A.; Okamoto, K. *J. Chem. Soc. Perkin Trans. 2* ***1988***, 1875.
[75]For an essay on borderline mechanisms in general, see Jencks, W.P. *Chem. Soc. Rev.* ***1982***, *10*, 345.

theories have been devised to explain these phenomena. One theory holds that intermediate behavior is caused by a mechanism that is neither "pure" S_N1 nor "pure" S_N2, but some "in-between" type. According to the second theory, there is no intermediate mechanism at all, and borderline behavior is caused by simultaneous operation, in the same flask, of both the S_N1 and S_N2 mechanisms; that is, some molecules react by the S_N1, while others react by the S_N2 mechanism.

One formulation of the intermediate-mechanism theory is that of Sneen.[76] The formulation is in fact very broad and applies not only to borderline behavior but to all nucleophilic substitutions at a saturated carbon.[77] According to Sneen, all S_N1 and S_N2 reactions can be accommodated by one basic mechanism (the *ion-pair mechanism*). The substrate first ionizes to an intermediate ion pair that is then converted to products:

$$\mathrm{RX} \underset{}{\overset{k_1}{\rightleftharpoons}} \mathrm{R^+\ X^-} \overset{k_2}{\rightleftharpoons} \text{Products}$$

The difference between the S_N1 and S_N2 mechanisms is that in the former case the *formation* of the ion pair (k_1) is rate determining, while in the S_N2 mechanism its *destruction* (k_2) is rate determining. Borderline behavior is found where the rates of formation and destruction of the ion pair are of the same order of magnitude.[78] However, a number of investigators have asserted that these results could also be explained in other ways.[79]

There is evidence for the Sneen formulation where the leaving group has a positive charge. In this case, there is a cation–molecule pair ($\mathrm{RX^+ \rightarrow R^+X}$)[80] instead of the ion pair that would be present if the leaving group were uncharged. Katritzky

[76]Sneen, R.A.; Felt, G.R.; Dickason, W.C. *J. Am. Chem. Soc.* ***1973***, *95*, 638 and references cited therein; Sneen, R.A. *Acc. Chem. Res.* ***1973***, *6*, 46.

[77]Including substitution at an allylic carbon; see Sneen, R.A.; Bradley, W.A. *J. Am. Chem. Soc.* ***1972***, *94*, 6975; Sneen, R.A.; Carter, J.V. *J. Am. Chem. Soc.* ***1972***, *94*, 6990; Bordwell, F.G.; Mecca, T.G. *J. Am. Chem. Soc.* ***1975***, *97*, 123, 127; Bordwell, F.G.; Wiley, P.F.; Mecca, T.G. *J. Am. Chem. Soc.* ***1975***, *97*, 132; Kevill, D.N.; Degenhardt, C.R. *J. Am. Chem. Soc.* ***1979***, *101*, 1465.

[78]For evidence for this point of view, see Sneen, R.A.; Felt, G.R.; Dickason, W.C. *J. Am. Chem. Soc.* ***1973***, *95*, 638 and references cited therein; Sneen, R.A. *Acc. Chem. Res.* ***1973***, *6*, 46; Robbins, H.M. *J. Am. Chem. Soc.* ***1972***, *94*, 7868; Graczyk, D.G.; Taylor, J.W. *J. Am. Chem. Soc.* ***1974***, *96*, 3255; Peeters, H.L.; Anteunis, M. *J. Org. Chem.* ***1975***, *40*, 312; Pross, A.; Aronovitch, H.; Koren, R. *J. Chem. Soc. Perkin Trans. 2* ***1978***, 197; Blandamer, M.J.; Robertson, R.E.; Scott, J.M.W.; Vrielink, A. *J. Am. Chem. Soc.* ***1980***, *102*, 2585; Stein, A.R. *Can. J. Chem.* ***1987***, *65*, 363.

[79]See, for example, Gregory, B.J.; Kohnstam, G.; Queen, A.; Reid, D.J. *Chem. Commun.* ***1971***, 797; Raber, D.J.; Harris, J.C.; Hall, R.E.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1971***, *93*, 4821; McLennan, D.J. *Acc. Chem. Res.* ***1976***, *9*, 281; McLennan, D.J.; Martin, P.L. *Tetrahedron Lett.* ***1973***, 4215; Raaen, V.F.; Juhlke, T.; Brown, F.J.; Collins, C.J. *J. Am. Chem. Soc.* ***1974***, *96*, 5928; Gregoriou, G.A. *Tetrahedron Lett.* ***1976***, 4605, 4767; Queen, A.; Matts, T.C. *Tetrahedron Lett.* ***1975***, 1503; Stein, A.R. *J. Org. Chem.* ***1976***, *41*, 519; Stephan, E. *Bull. Soc. Chim. Fr.* ***1977***, 779; Katritzky, A.R.; Musumarra, G.; Sakizadeh, K. *J. Org. Chem.* ***1981***, *46*, 3831. For a reply to some of these objections, see Sneen, R.A.; Robbins, H.M. *J. Am. Chem. Soc.* ***1972***, *94*, 7868. For a discussion, see Klumpp, G.W. *Reactivity in Organic Chemistry*, Wiley, NY, ***1982***, pp. 442–450.

[80]For ion-molecule pairs in other solvolysis reactions, see Thibblin, A. *J. Chem. Soc. Perkin Trans. 2* ***1987***, 1629.

and co-workers found that when such a reaction was run at varying high pressures, there was a minimum in the plot of rate constant versus pressure.[81] A minimum of this sort usually indicates a change in mechanism, and the interpretation in this case was that the normal S_N2 mechanism operates at higher pressures and the cation–molecule mechanism at lower pressures.

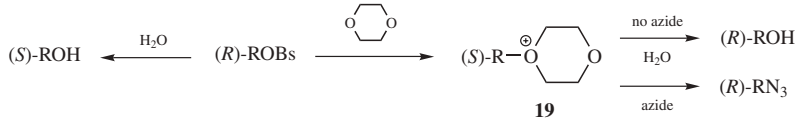
An alternative view that also favors an intermediate mechanism is that of Schleyer and co-workers,[82] who believe that the key to the problem is varying degrees of nucleophilic solvent assistance to ion-pair formation. They have proposed an S_N2(intermediate) mechanism.[83]

Among the experiments that have been cited for the viewpoint that borderline behavior results from simultaneous S_N1 and S_N2 mechanisms is the behavior of 4-methoxybenzyl chloride in 70% aqueous acetone.[84] In this solvent, hydrolysis (that is, conversion to 4-methoxybenzyl alcohol) occurs by an S_N1 mechanism. When azide ions are added, the alcohol is still a product, but now 4-methoxybenzyl azide is another product. Addition of azide ions increases the rate of ionization (by the salt effect) but *decreases* the rate of hydrolysis. If more carbocations are produced but fewer go to the alcohol, then some azide must be formed by reaction with carbocations: an S_N1 process. However, the rate of ionization is always *less* than the total rate of reaction, so some azide must also form by an S_N2 mechanism.[84] Thus, the conclusion is that S_N1 and S_N2 mechanisms operate simultaneously.[85]

Some nucleophilic substitution reactions that seem to involve a "borderline" mechanism actually do not. Thus, one of the principal indications that a "borderline" mechanism is taking place has been the finding of partial racemization and partial inversion. However, Weiner and Sneen have demonstrated that this type of stereochemical behavior is quite consistent with a strictly S_N2 process. These workers studied the reaction of optically active 2-octyl brosylate in 75% aqueous dioxane, under which conditions inverted 2-octanol was obtained in 77% optical purity.[86] When

[81]Katritzky, A.R.; Sakizadeh, K.; Gabrielsen, B.; le Noble, W.J. *J. Am. Chem. Soc.* ***1984***, *106*, 1879.
[82]Bentley, T.W.; Bowen, C.T.; Morten, D.H.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1981***, *103*, 5466.
[83]For additional evidence for this view, see Laureillard, J.; Casadevall, A.; Casadevall, E. *Tetrahedron* ***1984***, *40*, 4921; *Helv. Chim. Acta* ***1984***, *67*, 352; McLennan, D.J. *J. Chem. Soc. Perkin Trans. 2* ***1981***, 1316. For evidence against the S_N2 (intermediate) mechanism, see Allen, A.D.; Kanagasabapathy, V.M.; Tidwell, T.T. *J. Am. Chem. Soc.* ***1985***, *107*, 4513; Fărcaşiu, D.; Jähme, J.; Rüchardt, C. *J. Am. Chem. Soc.* ***1985***, *107*, 5717; Dietze, P.E.; Jencks, W.P. *J. Am. Chem. Soc.* ***1986***, *108*, 4549; Dietze, P.E.; Hariri, R.; Khattak, J. *J. Org. Chem.* ***1989***, *54*, 3317; Coles, C.J.; Maskill, H. *J. Chem. Soc. Perkin Trans. 2* ***1987***, 1083; Richard, J.P.; Amyes, T.L.; Vontor, T. *J. Am. Chem. Soc.* ***1991***, *113*, 5871.
[84]Kohnstam, G.; Queen, A.; Shillaker, B. *Proc. Chem. Soc.* ***1959***, 157; Amyes, T.L.; Richard, J.P. *J. Am. Chem. Soc.* ***1990***, *112*, 9507. For other evidence supporting the concept of simultaneous mechanisms, see Pocker, Y. *J. Chem. Soc.* ***1959***, 3939, 3944; Casapieri, P.; Swart, E.R. *J. Chem. Soc.* ***1963***, 1254; Ceccon, A.; Papa, I.; Fava, A. *J. Am. Chem. Soc.* ***1966***, *88*, 4643; Okamoto, K.; Uchida, N.; Saitô, S.; Shingu, H. *Bull. Chem. Soc. Jpn.* ***1966***, *39*, 307; Guinot, A.; Lamaty, G. *Chem. Commun.* ***1967***, 960; Queen, A. *Can. J. Chem.* ***1979***, *57*, 2646; Richard, J.P.; Rothenberg, M.E.; Jencks, W.P. *J. Am. Chem. Soc.* ***1984***, *106*, 1361; Richard, J.P.; Jencks, W.P. *J. Am. Chem. Soc.* ***1984***, *106*, 1373, 1383; Katritzky, A.R.; Brycki, B.E. *J. Phys. Org. Chem.* ***1988***, *1*, 1; Stein, A.R. *Can. J. Chem.* ***1989***, *67*, 297.
[85]These data have also been explained as being in accord with the ion-pair mechanism: Sneen, R.A.; Larsen, J.W. *J. Am. Chem. Soc.* ***1969***, *91*, 6031.
[86]Weiner, H.; Sneen, R.A. *J. Am. Chem. Soc.* ***1965***, *87*, 287.

sodium azide was added, 2-octyl azide was obtained along with the 2-octanol, *but the latter was now 100% inverted*. It is apparent that, in the original case, 2-octanol was produced by two different processes: an S_N2 reaction leading to inverted product, and another process in which some intermediate leads to racemization or retention. When azide ions were added, they scavenged this intermediate, so that the entire second process now went to produce azide, while the S_N2 reaction, unaffected by addition of azide, still went on to give inverted 2-octanol. What is the nature of the intermediate in the second process? At first thought we might suppose that it is a carbocation, so that this would be another example of simultaneous S_N1 and S_N2 reactions. However, solvolysis of 2-octyl brosylate in pure methanol or of 2-octyl methanesulfonate in pure water, in the absence of azide ions, gave methyl 2-octyl ether or 2-octanol, respectively, *with 100% inversion of configuration*, indicating that the mechanism in these solvents was pure S_N2. Since methanol and water are more polar than 75% aqueous dioxane and since an increase in polarity of solvent increases the rate of S_N1 reactions at the expense of S_N2 (p. 500), it is extremely unlikely that any S_N1 process could occur in 75% aqueous dioxane. The intermediate in the second process is thus not a carbocation. It's nature is suggested by the fact that, in the absence of azide ions, the amount of inverted 2-octanol decreased with an increasing percentage of dioxane in the solvent. Thus the intermediate is an oxonium ion (**19**) formed by an S_N2 attack *by dioxane*. This ion is not a stable product but reacts with water in another S_N2 process to produce 2-octanol with retained configuration.



19

That part of the original reaction that resulted in retention of configuration[87] is thus seen to stem from two successive S_N2 reactions and not from any "borderline" behavior.[88]

SET MECHANISMS

In certain reactions where nucleophilic substitutions would seem obviously indicated, there is evidence that radicals and/or radical ions are actually involved.[89]

[87]According to this scheme, the configuration of the isolated RN_3 should be retained. It was, however, largely inverted, owing to a competing S_N2 reaction where N_3^- directly attacks ROBs.

[88]For other examples, see Streitwieser, Jr., A.; Walsh, T.D.; Wolfe, Jr., J.R. *J. Am. Chem. Soc.* ***1965***, *87*, 3682; Streitwieser, Jr., A.; Walsh, T.D. *J. Am. Chem. Soc.* ***1965***, *87*, 3686; Beronius, P.; Nilsson, A.; Holmgren, A. *Acta Chem. Scand.* ***1972***, *26*, 3173. See also, Knier, B.L.; Jencks, W.P. *J. Am. Chem. Soc.* ***1980***, *102*, 6789.

[89]Kornblum, N.; Michel, R.E.; Kerber, R.C. *J. Am. Chem. Soc.* ***1966***, *88*, 5660, 5662; Russell, G.A.; Danen, W.C. *J. Am. Chem. Soc.* ***1966***, *88*, 5663; Bank, S.; Noyd, D.A. *J. Am. Chem. Soc.* ***1973***, *95*, 8203; Ashby, E.C.; Goel, A.B.; Park, W.S. *Tetrahedron Lett.* ***1981***, *22*, 4209. For discussions of the relationship between S_N2 and SET mechanisms, see Lewis, E.S. *J. Am. Chem. Soc.* ***1989***, *111*, 7576; Shaik, S.S. *Acta Chem. Scand.* ***1990***, *44*, 205.

The first step in such a process is transfer of an electron from the nucleophile to the substrate to form a radical anion:

Step 1 $R{-}X + \overline{Y}^{-} \longrightarrow R{-}X^{\bullet -} + Y^{\bullet}$

Mechanisms that begin this way are called SET *(single electron transfer) mechanisms*.[90] Once formed, the radical ion cleaves:

Step 2 $R{-}X^{\bullet -} \longrightarrow R^{\bullet} + \overline{X}^{-}$

The radicals formed in this way can go on to product by reacting with the Y• produced in Step 1 or with the original nucleophilic ion Y^{-}, in which case an additional step is necessary:

Step 3 $R^{\bullet} + Y^{\bullet} \longrightarrow R{-}Y$

or

Step 3 $R^{\bullet} + \overline{Y}^{-} \longrightarrow R{-}Y^{\bullet -}$

Step 4 $R{-}Y^{\bullet -} + R{-}X \longrightarrow R{-}Y + R{-}X^{\bullet -}$

In the latter case, the radical ion $R{-}X^{\bullet -}$ is formed by Step 4 as well as by Step 1, so that a chain reaction (p. 936) can take place.

One type of evidence for an SET mechanism is the finding of some racemization. A totally free radical would of course result in a completely racemized product RY, but it has been suggested[91] that inversion can also take place in some SET processes. The suggestion is that in Step 1 the Y^{-} still approaches from the back side, even although an ordinary S_N2 mechanism will not follow, and that the radical R•, once formed, remains in a solvent cage with Y• still opposite X^{-}, so that Steps 1, 2, and 3 can lead to inversion.

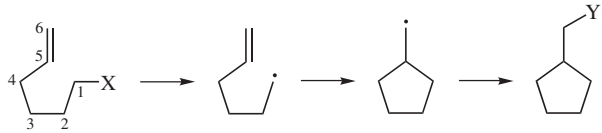
$$\overline{Y}^{-} + R{-}X \longrightarrow \underbrace{\left[Y^{\bullet}\ R{-}X^{\bullet -}\right]}_{\text{Solvent cage}} \longrightarrow \underbrace{\left[Y^{\bullet}\ R^{\bullet}\ X^{-}\right]}_{\text{Solvent cage}} \longrightarrow Y{-}R + \overline{X}^{-}$$

Reactions with SET mechanisms typically show predominant, although not 100%, inversion.

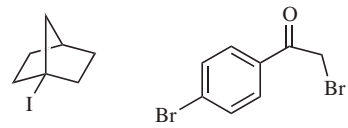
[90]For reviews, see Savéant, J. *Adv. Phys. Org. Chem.* ***1990***, *26*, 1; Rossi, R.A.; Pierini, A.B.; Palacios, S.M. *J. Chem. Educ.* ***1989***, *66*, 720; Ashby, E.C. *Acc. Chem. Res.* ***1988***, *21*, 414; Chanon, M.; Tobe, M.L. *Angew. Chem. Int. Ed.* ***1982***, *21*, 1. See also, Pross, A. *Acc. Chem. Res.* ***1985***, *18*, 212; Chanon, M. *Acc. Chem. Res.* ***1987***, *20*, 214. See Rossi, R.A.; Pierini, A.B.; Peñéñory, A.B. *Chem. Rev.* ***2003***, *103*, 71.

[91]Ashby, E.C.; Pham, T.N. *Tetrahedron Lett.* ***1987***, *28*, 3183; Daasbjerg, K.; Lund, T.; Lund, H. *Tetrahedron Lett.* ***1989***, *30*, 493.

Other evidence cited[92] for SET mechanisms has been detection of radical or radical ion intermediates by esr[93] or CIDNP; the finding that such reactions can take place at 1-norbornyl bridgeheads;[94] and the formation of cyclic side products when the substrate has a double bond in the 5,6 position (such substrates are called *radical probes*).



Free radicals with double bonds in this position are known to cyclize readily (p. 1011).[95]



20 **21**

The SET mechanism is chiefly found, where X = I or NO_2 (see **10-67**). A closely related mechanism, the $S_{RN}1$, takes place with aromatic substrates (Chapter 13).[96] In that mechanism, the initial attack is by an electron donor, rather than a nucleophile. The $S_{RN}1$ mechanism has also been invoked for reactions of enolate anions with 2-iodobicyclo[4.1.0]heptane.[97] An example is the reaction of 1-iodobicyclo[2.2.1]heptane (**20**) with $NaSnMe_3$ or $LiPPh_2$, and some other nucleophiles, to give the substitution product.[98] Another is the reaction of bromo 4-bromoacetophenone (**21**) with Bu_4NBr in cumene.[99] The two mechanisms, S_N2 versus SET, have been compared and contrasted.[100] There are also reactions where it is reported that radical, carbanion, and carbene pathways occur simultaneously.[101]

[92]See also, Chanon, M.; Tobe, M.L. *Angew. Chem. Int. Ed.* ***1982***, *21*, 1; Fuhlendorff, R.; Lund, T.; Lund, H.; Pedersen, J.A. *Tetrahedron Lett.* ***1987***, *28*, 5335.

[93]See, for example Russell, J.A.; Pecoraro, J.M. *J. Am. Chem. Soc.* ***1979***, *101*, 3331.

[94]Santiago, A.N.; Morris, D.G.; Rossi, R.A. *J. Chem. Soc., Chem. Commun.* ***1988***, 220.

[95]For criticisms of this method for demonstrating SET mechanisms, see Newcomb, M.; Kaplan, J. *Tetrahedron Lett.* ***1988***, *29*, 3449; Newcomb, M.; Curran, D.P. *Acc. Chem. Res.* ***1988***, *21*, 206; Newcomb, M. *Acta Chem. Scand.* ***1990***, *44*, 299. For replies to the criticism, see Ashby, E.C. *Acc. Chem. Res.* ***1988***, *21*, 414; Ashby, E.C.; Pham, T.N.; Amrollah-Madjdabadi, A.A. *J. Org. Chem.* ***1991***, *56*, 1596.

[96]In this book, we make the above distinction between the SET and $S_{RN}1$ mechanisms. However, many workers use the designation SET to refer to the $S_{RN}1$, the chain version of the SET, or both.

[97]Nazareno, M.A.; Rossi, R.A. *Tetrahedron* ***1994***, *50*, 9267; Nazareno, M.A.; Rossi, R.A. *J. Org. Chem.* ***1996***, *61*, 1645.

[98]Ashby, E.C.; Sun, X.; Duff, J.L. *J. Org. Chem.* ***1994***, *59*, 1270.

[99]Haberfield, P. *J. Am. Chem. Soc.* ***1995***, *117*, 3314.

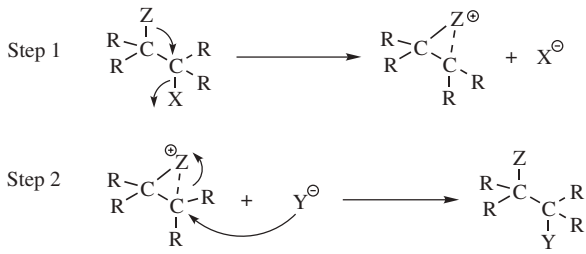
[100]Shaik, S.S. *Acta Chem. Scand.* ***1990***, *44*, 205.

[101]Ashby, E.C.; Park, B.; Patil, G.S.; Gadru, K.; Gurumurthy, R. *J. Org. Chem.* ***1993***, *58*, 424.

The mechanisms so far considered can, in theory at least, operate on any type of saturated (or for that matter unsaturated) substrate. There are other mechanisms that are more limited in scope.

The Neighboring-Group Mechanism[102]

It is occasionally found with certain substrates that (*1*) the rate of reaction is greater than expected, and (*2*) the configuration at a chiral carbon is *retained* and not inverted or racemized. In these cases, there is usually a group with an unshared pair of electrons β to the leaving group (or sometimes farther away). The mechanism operating in such cases is called the *neighboring-group mechanism* and consists essentially of two S_N2 substitutions, each causing an inversion so the net result is retention of configuration.[103] In the first step of this reaction, the neighboring group acts as a nucleophile, pushing out the leaving group but still retaining attachment to the molecule. In the second step, the external nucleophile displaces the neighboring group by a backside attack:



The reaction obviously must go faster than if Y were attacking directly, since if the latter process were faster, *it* would be happening. The neighboring group Z is said to be lending *anchimeric assistance*. The rate law followed in the neighboring-group mechanism is the first-order law shown in Eq. (10.2) or (10.3); that is, Y does not take part in the rate-determining step.

The reason attack by Z is faster than that by Y is that the group Z is more available. In order for Y to react, it must collide with the substrate, but Z is immediately available by virtue of its position. A reaction between the substrate and Y involves a large decrease in entropy of activation ($\Delta S^{\ddagger}$), since the reactants are far less free in the transition state than before. Reaction of Z involves a much smaller loss of $\Delta S^{\ddagger}$ (see p. 303).[104]

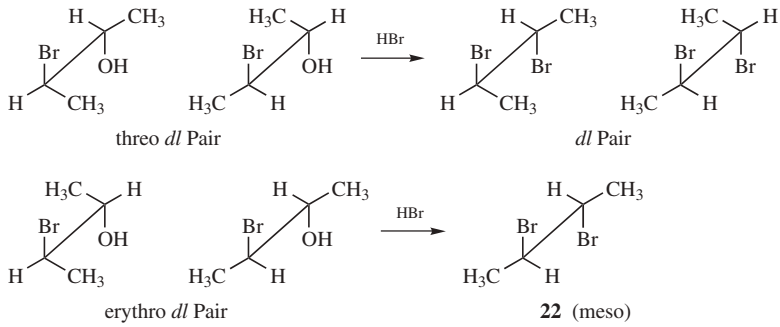
[102]For a monograph, see Capon, B.; McManus, S. *Neighboring Group Participation*, Vol. 1, Plenum, NY, ***1976***.

[103]There is evidence that this kind of process can happen intermolecularly (e.g., $RX + Z^- \rightarrow RZ + Y^-$). In this case Z^- acts as a catalyst for the reaction $RX + Y^- \rightarrow RY$: McCortney, B.A.; Jacobson, B.M.; Vreeke, M.; Lewis, E.S. *J. Am. Chem. Soc.* ***1990***, *112*, 3554.

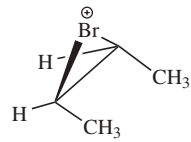
[104]For a review of the energetics of neighboring-group participation, see Page, M.I. *Chem. Soc. Rev.* ***1973***, *2*, 295.

It is not always easy to determine when a reaction rate has been increased by anchimeric assistance. In order to be certain, it is necessary to know what the rate would be without participation by the neighboring group. The obvious way to examine this question is to compare the rates of the reaction with and without the neighboring group, for example, $HOCH_2CH_2Br$ versus CH_3CH_2Br. However, this will certainly not give an accurate determination of the extent of participation, since the steric and field effects of H and OH are not the same. Furthermore, no matter what the solvent, the shell of solvent molecules that surrounds the polar protic OH group must differ greatly from that which surrounds the nonpolar H. Because of these considerations, it is desirable to have a large increase in the rate, preferably >50-fold, before a rate increase is attributed to neighboring-group participation.

The first important evidence for the existence of this mechanism was the demonstration that retention of configuration can occur if the substrate is suitable. It was shown that the threo *dl* pair of 3-bromo-2-butanol when treated with HBr gave *dl*-2,3-dibromobutane, while the erythro pair gave the meso isomer (**22**).[105]



This indicated that retention had taken place. Note that both products are optically inactive and so cannot be told apart by differences in rotation. The meso and *dl* dibromides have different boiling points and indexes of refraction and were identified by these properties. Even more convincing evidence was that either of the two threo isomers alone gave not just one of the enantiomeric dibromides, but the *dl* pair. The reason for this is that the intermediate present after the attack by the neighboring group (**23**) is symmetrical, so the external nucleophile Br^- can attack

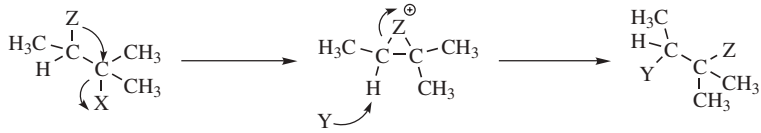


23

both carbon atoms equally well. Intermediate **23** is a bromonium ion, the existence of which has been demonstrated in several types of reactions.

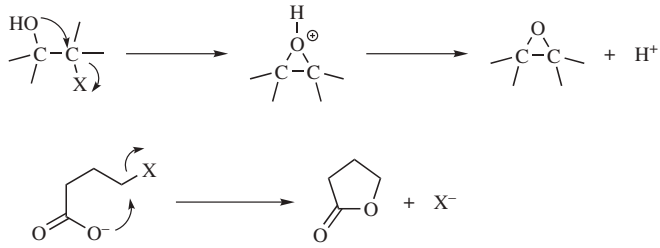
[105]Winstein, S.; Lucas, H.J. *J. Am. Chem. Soc.* ***1939***, *61*, 1576, 2845.

Although **23** is symmetrical, intermediates in most neighboring-group mechanisms are not, and it is therefore possible to get not a simple substitution product but a rearrangement. This will happen if Y attacks not the carbon atom from which X left, but the one to which Z was originally attached:

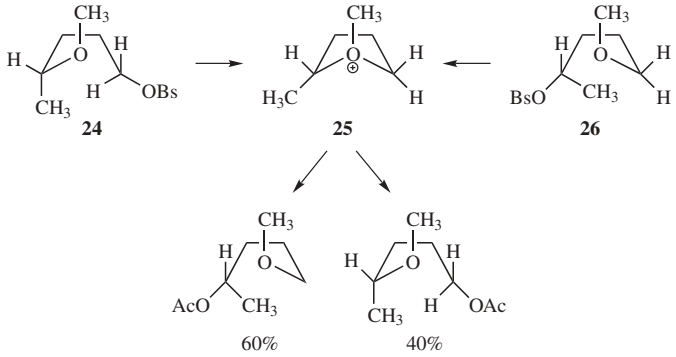


In such cases, substitution and rearrangement products are often produced together. For a discussion of rearrangements, see Chapter 18.

Another possibility is that the intermediate may be stable or may find some other way to stabilize itself. In such cases, Y never attacks at all and the product is cyclic. These are simple internal S_N2 reactions. Two examples are formation of epoxides and lactones:



The fact that acetolysis of both 4-methoxy-1-pentyl brosylate (**24**) and 5-methoxy-2-pentyl brosylate (**25**) gave the same mixture of products is further evidence for participation by a neighboring group.[106] In this case, the intermediate **26** is common to both substrates.

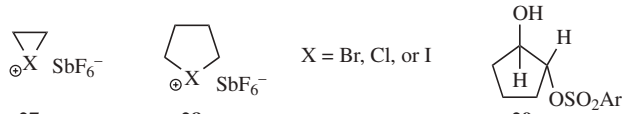


The neighboring-group mechanism operates only when the ring size is right for a particular type of Z. For example, for $MeO(CH_2)_nOBs$, neighboring-group

[106]Allred, E.L.; Winstein, S. *J. Am. Chem. Soc.* ***1967***, *89*, 3991, 3998.

participation was important for $n = 4$ or 5 (corresponding to a five- or six-membered intermediate), but not for $n = 2$, 3, or 6.[107] However, optimum ring size is not the same for all reactions, even with a particular Z. In general, the most rapid reactions occur when the ring size is three, five, or six, depending on the reaction type. The likelihood of four-membered ring neighboring-group participation is increased when there are alkyl groups a or β to the neighboring group.[108]

The following are some of the more important neighboring groups: COO^- (but not COOH), COOR, COAr, OCOR,[109] OR, OH, O^-,[110] NH_2, NHR, NR_2, NHCOR, SH, SR, S^-,[111] SO_2Ph,[112] I, Br, and Cl. The effectiveness of halogens as neighboring groups decreases in the order I > Br > Cl.[113] The Cl is a very weak neighboring group and can be shown to act in this way only when the solvent does not interfere. For example, when 5-chloro-2-hexyl tosylate is solvolyzed in acetic acid, there is little participation by the Cl, but when the solvent is changed to trifluoroacetic acid, which is much less nucleophilic, neighboring-group participation by the Cl becomes the major reaction pathway.[114] Thus, Cl acts as a neighboring group *only when there is need for it* (for other examples of the *principle of increasing electron demand*, see below; p. 454).



27 **28** **29**

A number of intermediates of halogen participation (halonium ions),[115] for example, **27** and **28**, have been prepared as stable salts in SbF_5-SO_2 or SbF_5-SO_2ClF solutions.[116] Some have even been crystallized. Attempts to prepare

[107]Allred, E.L.; Winstein, S. *J. Am. Chem. Soc.* ***1967***, *89*, 4012.

[108]Eliel, E.L.; Clawson, L.; Knox, D.E. *J. Org. Chem.* ***1985***, *50*, 2707; Eliel, E.L.; Knox, D.E. *J. Am. Chem. Soc.* ***1985***, *107*, 2946.

[109]For an example of OCOR as a neighboring group where the ring size is seven membered, see Wilen, S.H.; Delguzzo, L.; Saferstein, R. *Tetrahedron* ***1987***, *43*, 5089.

[110]For a review of oxygen functions as neighboring groups, see Perst, H. *Oxonium Ions in Organic Chemistry*; Verlag Chemie, Deerfield Beach, FL, ***1971***, pp. 100–127. There is evidence that the oxygen in an epoxy group can also act as a neighboring group: Francl, M.M.; Hansell, G.; Patel, B.P.; Swindell, C.S. *J. Am. Chem. Soc.* ***1990***, *112*, 3535.

[111]For a review of sulfur-containing neighboring groups, see Block, E. *Reactions of Organosulfur Compounds*, Academic Press, NY, ***1978***, pp. 141–145.

[112]Lambert, J.B.; Beadle, B.M.; Kuang, K. *J. Org. Chem.* ***1999***, *64*, 9241.

[113]Peterson, P.E. *Acc. Chem. Res.* ***1971***, *4*, 407, and references cited therein.

[114]Peterson, P.E.; Bopp, R.J.; Chevli, D.M.; Curran, E.L.; Dillard, D.E.; Kamat, R.J. *J. Am. Chem. Soc.* ***1967***, *89*, 5902. See also, Reich, I.L.; Reich, H.J. *J. Am. Chem. Soc.* ***1974***, *96*, 2654.

[115]For a monograph, see Olah, G.A. *Halonium Ions*, Wiley, NY, ***1975***. For a review, see Koster, G.F., in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups*, *Supplement D*, pt. 2, Wiley, NY, ***1983***, pp. 1265–1351.

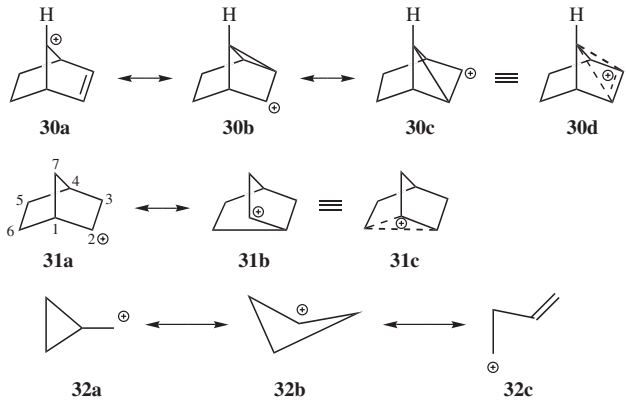
[116]See, for example Olah, G.A.; Peterson, P.E. *J. Am. Chem. Soc.* ***1968***, *90*, 4675; Henrichs, P.M.; Peterson, P.E. *J. Am. Chem. Soc.* ***1973***, *95*, 7449, *J. Org. Chem.* ***1976***, *41*, 362; Olah, G.A.; Liang, G.; Staral, J. *J. Am. Chem. Soc.* ***1974***, *96*, 8112; Vančik, H.; Percač, K.; Sunko, D.E. *J. Chem. Soc., Chem. Commun.* ***1991***, 807.

four-membered homologs of **27** and **28** were not successful.[117] There is no evidence that F can act as a neighboring group.[113]

The principle that a neighboring group lends assistance in proportion to the need for such assistance also applies to differences in leaving-group ability. Thus, *p*-$NO_2C_6H_4SO_2O$ (the nosylate group) is a better leaving group than *p*-$MeC_6H_4SO_2O$ (the tosylate group). Experiments have shown that the OH group in *trans*-2-hydroxycyclopentyl arenesulfonates **29** acts as a neighboring group when the leaving group is tosylate but not when it is nosylate, apparently because the nosylate group leaves so rapidly that it does not require assistance.[118]

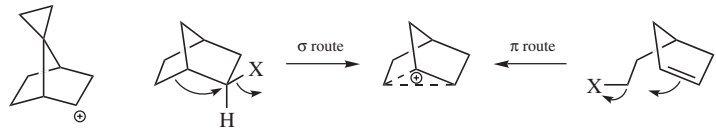
Neighboring-Group Participation by π and σ Bonds: Nonclassical Carbocations[119]

For all the neighboring groups listed in the preceding section, the nucleophilic attack is made by an atom with an unshared pair of electrons. In this section, we consider neighboring-group participation by C=C π bonds and C–C and C–H σ bonds. There has been a great deal of controversy over whether such bonds can act as neighboring groups and about the existence and structure of the intermediates involved. These intermediates are called *nonclassical* (or *bridged*) carbocations. In classical carbocations (Chapter 5) the positive charge is localized on one carbon atom or delocalized by resonance involving an unshared pair of electrons or a double or triple bond in the allylic position. In a nonclassical carbocation, the positive charge is delocalized by a double or triple bond that is not in the allylic position or by a single bond. Examples are the 7-norbornenyl cation (**30**), the norbornyl cation



[117]Olah, G.A.; Bollinger, J.M.; Mo, Y.K.; Brinich, J.M. *J. Am. Chem. Soc.* ***1972***, *94*, 1164.
[118]Haupt, F.C.; Smith, M.R. *Tetrahedron Lett.* ***1974***, 4141.
[119]For monographs, see Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 3, Wiley, NY, ***1972***; Bartlett, P.D. *Nonclassical Ions*, W.A. Benjamin, NY, ***1965***. For reviews, see Barkhash, V.A. *Top. Curr. Chem.* ***1984***, *116/117*, 1; Kirmse, W. *Top. Curr. Chem.* ***1979***, *80*, 125, pp. 196–288; McManus, S.P.; Pittman, Jr., C.U., in McManus, S.P. *Organic Reactive Intermediates*, Academic Press, NY, ***1973***, pp. 302–321; Bethell, D.; Gold, V. *Carbonium Ions*, Academic Press, NY, ***1967***; pp. 222–282. For a related review, see Prakash, G.K.S.; Iyer, P.S. *Rev. Chem. Intermed.* ***1988***, *9*, 65.

(**31**),[120] and the cyclopropylmethyl cation (**32**). A cyclopropyl group (as in **33**) is capable of stabilizing the norbornyl cation, inhibiting this rearrangement.[121] Carbocation **30** is called a *homoallylic* carbocation, because in **30a** there is one carbon atom between the positively charged carbon and the double bond. Many of these carbocations can be produced in more than one way if the proper substrates are chosen. For example, **31** can be generated by the departure of a leaving group from



33 **34** **31** **35**

34 or from **35**.[122] The first of these pathways is called the σ route to a nonclassical carbocation, because participation of a σ bond is involved. The second is called the π route.[123] The argument against the existence of nonclassical carbocations is essentially that the structures **30a–c** (or **31a**, **31b**, etc.) are not canonical forms but real structures and that there is rapid equilibration among them. This debate remains an active area of interest for some reactions.[124] In one study, the solvolysis and rearrangement of 2-bicyclo[3.2.2]nonanyl tosylate in methanol generated ethers derived from the 2-bicyclo[3.2.2]nonanyl and 2-bicyclo[3.3.1]nonanyl systems that were rationalized in terms of a classical carbocation.[125] Density functional and *ab initio* calculations indicated that the products of the 2-bicyclo[3.2.2]nonanyl tosylate solvolysis were found to have nonclassical structures.[126]

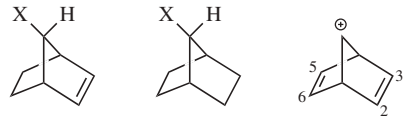
In discussing nonclassical carbocations, we must be careful to make the distinction between neighboring-group participation and the existence of nonclassical carbocations.[127] If a nonclassical carbocation exists in any reaction, then an ion with electron delocalization, as shown in the above examples, is a discrete reaction intermediate. If a carbon–carbon double or single bond participates in the departure of the leaving group to form a carbocation, it may be that a nonclassical carbocation is involved, but there is no necessary relation. In any particular case either or both of these possibilities can be taking place.

In the following pages, we consider some of the evidence bearing on the questions of the participation of π and s bonds and on the existence of nonclassical

[120]Sieber, S.; Schleyer, P.v.R.; Vančik, H.; Mesić, M.; Sunko, D.E. *Angew. Chem. Int. Ed.* ***1993***, *32*, 1604; Schleyer, P.v.R.; Sieber, S. *Angew. Chem. Int. Ed.* ***1993***, *32*, 1606.
[121]Herrmann, R.; Kirmse, W. *Liebigs Ann. Chem.* ***1995***, 703.
[122]Lawton, R.G. *J. Am. Chem. Soc.* ***1961***, *83*, 2399; Bartlett, P.D.; Bank, S.; Crawford, R.J.; Schmid, G.H. *J. Am. Chem. Soc.* ***1965***, *88*, 1288.
[123]Winstein, S.; Carter, P. *J. Am. Chem. Soc.* ***1961***, *83*, 4485.
[124]For example see Brunelle, P.; Sorensen, T.S.; Taeschler, C. *J. Org. Chem.* ***2001***, *66*, 7294.
[125]Okazaki, T.; Terakawa, E.; Kitagawa, T.; Takeuchi, K. *J. Org. Chem.* ***2000***, *65*, 1680.
[126]Smith, W. B. *J. Org. Chem.* ***2001***, *66*, 376.
[127]This was pointed out by Cram, D.J. *J. Am. Chem. Soc.* ***1964***, *86*, 3767.

carbocations,[128] although a thorough discussion is beyond the scope of this book.[89]

1. C=C *as a Neighboring Group*.[129] The most striking evidence that C=C can act as a neighboring group is that acetolysis of **36**-OTs is 10^{11} times faster than that of **37**-OTs and *proceeds with retention of configuration*.[130] The rate data alone do not necessarily prove that acetolysis of **36**-OTs involves a



36 **37** **38**

nonclassical intermediate (**30d**), but it is certainly strong evidence that the C=C group assists in the departure of the OTs. Evidence that **30** is indeed a nonclassical ion comes from an NMR study of the relatively stable norbornadienyl cation (**38**). The spectrum shows that the 2 and 3 protons are not equivalent to the 5 and 6 protons.[131] Thus there is interaction between the charged carbon and one double bond, which is evidence for the existence of **30d**.[132] In the case of **36**, the double bond is geometrically fixed in an especially favorable position for backside attack on the carbon bearing the leaving group (hence the very large rate enhancement), but there is much evidence that other double bonds in the homoallylic position,[133] as well as in

[128]The arguments against nonclassical ions are summed up in Brown, H.C. *The Nonclassical Ion Problem*; Plenum, NY, ***1977***. This book also includes rebuttals by Schleyer, P.v.R. See also, Brown, H.C. *Pure Appl. Chem.* ***1982***, *54*, 1783.

[129]For reviews, see Story, P.R.; Clark, Jr., B.C., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 3, Wiley, NY, ***1972***, pp. 1007–1060; Richey, Jr., H.G., in Zabicky, J. *The Chemistry of Alkenes*, Vol. 2; Wiley, NY, ***1970***, pp. 77–101.

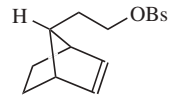
[130]Winstein, S.; Shatavsky, M. *J. Am. Chem. Soc.* ***1956***, *78*, 592.

[131]Story, P.R.; Snyder, L.C.; Douglass, D.C.; Anderson, E.W.; Kornegay, R.L. *J. Am. Chem. Soc.* ***1963***, *85*, 3630. For a discussion, see Story, P.R.; Clark, Jr., B.C., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 3, Wiley, NY, ***1972***, pp. 1026–1041. See also, Lustgarten, R.K.; Brookhart, M.; Winstein, S. *J. Am. Chem. Soc.* ***1972***, *94*, 2347.

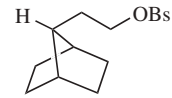
[132]For further evidence for the nonclassical nature of **30**, see Brookhart, M.; Diaz, A.; Winstein, S. *J. Am. Chem. Soc.* ***1966***, *88*, 3135; Richey, Jr., H.G.; Lustgarten, R.K. *J. Am. Chem. Soc.* ***1966***, *88*, 3136; Gassman, P.G.; Doherty, M.M. *J. Am. Chem. Soc.* ***1982***, *104*, 3742 and references cited therein; Laube, T. *J. Am. Chem. Soc.* ***1989***, *111*, 9224.

[133]For examples, see Shoppee, C.W. *J. Chem. Soc.* ***1946***, 1147; LeBel, N.A.; Huber, J.E. *J. Am. Chem. Soc.* ***1963***, *85*, 3193; Closson, W.D.; Kwiatkowski, G.T. *Tetrahedron* ***1965***, *21*, 2779; Brown, H.C.; Peters, E.N.; Ravindranathan, M. *J. Am. Chem. Soc.* ***1975***, *97*, 7449; Schleyer, P.v.R.; Bentley, T.W.; Koch, W.; Kos, A.J.; Schwarz, H. *J. Am. Chem. Soc.* ***1987***, *109*, 6953; Fernández-Mateos, A.; Rentzsch, M.; Sánchez, L.R.; González, R.R. *Tetrahedron* ***2001***, *57*, 4873.

positions farther away,[134] can also lend anchimeric assistance, although generally with much lower rate ratios. One example of the latter is the compound β-(*syn*-7-norbornenyl)ethyl brosylate (**39**), which at 25°C undergoes acetolysis ~140,000 times faster than the saturated analog **40**.[135] Triple bonds[136] and allenes[137] can also act as neighboring groups.

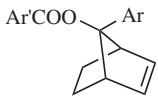


39



40

We have already seen evidence that participation by a potential neighboring group can be reduced or eliminated if an outside nucleophile is present that is more effective than the neighboring group in attacking the central carbon (p. 450), or if a sufficiently good leaving group is present (p. 450). In another example of the principle of increasing electron demand, Gassman and co-workers have shown that neighboring-group participation can also be reduced if the stability of the potential carbocation is increased. They found that the presence of a *p*-anisyl group at the 7 position of **36** and **37** exerts a powerful leveling effect on the rate differences. Thus, solvolysis in acetone–water at 85°C of **38** was only ~2.5 times faster than that of the saturated



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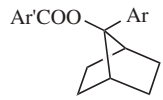
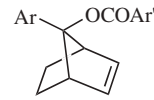


42



43

Ar = *p*-$MeOC_6H_4$
Ar' = *p*-$NO_2C_6H_4$

compound **42**.[138] Furthermore, both **41** and its stereoisomer **43** gave the same mixture of solvolysis products, showing that the stereoselectivity in the solvolysis of **36** is not present here. The difference between **41** and **36** is that in the case of **41** the positive charge generated at the 7 position in the transition state is greatly stabilized by the *p*-anisyl group. Apparently, the stabilization by the *p*-anisyl group is so great that further stabilization that would come from

[134]For examples, see LeNy, G. *C. R. Acad. Sci.* ***1960***, *251*, 1526; Goering, H.L.; Closson, W.D. *J. Am. Chem. Soc.* ***1961***, *83*, 3511; Bartlett, P.D.; Trahanovsky, W.S.; Bolon, D.A.; Schmid, G.H. *J. Am. Chem. Soc.* ***1965***, *87*, 1314; Bly, R.S.; Swindell, R.T. *J. Org. Chem.* ***1965***, *30*, 10; Marvell, E.N.; Sturmer, D.; Knutson, R.S. *J. Org. Chem.* ***1968***, *33*, 2991; Cogdell, T.J. *J. Org. Chem.* ***1972***, *37*, 2541; Ferber, P.H.; Gream, G.E. *Aust. J. Chem.* ***1981***, *34*, 1051; Orlović, M.; Borčić, S.; Humski, K.; Kronja, O.; Imper, V.; Polla, E.; Shiner, Jr., V.J. *J. Org. Chem.* ***1991***, *56*, 1874; Winstein, S.; Carter, P. *J. Am. Chem. Soc.* ***1961***, *83*, 4485.

[135]Bly, R.S.; Bly, R.K.; Bedenbaugh, A.O.; Vail, O.R. *J. Am. Chem. Soc.* ***1967***, *89*, 880.

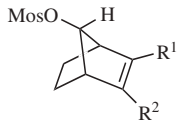
[136]See, for example, Closson, W.D.; Roman, S.A. *Tetrahedron Lett.* ***1966***, 6015; Hanack, M.; Herterich, I.; Vött, V. *Tetrahedron Lett.* ***1967***, 3871; Lambert, J.B.; Papay, J.J.; Mark, H.W. *J. Org. Chem.* ***1975***, *40*, 633; Peterson, P.E.; Vidrine, D.W. *J. Org. Chem.* ***1979***, *44*, 891. For a review of participation by triple bonds and allylic groups, see Rappoport, Z. *React. Intermed. (Plenum)* ***1983***, *3*, 440.

[137]Bly, R.S.; Koock, S.U. *J. Am. Chem. Soc.* ***1969***, *91*, 3292, 3299; Von Lehman, T.; Macomber, R. *J. Am. Chem. Soc.* ***1975***, *97*, 1531.

[138]Gassman, P.G.; Zeller, J.; Lamb, J.T. *Chem. Commun.* ***1968***, 69.

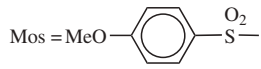
participation by the C=C bond is not needed.[139] The use of a phenyl instead of a *p*-anisyl group is not sufficient to stop participation by the double bond completely, although it does reduce it.[140] These results permit us to emphasize our previous conclusion that *a neighboring group lends anchimeric assistance only when there is sufficient demand for it*.[141] The π-bond of a neighboring alkene group can assist solvolysis via π-participation.[142]

The ability of C=C to serve as a neighboring group can depend on its electron density. When the strongly electron-withdrawing CF_3 group was attached to a double bond carbon of **44**, the solvolysis rate was lowered by a factor of about 10^6.[143]



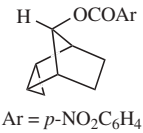
44

Relative Rates	
$R^1 = R^2 = H$	1.4×10^{12}
$R^1 = H$, $R^2 = CF_3$	1.5×10^6
$R^1 = R^2 = CF_3$	1



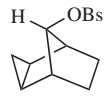
A second CF_3 group had an equally strong effect. In this case, two CF_3 groups decrease the electron density of the C=C bond to the point that the solvolysis rate for **44** ($R^1 = R^2 = CF_3$) was about the same as (actually ~17 times slower than) the rate for the saturated substrate **37** (X = OMos). Thus, the two CF_3 groups completely remove the ability of the C=C bond to act as a neighboring group.

2. *Cyclopropyl*[144] *as a Neighboring Group*.[145] On p. 217 we saw that the properties of a cyclopropane ring are in some ways similar to those of a double bond. Therefore it is not surprising that a suitably placed cyclopropyl ring can

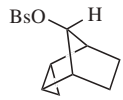


Ar = *p*-$NO_2C_6H_4$

45



46



47

[139]Nevertheless, there is evidence from ^{13}C NMR spectra that some π participation is present, even in the cation derived from **38:** Olah, G.A.; Berrier, A.L.; Arvanaghi, M.; Prakash, G.K.S. *J. Am. Chem. Soc.* ***1981***, *103*, 1122.

[140]Gassman, P.G.; Fentiman, Jr., A.F. *J. Am. Chem. Soc.* ***1969***, *91*, 1545; ***1970***, *92*, 2549.

[141]For a discussion of the use of the tool of increasing electron demand to probe neighboring-group activity by double bonds, sigma bonds, and aryl rings, see Lambert, J.B.; Mark, H.W.; Holcomb, A.G.; Magyar, E.S. *Acc. Chem. Res.* ***1979***, *12*, 317.

[142]Malnar, I.; Jurić, S.; Vrček, V.; Gjuranovič, Ž.; Mihalič, Z.; Kronja, O. *J. Org. Chem.* ***2002***, *67*, 1490.

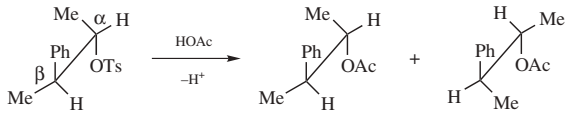
[143]Gassman, P.G.; Hall, J.B. *J. Am. Chem. Soc.* ***1984***, *106*, 4267.

[144]In this section, we consider systems in which at least one carbon separates the cyclopropyl ring from the carbon bearing the leaving group. For a discussion of systems in which the cyclopropyl group is directly attached to the leaving-group carbon, see p. $$$.

[145]For a review, see Haywood-Farmer, J. *Chem. Rev.* ***1974***, *74*, 315.

also be a neighboring group. Thus *endo-anti*-tricyclo[3.2.1.$0^{2,4}$]octan-8-yl *p*-nitrobenzoate (**45**) solvolyzed $\sim 10^{14}$ times faster that the *p*-nitrobenzoate of **37**-OH.[146] Obviously, a suitably placed cyclopropyl ring can be even more effective[147] as a neighboring group than a double bond.[148] The need for suitable placement is emphasized by the fact that **47** solvolyzed only about five times faster than **37**-OBs,[149] while **46** solvolyzed three times *slower* than **37**-OBs.[150] In the case of **45** and of all other cases known where cyclopropyl lends considerable anchimeric assistance, the developing *p* orbital of the carbocation is orthogonal to the participating bond of the cyclopropane ring.[151] An experiment designed to test whether a developing *p* orbital that would be parallel to the participating bond would be assisted by that bond showed no rate enhancement.[151] This is in contrast to the behavior of cyclopropane rings directly attached to positively charged carbons, where the *p* orbital is parallel to the plane of the ring (pp. 241, 464). Rate enhancements, although considerably smaller, have also been reported for suitably placed cyclobutyl rings.[152]

3. *Aromatic Rings as Neighboring Groups*.[153] There is a great deal of evidence that aromatic rings in the β position can function as neighboring



48 **49** **50**

[146]Tanida, H.; Tsuji, T.; Irie, T. *J. Am. Chem. Soc.* ***1967***, *89*, 1953; Battiste, M.A.; Deyrup, C.L.; Pincock, R.E.; Haywood-Farmer, J. *J. Am. Chem. Soc.* ***1967***, *89*, 1954.

[147]For a competitive study of cyclopropyl versus double-bond participation, see Lambert, J.B.; Jovanovich, A.P.; Hamersma, J.W.; Koeng, F.R.; Oliver, S.S. *J. Am. Chem. Soc.* ***1973***, *95*, 1570.

[148]For other evidence for anchimeric assistance by cyclopropyl, see Sargent, G.D.; Lowry, N.; Reich, S.D. *J. Am. Chem. Soc.* ***1967***, *89*, 5985; Battiste, M.A.; Haywood-Farmer, J.; Malkus, H.; Seidl, P.; Winstein, S. *J. Am. Chem. Soc.* ***1970***, *92*, 2144; Coates, R.M.; Yano, K. *Tetrahedron Lett.* ***1972***, 2289; Masamune, S.; Vukov, R.; Bennett, M.J.; Purdham, J.T. *J. Am. Chem. Soc.* ***1972***, *94*, 8239; Gassman, P.G.; Creary, X. *J. Am. Chem. Soc.* ***1973***, *95*, 2729; Costanza, A.; Geneste, P.; Lamaty, G.; Roque, J. *Bull. Soc. Chim. Fr.* ***1975***, 2358; Takakis, I.M.; Rhodes, Y.E. *Tetrahedron Lett.* ***1983***, *24*, 4959.

[149]Battiste, M.A.; Deyrup, C.L.; Pincock, R.E.; Haywood-Farmer, J. *J. Am. Chem. Soc.* ***1967***, *89*, 1954; Haywood-Farmer, J.; Pincock, R.E. *J. Am. Chem. Soc.* ***1969***, *91*, 3020; Haywood-Farmer, J. *Chem. Rev.* ***1974***, *74*, 315; Haywood-Farmer, J. *Chem. Rev.* ***1974***, *74*, 315.

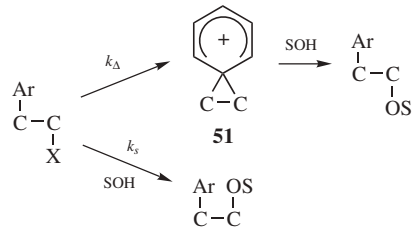
[150]Haywood-Farmer, J.; Pincock, R.E.; Wells, J.I. *Tetrahedron* ***1966***, *22*, 2007; Haywood-Farmer, J.; Pincock, R.E. *J. Am. Chem. Soc.* ***1969***, *91*, 3020. For some other cases where there was little or no rate enhancement by cyclopropyl, see Wiberg, K.B.; Wenzinger, G.R. *J. Org. Chem.* ***1965***, *30*, 2278; Sargent, G.D.; Taylor, R.L.; Demisch, W.H. *Tetrahedron Lett.* ***1968***, 2275; Rhodes, Y.E.; Takino, T. *J. Am. Chem. Soc.* ***1970***, *92*, 4469; Hanack, M.; Krause, P. *Liebigs Ann. Chem.* ***1972***, *760*, 17.

[151]Gassman, P.G.; Seter, J.; Williams, F.J. *J. Am. Chem. Soc.* ***1971***, *93*, 1673. For a discussion, see Haywood-Farmer, J.; Pincock, R.E. *J. Am. Chem. Soc.* ***1969***, *91*, 3020. See also, Chenier, P.J.; Jenson, T.M.; Wulff, W.D. *J. Org. Chem.* ***1982***, *47*, 770.

[152]For example, see Sakai, M.; Diaz, A.; Winstein, S. *J. Am. Chem. Soc.* ***1970***, *92*, 4452; Battiste, M.A.; Nebzydoski, J.W. *J. Am. Chem. Soc.* ***1970***, *92*, 4450; Schipper, P.; Driessen, P.B.J.; de Haan, J.W.; Buck, H.M. *J. Am. Chem. Soc.* ***1974***, *96*, 4706; Ohkata, K.; Doecke, C.W.; Klein, G.; Paquette, L.A. *Tetrahedron Lett.* ***1980***, *21*, 3253.

[153]For a review, see Lancelot, L.A.; Cram, D.J.; Schleyer, P.v.R., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 3; Wiley, NY, ***1972***, pp. 1347–1483.

groups.[154] Stereochemical evidence was obtained by solvolysis of L-*threo*-3-phenyl-2-butyl tosylate (**48**) in acetic acid.[155] Of the acetate product 96% was the threo isomer and only about 4% was erythro. Moreover, both the (+) and (−) threo isomers (**49** and **50**) were produced in approximately equal amounts (a racemic mixture). When solvolysis was conducted in formic acid, even less erythro isomer was obtained. This result is similar to that found on reaction of 3-bromo-2-butanol with HBr (p. 446) and leads to the conclusion that configuration is retained because phenyl acts as a neighboring group. However, evidence from rate studies is not so simple. If β-aryl groups assist the departure of the leaving group, solvolysis rates should be enhanced. In general, they are not. However, solvolysis rate studies in 2-arylethyl systems are complicated by the fact that, for primary and secondary systems, two pathways can exist.[156] In one of these (designated k_Δ), the aryl, behaving as a neighboring group, pushes out the leaving group to give a bridged ion, called a *phenonium ion* (**51**), and is in turn pushed out by the solvent SOH, so



the net result is substitution with retention of configuration (or rearrangement, if **51** is opened from the other side). The other pathway (k_s) is simple S_N2 attack by the solvent at the leaving-group carbon. The net result here is substitution with inversion and no possibility of rearrangement. Whether the leaving group is located at a primary or a secondary carbon, there is no cross-over between these pathways; they are completely independent.[157] (Both the k_Δ and k_s pathways are unimportant when the leaving group is at a tertiary carbon.) In these cases, the mechanism is S_N1 and open carbocations $ArCH_2CR_2^+$ are intermediates. This pathway is designated k_c. Which of the two pathways (k_s or k_Δ) predominates in any given case depends on the solvent and on the nature of the aryl group. As expected from the results we have seen for Cl as a neighboring group (p. 450), the k_Δ/k_s ratio is highest for solvents that are poor nucleophiles and so compete very poorly with the aryl

[154]Kevill, D.N.; D'Souza, M.J. *J. Chem. Soc. Perkin Trans. 2* ***1997***, 257; Fujio, M.; Goto, N.; Dairokuno, T.; Goto, M.; Saeki, Y.; Okusako, Y.; Tsuno, Y. *Bull. Chem. Soc. Jpn.* ***1992***, *65*, 3072.
[155]Cram, D.J. *J. Am. Chem. Soc.* ***1949***, *71*, 3863; ***1952***, *74*, 2129.
[156]Brookhart, M.; Anet, F.A.L.; Cram, D.J.; Winstein, S. *J. Am. Chem. Soc.* ***1966***, *88*, 5659; Lee, C.C.; Unger, D.; Vassie, S. *Can. J. Chem.* ***1972***, *50*, 1371.
[157]Brown, H.C.; Kim, C.J.; Lancelot, C.J.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1970***, *92*, 5244; Brown, H.C.; Kim, C.J. *J. Am. Chem. Soc.* ***1971***, *93*, 5765.

group. For several common solvents the k_Δ/k_s ratio increases in the order $EtOH < CH_3COOH < HCOOH < CF_3COOH$.[158] In accord with this, the following percentages of retention were obtained in solvolysis of 1-phenyl-2-propyl tosylate at 50°C: solvolysis in EtOH 7%, CH_3COOH 35%, HCOOH 85%.[158] This indicates that k_s predominates in EtOH (phenyl participates very little), while k_Δ predominates in HCOOH. Trifluoroacetic acid is a solvent of particularly low nucleophilic power, and in this solvent the reaction proceeds entirely by k_Δ;[159] deuterium labeling showed 100% retention.[160] This case provides a clear example of neighboring-group rate enhancement by phenyl: The rate of solvolysis of $PhCH_2CH_2OTs$ at 75°C in CF_3COOH is 3040 times the rate for CH_3CH_2OTs.[159]

With respect to the aromatic ring, the k_Δ pathway is electrophilic aromatic substitution (Chapter 11). We predict that groups on the ring that activate that reaction (p. 665) will increase, and deactivating groups will decrease, the rate of this pathway. This prediction has been borne out by several investigations. The *p*-nitro derivative of **48** solvolyzed in acetic acid 190 times slower than **48**, and there was much less retention of configuration; the acetate produced was only 7% threo and 93% erythro.[161] At 90°C, acetolysis of $p\text{-}ZC_6H_4CH_2CH_2OTs$ gave the rate ratios shown in Table 10.1.[162] Throughout this series k_s is fairly constant, as it should be since it is affected only by the rather remote field effect of Z. It is k_Δ that changes substantially as Z is changed from activating to deactivating. The evidence is thus fairly clear that participation by aryl groups depends greatly on the nature of the group. For some groups (e.g., *p*-nitrophenyl), in some solvents (e.g., acetic acid), there is essentially no neighboring-group participation at all,[163] while for others (e.g., *p*-methoxyphenyl), neighboring-group participation is substantial. The combined effect of solvent and structure is shown in Table 10.2, where the figures shown were derived by three different methods.[164] The decrease in neighboring-group effectiveness when aromatic rings are substituted by electron-withdrawing groups is reminiscent of the similar case of C=C bonds substituted by CF_3 groups (p. 454).

[158]Diaz, A.; Winstein, S. *J. Am. Chem. Soc.* ***1969***, *91*, 4300. See also, Schadt, F.L.; Lancelot, C.J.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1978***, *100*, 228.

[159]Nordlander, J.E.; Kelly, W.J. *J. Am. Chem. Soc.* ***1969***, *91*, 996.

[160]Jablonski, R.J.; Snyder, E.I. *J. Am. Chem. Soc.* ***1969***, *91*, 4445.

[161]Thompson, J.A.; Cram, D.J. *J. Am. Chem. Soc.* ***1969***, *91*, 1778. See also, Tanida, H.; Tsuji, T.; Ishitobi, H.; Irie, T. *J. Org. Chem.* ***1969***, *34*, 1086; Kingsbury, C.A.; Best, D.C. *Bull. Chem. Soc. Jpn.* ***1972***, *45*, 3440.

[162]Coke, J.L.; McFarlane, F.E.; Mourning, M.C.; Jones, M.G. *J. Am. Chem. Soc.* ***1969***, *91*, 1154; Jones, M.G.; Coke, J.L. *J. Am. Chem. Soc.* ***1969***, *91*, 4284. See also, Harris, J.M.; Schadt, F.L.; Schleyer, P.v.R.; Lancelot, C.J. *J. Am. Chem. Soc.* ***1969***, *91*, 7508.

[163]The k_Δ pathway is important for *p*-nitrophenyl in CF_3COOH: Ando, T.; Shimizu, N.; Kim, S.; Tsuno, Y.; Yukawa, Y. *Tetrahedron Lett.* ***1973***, 117.

[164]Lancelot, C.J.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1969***, *91*, 4291, 4296; Lancelot, C.J.; Harper, J.J.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1969***, *91*, 4294; Schleyer, P.v.R.; Lancelot, C.J. *J. Am. Chem. Soc.* ***1969***, *91*, 4297.

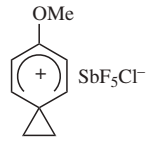
TABLE 10.1. Approximate k_Δ/k_s Ratios for Acetolysis of p-$ZC_6H_4CH_2CH_2OTs$ at 90°C[162]

Z	k_Δ/k_s
MeO	30
Me	11
H	1.3
Cl	0.3

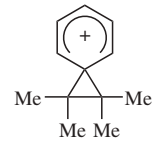
TABLE 10.2. Percent of Product Formed by the k_Δ Pathway in Solvolysis of p-$ZC_6H_4CH_2CH_2OTs$[164]

Z	Solvent	Percent by k_Δ
H	CH_3COOH	35–38
H	HCOOH	72–79
MeO	CH_3COOH	91–93
MeO	HCOOH	99

Several phenonium ions have been prepared as stable ions in solution where they can be studied by NMR, among them **52**,[165] **53**,[166] and the unsubstituted **51**.[167] These were prepared[168] by the method shown for **51**: treatment of the corresponding β-arylethyl chloride with SbF_5—SO_2 at low temperatures. These conditions are even more extreme than the solvolysis in CF_3COOH mentioned earlier. The absence of any nucleophile at all eliminates

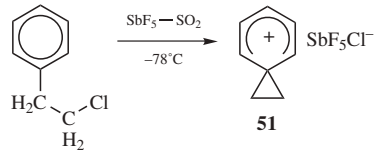


52



53

not only the k_s pathways, but also nucleophilic attack on **51**. Although **51** is not in equilibrium with the open-chain ion $PhCH_2CH_2^+$ (which is primary



51

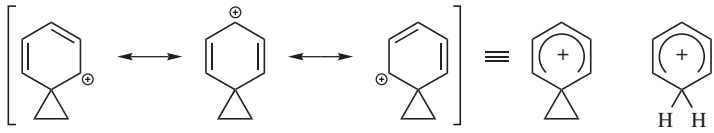
[165]Olah, G.A.; Comisarow, M.B.; Namanworth, E.; Ramsey, B. *J. Am. Chem. Soc.* ***1967***, *89*, 5259; Ramsey, B.; Cook, Jr., J.A.; Manner, J.A. *J. Org. Chem.* ***1972***, *37*, 3310.

[166]Olah, G.A.; Comisarow, M.B.; Kim, C.J. *J. Am. Chem. Soc.* ***1969***, *91*, 1458. See, however, Ramsey, B.; Cook, Jr., J.A.; Manner, J.A. *J. Org. Chem.* ***1972***, *37*, 3310.

[167]Olah, G.A.; Spear, R.J.; Forsyth, D.A. *J. Am. Chem. Soc.* ***1976***, *98*, 6284.

[168]For some others, see Olah, G.A.; Singh, B.P.; Liang, G. *J. Org. Chem.* ***1984***, *49*, 2922; Olah, G.A.; Singh, B.P. *J. Am. Chem. Soc.* ***1984***, *106*, 3265.

and hence unstable), **53** is in equilibrium with the open-chain tertiary ions $PhCMe_2C^+Me_2$ and PhC^+MeCMe_3, although only **53** is present in appreciable concentration. Proton and ^{13}C NMR show that **51**, **52**, and **53** are classical carbocations where the only resonance is in the six-membered ring. The three-membered ring is a normal cyclopropane ring that is influenced only to a relatively small extent by the positive charge on the adjacent ring. Nuclear magnetic resonance spectra show that the six-membered rings have no aromatic character, but are similar in structure to the arenium ions, for example,



54

54, that are intermediates in electrophilic aromatic substitution (Chapter 11). A number of phenonium ions, including **51**, have also been reported to be present in the gas phase, where their existence has been inferred from reaction products and from ^{13}C labeling.[169]

It is thus clear that β-aryl groups can function as neighboring groups.[170] Much less work has been done on aryl groups located in positions farther away from the leaving group, but there is evidence that these too can lend anchimeric assistance.[171]

4. *The Carbon–Carbon Single Bond as a Neighboring Group.*[172]

a. *The 2-Norbornyl System.* In the investigations to determine whether a C—C σ bond can act as a neighboring group, by far the greatest attention

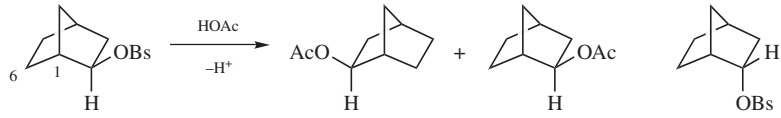
[169]Fornarini, S.; Muraglia, V. *J. Am. Chem. Soc.* ***1989***, *111*, 873; Mishima, M.; Tsuno, Y.; Fujio, M. *Chem. Lett.* ***1990***, 2277.

[170]For additional evidence, see Tanida, H. *Acc. Chem. Res.* ***1968***, *1*, 239; Kingsbury, C.A.; Best, D.C. *Tetrahedron Lett.* ***1967***, 1499; Braddon, D.V.; Wiley, G.A.; Dirlam, J.; Winstein, S. *J. Am. Chem. Soc.* ***1968***, *90*, 1901; Tanida, H.; Ishitobi, H.; Irie, T. *J. Am. Chem. Soc.* ***1968***, *90*, 2688; Brown, H.C.; Tritle, G.L. *J. Am. Chem. Soc.* ***1968***, *90*, 2689; Bentley, M.D.; Dewar, M.J.S. *J. Am. Chem. Soc.* ***1970***, *92*, 3996; Raber, D.J.; Harris, J.M.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1971***, *93*, 4829; Shiner, Jr., V.J.; Seib, R.C. *J. Am. Chem. Soc.* ***1976***, *98*, 862; Faïn, D.; Dubois, J.E. *Tetrahedron Lett.* ***1978***, 791; Yukawa, Y.; Ando, T.; Token, K.; Kawada, M.; Matsuda, K.; Kim, S.; Yamataka, H. *Bull. Chem. Soc. Jpn.* ***1981***, *54*, 3536; Ferber, P.H.; Gream, G.E. *Aust. J. Chem.* ***1981***, *34*, 2217; Fujio, M.; Goto, M.; Seki, Y.; Mishima, M.; Tsuno, Y.; Sawada, M.; Takai, Y. *Bull. Chem. Soc. Jpn.* ***1987***, *60*, 1097. For a discussion of evidence obtained from isotope effects, see Scheppele, S.E. *Chem. Rev.* ***1972***, *72*, 511, p. 522.

[171]Heck, R.; Winstein, S. *J. Am. Chem. Soc.* ***1957***, *79*, 3105; Muneyuki, R.; Tanida, H. *J. Am. Chem. Soc.* ***1968***, *90*, 656; Ouellette, R.J.; Papa, R.; Attea, M.; Levin, C. *J. Am. Chem. Soc.* ***1970***, *92*, 4893; Jackman, L.M.; Haddon, V.R. *J. Am. Chem. Soc.* ***1974***, *96*, 5130; Gates, M.; Frank, D.L.; von Felten, W.C. *J. Am. Chem. Soc.* ***1974***, *96*, 5138; Ando, T.; Yamawaki, J.; Saito, Y. *Bull. Chem. Soc. Jpn.* ***1978***, *51*, 219.

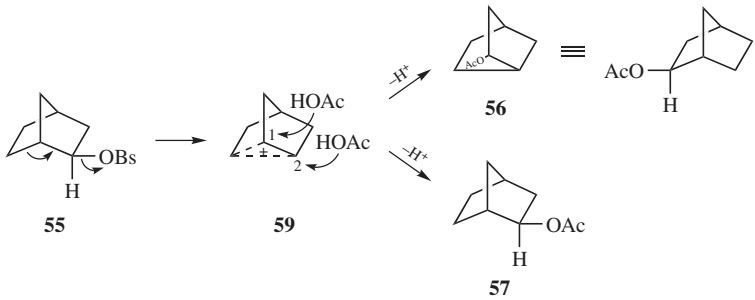
[172]For a review pertaining to studies of this topic at low temperatures, see Olah, G.A. *Angew. Chem. Int. Ed.* ***1973***, *12*, 173, pp. 192–198.

has been paid to the 2-norbornyl system.[173] Winstein and Trifan found that solvolysis in acetic acid of optically active *exo*-2-norbornyl brosylate (**55**) gave a racemic mixture of the two exo acetates; no endo isomers were formed:[174]



55 **56** **57** **58**

Furthermore, **55** solvolyzed ~350 times faster than its endo isomer **58**. Similar high exo/endo rate ratios have been found in many other [2.2.1] systems. These two results—(*1*) that solvolysis of an optically active exo isomer gave only racemic exo isomers and (*2*) the high exo/endo rate ratio—were interpreted by Winstein and Trifan as indicating that the 1,6 bond assists in the departure of the leaving group and that a nonclassical intermediate (**59**) is involved. They reasoned that solvolysis of the endo isomer **58** is not assisted by the 1,6 bond because it is not in a favorable position for backside attack,



55 **59**

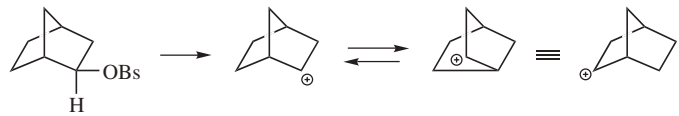
and that consequently solvolysis of **58** takes place at a ''normal'' rate. Therefore the much faster rate for the solvolysis of **55** must be caused by anchimeric assistance. The stereochemistry of the product is also explained by the intermediacy of **59**, since in **59** the 1 and 2 positions are equivalent and would be attacked by the nucleophile with equal facility, but only from the exo direction in either case. Incidentally, acetolysis of **58** also leads exclusively to the exo acetates (**56** and **57**), so that in this case Winstein and Trifan postulated that a classical ion (**60**)

[173]For reviews, see Olah, G.A.; Prakash, G.K.S.; Williams, R.E. *Hypercarbon Chemistry*, Wiley, NY, ***1987***, pp. 157–170; Grob, C.A. *Angew. Chem. Int. Ed.* ***1982***, *21*, 87; Sargent, G.D., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 3, Wiley, NY, ***1972***, pp. 1099–1200; Sargent, G.D. *Q. Rev. Chem. Soc.* ***1966***, *20*, 301; Gream, G.E. *Rev. Pure Appl. Chem.* ***1966***, *16*, 25. For a closely related review, see Kirmse, W. *Acc. Chem. Res.* ***1986***, *19*, 36. See also, Ref. 177.

[174]Winstein, S.; Clippinger, E.; Howe, R.; Vogelfanger, E. *J. Am. Chem. Soc.* ***1965***, *87*, 376.

is first formed, and then converted to the more stable **59**. Evidence for this interpretation is that the product from solvolysis of **58** is not racemic but contains somewhat more **57** than **56** (corresponding to 3–13% inversion, depending on the solvent),[174] suggesting that when **60** is formed, some of it goes to give **57** before it can collapse to **59**.

The concepts of σ participation and the nonclassical ion **59** were challenged by H.C. Brown,[128] who suggested that the two results can also be explained by postulating that **55** solvolyzes without participation of the 1,6 bond to give the classical ion **60**, which is in rapid equilibrium with **61**. This



55 **60** **61**

rapid interconversion has been likened to the action of a windshield wiper.[175] Obviously, in going from **60** to **61** and back again, **59** must be present, but in Brown's view it is a transition state and not an intermediate. Brown's explanation for the stereochemical result was that exclusive exo attack is a property to be expected from any 2-norbornyl system, not only for the cation but even for reactions not involving cations, because of steric hindrance to attack from the endo side. There is a large body of data that shows that exo attack on norbornyl systems is fairly general in many reactions. A racemic mixture will be obtained if **60** and **61** are present in equal amounts, since they are equivalent and exo attack on **60** and **61** gives, respectively, **57** and **56**. Brown explained the high exo/endo rate ratios by contending that it is not the endo rate that is normal and the exo rate abnormally high, but the exo rate that is normal and the endo rate abnormally *low*, because of steric hindrance to removal of the leaving group in that direction.[176]

A vast amount of work has been done[177] on solvolysis of the 2-norbornyl system in an effort to determine whether the 1,6 bond

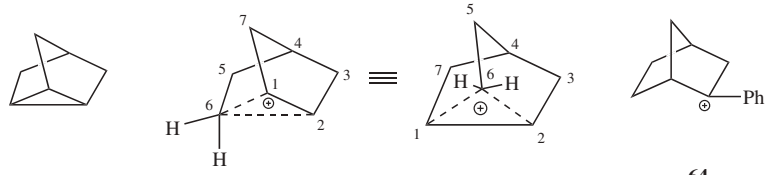
[175]Another view is somewhere in between: There are two interconverting ions, but each is asymmetrically bridged: Bielmann, R.; Fuso, F.; Grob, C.A. *Helv. Chim. Acta* ***1988***, *71*, 312; Flury, P.; Grob, C.A.; Wang, G.Y.; Lennartz, H.; Roth, W.R. *Helv. Chim. Acta* ***1988***, *71*, 1017.

[176]For evidence against steric hindrance as the only cause of this effect, see Menger, F.M.; Perinis, M.; Jerkunica, J.M.; Glass, L.E. *J. Am. Chem. Soc.* ***1978***, *100*, 1503.

[177]For thorough discussions, see Lenoir, D.; Apeloig, Y.; Arad, D.; Schleyer, P.v.R. *J. Org. Chem.* ***1988***, *53*, 661; Grob, C.A. *Acc. Chem. Res.* ***1983***, *16*, 426; Brown, H.C. *Acc. Chem. Res.* ***1983***, *16*, 432; Walling, C. *Acc. Chem. Res.* ***1983***, *16*, 448; Allred, E.L.; Winstein, S. *J. Am. Chem. Soc.* ***1967***, *89*, 3991, 3998; Nordlander, J.E.; Kelly, W.J. *J. Am. Chem. Soc.* ***1969***, *91*, 996. For commentary on the controversy, see Arnett, E.M.; Hofelich, T.C.; Schriver, G.W. *React. Intermed. (Wiley)* ***1985***, *3*, 189, pp. 193–202.

participates and whether **59** is an intermediate. Most,[178] although not all,[179] chemists now accept the intermediacy of **59**.

Besides the work done on solvolysis of 2-norbornyl compounds, the 2-norbornyl cation has also been extensively studied at low temperatures; there is much evidence that under these conditions the ion is definitely nonclassical. Olah and co-workers have prepared the 2-norbornyl cation in stable solutions at temperatures below −150°C in SbF_5—SO_2 and FSO_3H—SbF_5—SO_2, where the structure is static and hydride shifts are absent.[180] Studies by proton and ^{13}C NMR, as well as by laser Raman spectra and X-ray electron spectroscopy, led to the conclusion[181] that under these conditions the ion is nonclassical.[182] A similar result has been reported for the 2-norbornyl cation in the solid state where at 77 and even 5 K, ^{13}C NMR spectra gave no evidence of the freezing out of a single classical ion.[183]



Nortricyclane **62** **63** **64**

[178]For some recent evidence in favor of a nonclassical **59**, see Arnett, E.M.; Petro, C.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1979***, *101*, 522: Albano, C.; Wold, S. *J. Chem. Soc. Perkin Trans. 2* ***1980***, 1447; Wilcox, C.F.; Tuszynski, W.J. *Tetrahedron Lett.* ***1982***, *23*, 3119; Kirmse, W.; Siegfried, R. *J. Am. Chem. Soc.* ***1983***, *105*, 950; Creary, X.; Geiger, C.C. *J. Am. Chem. Soc.* ***1983***, *105*, 7123; Chang, S.; le Noble, W.J. *J. Am. Chem. Soc.* ***1984***, *106*, 810; Kirmse, W.; Brandt, S. *Chem. Ber.* ***1984***, *117*, 2510; Wilcox, C.F.; Brungardt, B. *Tetrahedron Lett.* ***1984***, *25*, 3403; Lajunen, M. *Acc. Chem. Res.* ***1985***, *18*, 254; Sharma, R.B.; Sen Sharma, D.K.; Hiraoka, K.; Kebarle, P. *J. Am. Chem. Soc.* ***1985***, *107*, 3747; Servis, K.L.; Domenick, R.L.; Forsyth, D.A.; Pan, Y. *J. Am. Chem. Soc.* ***1987***, *109*, 7263; Lenoir, D.; Apeloig, Y.; Arad, D.; Schleyer, P.v.R. *J. Org. Chem.* ***1988***, *53*, 661.

[179]For some evidence against a nonclassical **59** see Dewar, M.J.S.; Haddon, R.C.; Komornicki, A.; Rzepa, H. *J. Am. Chem. Soc.* ***1977***, *99*, 377; Lambert, J.B.; Mark, H.W. *J. Am. Chem. Soc.* ***1978***, *100*, 2501; Christol, H.; Coste, J.; Pietrasanta, F.; Plénat, F.; Renard, G. *J. Chem. Soc. (S)* ***1978***, 62; Brown, H.C.; Rao, C.G. *J. Org. Chem.* ***1979***, *44*, 133, 3536; ***1980***, *45*, 2113; Liu, K.; Yen, C.; Hwang, H. *J. Chem. Res.(S)* ***1980***, 152; Werstiuk, N.H.; Dhanoa, D.; Timmins, G. *Can. J. Chem.* ***1983***, *61*, 2403; Brown, H.C.; Ikegami, S.; Vander Jagt, D.L. *J. Org. Chem.* ***1985***, *50*, 1165; Nickon, A.; Swartz, T.D.; Sainsbury, D.M.; Toth, B.R. *J. Org. Chem.* ***1986***, *51*, 3736. See also, Brown, H.C. *Top. Curr. Chem.* ***1979***, *80*, 1.

[180]The presence of hydride shifts (p. $$$) under solvolysis conditions has complicated the interpretation of the data.

[181]Olah, G.A. *Acc. Chem. Res.* ***1976***, *9*, 41; Olah, G.A.; Liang, G.; Mateescu, G.D.; Riemenschneider, J.L. *J. Am. Chem. Soc.* ***1973***, *95*, 8698; Saunders, M.; Kates, M.R. *J. Am. Chem. Soc.* ***1980***, *102*, 6867; ***1983***, *105*, 3571; Olah, G.A.; Prakash, G.K.S.; Saunders, M. *Acc. Chem. Res.* ***1983***, *16*, 440. See also, Schleyer, P.v.R.; Lenoir, D.; Mison, P.; Liang, G.; Prakash, G.K.S.; Olah, G.A. *J. Am. Chem. Soc.* ***1980***, *102*, 683; Johnson, S.A.; Clark, D.T. *J. Am. Chem. Soc.* ***1988***, *110*, 4112.

[182]This conclusion has been challenged: Fong, F.K. *J. Am. Chem. Soc.* ***1974***, *96*, 7638; Kramer, G.M. *Adv. Phys. Org. Chem.* ***1975***, *11*, 177; Brown, H.C.; Periasamy, M.; Kelly, D.P.; Giansiracusa, J.J. *J. Org. Chem.* ***1982***, *47*, 2089; Kramer, G.M.; Scouten, C.G. *Adv. Carbocation Chem.* ***1989***, *1*, 93. See, however, Olah, G.A.; Prakash, G.K.S.; Farnum, D.G.; Clausen, T.P. *J. Org. Chem.* ***1983***, *48*, 2146.

[183]Yannoni, C.S.; Macho, V.; Myhre, P.C. *J. Am. Chem. Soc.* ***1982***, *104*, 907, 7380; *Bull. Soc. Chim. Belg.* ***1982***, *91*, 422; Myhre, P.C.; Webb, G.G.; Yannoni, C.S. *J. Am. Chem. Soc.* ***1990***, *112*, 8991.

Olah and co-workers represented the nonclassical structure as a corner-protonated nortricyclane (**62**); the symmetry is better seen when the ion is drawn as in **63**. Almost all the positive charge resides on C-1 and C-2 and very little on the bridging carbon C-6. Other evidence for the nonclassical nature of the 2-norbornyl cation in stable solutions comes from heat of reaction measurements that show that the 2-norbornyl cation is more stable (by ~6–10 kcal mol^{-1} or 25–40 kJ mol^{-1}) than would be expected without the bridging.[184] Studies of ir spectra of the 2-norbornyl cation in the gas phase also show the nonclassical structure.[185] *Ab initio* calculations show that the nonclassical structure corresponds to an energy minimum.[186]

The spectra of other norbornyl cations have also been investigated at low temperatures. Spectra of the tertiary 2-methyl- and 2-ethylnorbornyl cations show less delocalization,[187] and the 2-phenylnorbornyl cation (**64**) is essentially classical,[188] as are the 2-methoxy-[189] and 2-chloronorbornyl cations.[190] We may recall (p. 242) that methoxy and halo groups also stabilize a positive charge. The ^{13}C NMR data show that electron-withdrawing groups on the benzene ring of **64** cause the ion to become less classical, while electron-donating groups enhance the classical nature of the ion.[191]

b. *The Cyclopropylmethyl System*. Apart from the 2-norbornyl system, the greatest amount of effort in the search for C—C participation has been devoted to the cyclopropylmethyl system.[192] It has long been known that cyclopropylmethyl substrates solvolyze with abnormally high rates and

[184]For some examples, see Hogeveen, H.; Gaasbeek, C.J. *Recl. Trav. Chim. Pays-Bas* ***1969***, *88*, 719; Hogeveen, H. *Recl. Trav. Chim. Pays-Bas* ***1970***, *89*, 74; Solomon, J.J.; Field, F.H. *J. Am. Chem. Soc.* ***1976***, *98*, 1567; Staley, R.H.; Wieting, R.D.; Beauchamp, J.L. *J. Am. Chem. Soc.* ***1977***, *99*, 5964; Arnett, E.M.; Pienta, N.; Petro, C. *J. Am. Chem. Soc.* ***1980***, *102*, 398; Saluja, P.P.S.; Kebarle, P. *J. Am. Chem. Soc.* ***1979***, *101*, 1084; Schleyer, P.v.R.; Chandrasekhar, J. *J. Org. Chem.* ***1981***, *46*, 225; Lossing, F.P.; Holmes, J.L. *J. Am. Chem. Soc.* ***1984***, *106*, 6917.

[185]Koch, W.; Liu, B.; DeFrees, D.J.; Sunko, D.E.; Vančik, H. *Angew. Chem. Int. Ed.* ***1990***, *29*, 183.

[186]See, for example Koch, W.; Liu, B.; DeFrees, D.J. *J. Am. Chem. Soc.* ***1989***, *111*, 1527.

[187]Olah, G.A.; DeMember, J.R.; Lui, C.Y.; White, A.M. *J. Am. Chem. Soc.* ***1969***, *91*, 3958. See also, Laube, T. *Angew. Chem. Int. Ed.* ***1987***, *26*, 560; Forsyth, D.A.; Panyachotipun, C. *J. Chem. Soc., Chem. Commun.* ***1988***, 1564.

[188]Olah, G.A. *Acc. Chem. Res.* ***1976***, *9*, 41; Farnum, D.G.; Mehta, G. *J. Am. Chem. Soc.* ***1969***, *91*, 3256. See also, Schleyer, P.v.R.; Kleinfelter, D.C.; Richey, Jr., H.G. *J. Am. Chem. Soc.* ***1963***, *85*, 479; Farnum, D.G.; Wolf, A.D. *J. Am. Chem. Soc.* ***1974***, *96*, 5166.

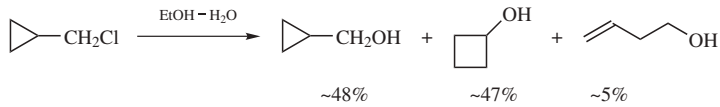
[189]Nickon, A.; Lin, Y. *J. Am. Chem. Soc.* ***1969***, *91*, 6861. See also, Montgomery, L.K.; Grendze, M.P.; Huffman, J.C. *J. Am. Chem. Soc.* ***1987***, *109*, 4749.

[190]Fry, A.J.; Farnham, W.B. *J. Org. Chem.* ***1969***, *34*, 2314.

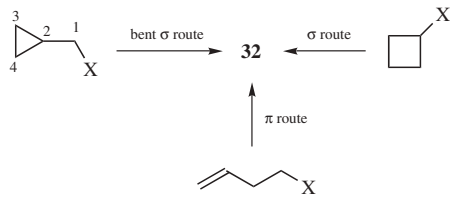
[191]Olah, G.A.; Prakash, G.K.S.; Liang, G. *J. Am. Chem. Soc.* ***1977***, *99*, 5683; Farnum, W.B.; Botto, R.E.; Chambers, W.T.; Lam, B. *J. Am. Chem. Soc.* ***1978***, *100*, 3847. See also, Olah, G.A.; Berrier, A.L.; Prakash, G.K.S. *J. Org. Chem.* ***1982***, *47*, 3903.

[192]For reviews, see, in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 3, Wiley, NY, ***1972***, the articles by Richey, Jr., H.G. pp. 1201–1294, and by Wiberg, K.B.; Hess, Jr., B.A.; Ashe III, A.J. pp. 1295–1345; Hanack, M.; Schneider, H. *Fortschr. Chem. Forsch.* ***1967***, *8*, 554, *Angew. Chem. Int. Ed.* ***1967***, *6*, 666; Sarel, S.; Yovell, J.; Sarel-Imber, M. *Angew. Chem. Int. Ed.* ***1968***, *7*, 577.

that the products often include not only unrearranged cyclopropylmethyl, but also cyclobutyl and homoallylic compounds. An example is[193]

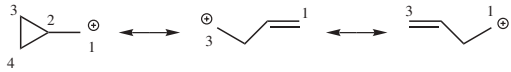


Cyclobutyl substrates also solvolyze abnormally rapidly and give similar products. Furthermore, when the reactions are carried out with labeled substrates, considerable, although not complete, scrambling is observed. For these reasons, it has been suggested that a common intermediate (some kind of nonclassical intermediate, e.g., **32**, p. 450) is present in these cases. This common intermediate could then be obtained by three routes:



In recent years, much work has been devoted to the study of these systems, and it is apparent that matters are not so simple. Although there is much that is still not completely understood, some conclusions can be drawn.

i. In solvolysis of simple primary cyclopropylmethyl systems the rate is enhanced because of participation by the σ bonds of the ring.[194] The ion that forms initially is an unrearranged cyclopropylmethyl cation[195] that is *symmetrically* stabilized, that is, both the 2,3 and 2,4 σ bonds help stabilize the positive charge. We have already seen (p. 240) that a cyclopropyl group stabilizes an adjacent positive charge even better than a phenyl group. One way of representing the structure of this cation is as shown in **65**. Among the



65

evidence that **65** is a symmetrical ion is that substitution of one or more methyl groups in the 3 and 4 positions increases the rate of solvolysis of cyclopropylcarbinyl 3,5-dinitrobenzoates by approximately a factor of 10 for *each* methyl group.[196] If only one of the σ bonds (say, the 2,3 bond)

[193]Roberts, D.D.; Mazur, R.H. *J. Am. Chem. Soc.* ***1951***, *73*, 2509.

[194]See, for example, Roberts, D.D.; Snyder, Jr., R.C. *J. Org. Chem.* ***1979***, *44*, 2860, and references cited therein.

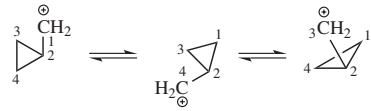
[195]Wiberg, K.B.; Ashe III, A.J. *J. Am. Chem. Soc.* ***1968***, *90*, 63.

[196]Schleyer, P.v.R.; Van Dine, G.W. *J. Am. Chem. Soc.* ***1966***, *88*, 2321. See also, Kevill, D.N.; Abduljaber, M.H. *J. Org. Chem.* ***2000***, *65*, 2548.

stabilizes the cation, then methyl substitution at the 3 position should increase the rate, and a second methyl group at the 3 position should increase it still more, but a second methyl group at the 4 position should have little effect.[197]

ii. The most stable geometry of simple cyclopropylmethyl cations is the bisected one shown on p. 240. There is much evidence that in systems where this geometry cannot be obtained, solvolysis is greatly slowed.[198]

iii. Once a cyclopropylmethyl cation is formed, it can rearrange to two other cyclopropylmethyl cations:



This rearrangement, which accounts for the scrambling, is completely stereospecific.[199] The rearrangements probably take place through a nonplanar cyclobutyl cation intermediate or transition state. The formation of cyclobutyl and homoallylic products from a cyclopropylmethyl cation is also completely stereospecific. These products may arise by direct attack of the nucleophile on **65** or on the cyclobutyl cation intermediate.[200] A planar cyclobutyl cation is ruled out in both cases because it would be symmetrical and the stereospecificity would be lost.

iv. The rate enhancement in the solvolysis of secondary cyclobutyl substrates is probably caused by participation by a bond leading directly to **65**, which accounts for the fact that solvolysis of cyclobutyl and of cyclopropylmethyl

substrates often gives similar product mixtures. There is no evidence that requires the cyclobutyl cations to be intermediates in most secondary cyclobutyl systems, although tertiary cyclobutyl cations can be solvolysis intermediates.

v. The unsubstituted cyclopropylmethyl cation has been generated in super acid solutions at low temperatures, where ^{13}C NMR spectra have led to

[197]For a summary of additional evidence for the symmetrical nature of cyclopropylmethyl cations, see Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 3, Wiley, NY, ***1972***, the article by Wiberg, K.B.; Hess, Jr., B.A.; Ashe III, A.J. pp. 1300–1303.

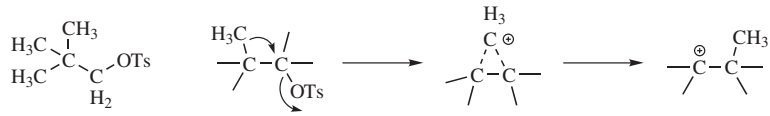
[198]For example, see Ree, B.; Martin, J.C. *J. Am. Chem. Soc.* ***1970***, *92*, 1660; Rhodes, Y.E.; DiFate, V.G. *J. Am. Chem. Soc.* ***1972***, *94*, 7582. See, however, Brown, H.C.; Peters, E.N. *J. Am. Chem. Soc.* ***1975***, *97*, 1927.

[199]Wiberg, K.B.; Szeimies, G. *J. Am. Chem. Soc.* ***1968***, *90*, 4195; ***1970***, *92*, 571; Majerski, Z.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1971***, *93*, 665.

[200]Koch, W.; Liu, B.; DeFrees, D.J. *J. Am. Chem. Soc.* ***1988***, *110*, 7325; Saunders, M.; Laidig, K.E.; Wiberg, K.B.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1988***, *110*, 7652.

the conclusion that it consists of a mixture of the bicyclobutonium ion **32** and the bisected cyclopropylmethyl cation **65**, in equilibrium with **32**.[201] Molecular-orbital calculations show that these two species are energy minima, and that both have nearly the same energy.[200]

c. *Methyl as a Neighboring Group*. Both the 2-norbornyl and cyclopropylmethyl system contain a σ bond that is geometrically constrained to be in a particularly favorable position for participation as a neighboring group. However, there have been a number of investigations to determine whether a C—C bond can lend anchimeric assistance even in a simple open-chain compound, such as neopentyl tosylate. On solvolysis, neopentyl systems undergo almost exclusive rearrangement and **66** must lie on the reaction path, but the two questions that have been asked are (*1*) Is the departure of the



Neopentyl tosylate **66**

leaving group concerted with the formation of the CH_3—C bond (i.e., does the methyl participate)? (*2*) Is **66** an intermediate or only a transition state? With respect to the first question, there is evidence, chiefly from isotope effect studies, that indicates that the methyl group in the neopentyl system does indeed participate,[202] although it may not greatly enhance the rate. As to the second question, evidence that **66** is an intermediate is that small amounts of cyclopropanes (10–15%) can be isolated in these reactions.[203] Cation **66** is a protonated cyclopropane and would give cyclopropane on loss of a proton.[204] In an effort to isolate a species that has structure **66**, the 2,3,3-trimethyl-2-butyl cation was prepared in super acid solutions at low temperatures.[205] However, ^{1}H and ^{13}C NMR, as well as Raman spectra,

[201]Staral, J.S.; Yavari, I.; Roberts, J.D.; Prakash, G.K.S.; Donovan, D.J.; Olah, G.A. *J. Am. Chem. Soc.* ***1978***, *100*, 8016. See also, Olah, G.A.; Spear, R.J.; Hiberty, P.C.; Hehre, W.J. *J. Am. Chem. Soc.* ***1976***, *98*, 7470; Saunders, M.; Siehl, H. *J. Am. Chem. Soc.* ***1980***, *102*, 6868; Brittain, W.J.; Squillacote, M.E.; Roberts, J.D. *J. Am. Chem. Soc.* ***1984***, *106*, 7280; Siehl, H.; Koch, E. *J. Chem. Soc., Chem. Commun.* ***1985***, 496; Prakash, G.K.S.; Arvanaghi, M.; Olah, G.A. *J. Am. Chem. Soc.* ***1985***, *107*, 6017; Myhre, P.C.; Webb, G.G.; Yannoni, C.S. *J. Am. Chem. Soc.* ***1990***, *112*, 8992.

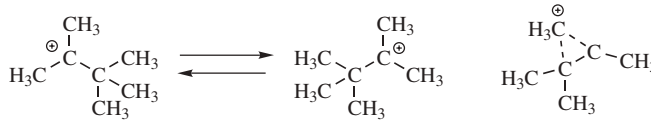
[202]For example, see Dauben, W.G.; Chitwood, J.L. *J. Am. Chem. Soc.* ***1968***, *90*, 6876; Ando, T.; Morisaki, H. *Tetrahedron Lett.* ***1979***, 121; Shiner, V.J.; Tai, J.J. *J. Am. Chem. Soc.* ***1981***, *103*, 436; Yamataka, H.; Ando, T.; Nagase, S.; Hanamura, M.; Morokuma, K. *J. Org. Chem.* ***1984***, *49*, 631. For an opposing view, see Zamashchikov, V.V.; Rudakov, E.S.; Bezbozhnaya, T.V.; Matveev, A.A. *J. Org. Chem. USSR* ***1984***, *20*, 11.

[203]Skell, P.S.; Starer, I. *J. Am. Chem. Soc.* ***1960***, *82*, 2971; Silver, M.S. *J. Am. Chem. Soc.* ***1960***, *82*, 2971; Friedman, L.; Bayless, J.H. *J. Am. Chem. Soc.* ***1969***, *91*, 1790; Friedman, L.; Jurewicz, A.T. *J. Am. Chem. Soc.* ***1969***, *91*, 1800, 1803; Dupuy, W.E.; Hudson, H.R.; Karam, P.A. *Tetrahedron Lett.* ***1971***, 3193; Silver, M.S.; Meek, A.G. *Tetrahedron Lett.* ***1971***, 3579; Dupuy, W.E.; Hudson, H.R. *J. Chem. Soc. Perkin Trans. 2* ***1972***, 1715.

[204]For further discussions of protonated cyclopropanes, see pp. $$$, $$$.

[205]Olah, G.A.; DeMember, J.R.; Commeyras, A.; Bribes, J.L. *J. Am. Chem. Soc.* ***1971***, *93*, 459.

showed this to be a pair of rapidly equilibrating open ions.

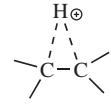


67

Of course, **67** must lie on the reaction path connecting the two open ions, but it is evidently a transition state and not an intermediate. However, evidence from X-ray photoelectron spectroscopy (ESCA) has shown that the 2-butyl cation is substantially methyl bridged.[206]

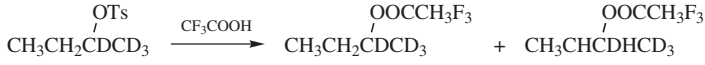
d. *Silylalkyl as a Neighboring Group.* Rates of solvolysis are enhanced in molecules that contain a silylalkyl or silylaryl group β- to the carbon bearing the leaving group. This is attributed to formation of a cyclic transition state involving the silicon.[207]

5. *Hydrogen as a Neighboring Group*. The questions relating to hydrogen are similar to those relating to methyl. There is no question that hydride can migrate, but the two questions are (*1*) Does the hydrogen participate in the



68

departure of the leaving group? (*2*) Is **68** an intermediate or only a transition state? There is some evidence that a β hydrogen can participate.[208] Evidence that **68** can be an intermediate in solvolysis reactions comes from



69 **70** **71**

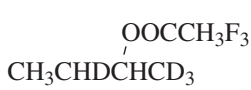
a study of the solvolysis in trifluoroacetic acid of deuterated *sec*-butyl tosylate **69**. In this solvent of very low nucleophilic power, the products were

[206]Johnson, S.A.; Clark, D.T. *J. Am. Chem. Soc.* ***1988***, *110*, 4112. See also, Carneiro, J.W.; Schleyer, P.v.R.; Koch, W.; Raghavachari, K. *J. Am. Chem. Soc.* ***1990***, *112*, 4064.

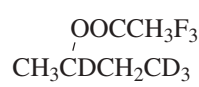
[207]Fujiyama, R.; Munechika, T. *Tetrahedron Lett.* ***1993***, *34*, 5907.

[208]See, for example, Shiner, Jr., V.J.; Jewett, J.G. *J. Am. Chem. Soc.* ***1965***, *87*, 1382; Tichy, M.; Hapala, J.; Sicher, J. *Tetrahedron Lett.* ***1969***, 3739; Myhre, P.C.; Evans, E. *J. Am. Chem. Soc.* ***1969***, *91*, 5641; Inomoto, Y.; Robertson, R.E.; Sarkis, G. *Can. J. Chem.* ***1969***, *47*, 4599; Shiner, V.J.; Stoffer, J.O. *J. Am. Chem. Soc.* ***1970***, *92*, 3191; Krapcho, A.P.; Johanson, R.G. *J. Org. Chem.* ***1971***, *36*, 146; Chuit, C.; Felkin, H.; Le Ny, G.; Lion, C.; Prunier, L. *Tetrahedron* ***1972***, *28*, 4787; Stéhelin, L.; Kanellias, L.; Ourisson, G. *J. Org. Chem.* ***1973***, *38*, 847, 851; Hirsl-Staršević, S.; Majerski, Z.; Sunko, D.E. *J. Org. Chem.* ***1980***, *45*, 3388; Buzek, P.; Schleyer, P.v.R.; Sieber, S.; Koch, W.; Carneiro, J.W. de M.; Vančik, H.; Sunko, D.E. *J. Chem. Soc., Chem. Commun.* ***1991***, 671; Imhoff, M.A.; Ragain, R.M.; Moore, K.; Shiner, V.J. *J. Org. Chem.* ***1991***, *56*, 3542.

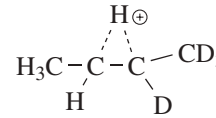
an equimolar mixture of **70** and **71**,[209] but *no* **72** or **73** was found. If this



72



73



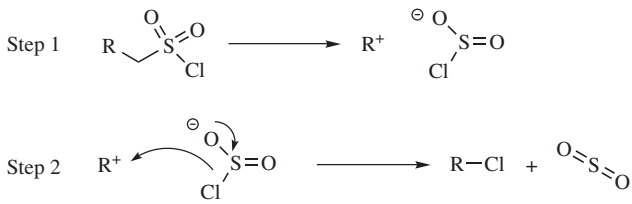
74

reaction did not involve neighboring hydrogen at all (pure S_N2 or S_N1), the product would be only **70**. On the other hand, if hydrogen does migrate, but only open cations are involved, then there should be an equilibrium among these four cations:

leading not only to **70** and **71**, but also to **72** and **73**. The results are most easily compatible with the intermediacy of the bridged ion **74**, which can then be attacked by the solvent equally at the 2 and 3 positions. Attempts to prepare **68** as a stable ion in super acid solutions at low temperatures have not been successful.[208]

The S_Ni Mechanism

In a few reactions, nucleophilic substitution proceeds with retention of configuration, even where there is no possibility of a neighboring-group effect. In the S_Ni mechanism (*substitution nucleophilic internal*), part of the leaving group must be able to attack the substrate, detaching itself from the rest of the leaving group in the process. The IUPAC designation is $D_N + A_ND_e$. The first step is the same as the very first step of the S_N1 mechanism dissociation into an intimate ion pair.[210] But in the second step part of the leaving group attacks, necessarily from the front since it is unable to get to the rear, which results in retention of configuration.



[209]Dannenberg, J.J.; Goldberg, B.J.; Barton, J.K.; Dill, K.; Weinwurzel, D.H.; Longas, M.O. *J. Am. Chem. Soc.* ***1981***, *103*, 7764. See also, Dannenberg, J.J.; Barton, J.K.; Bunch, B.; Goldberg, B.J.; Kowalski, T. *J. Org. Chem.* ***1983***, *48*, 4524; Allen, A.D.; Ambidge, I.C.; Tidwell, T.T. *J. Org. Chem.* ***1983***, *48*, 4527.

[210]Lee, C.C.; Finlayson, A.J. *Can. J. Chem.* ***1961***, *39*, 260; Lee, C.C.; Clayton, J.W.; Lee, C.C.; Finlayson, A.J. *Tetrahedron* ***1962***, *18*, 1395.

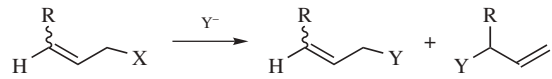
The example shown is the most important case of this mechanism yet discovered, since the reaction of alcohols with thionyl chloride to give alkyl halides usually proceeds in this way, with the first step in this case being $ROH + SOCl_2 \rightarrow ROSOCl$ (these alkyl chlorosulfites can be isolated).

Evidence for this mechanism is as follows: the addition of pyridine to the mixture of alcohol and thionyl chloride results in the formation of alkyl halide with *inverted* configuration. Inversion results because the pyridine reacts with ROSOCl to give $ROSONC_5H_5$ before anything further can take place. The Cl^- freed in this process now attacks from the rear. The reaction between alcohols and thionyl chloride is second order, which is predicted by this mechanism, but the decomposition by simple heating of ROSOCl is first order.[211]

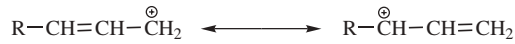
The S_Ni mechanism is relatively rare. Another example is the decomposition of ROCOCl (alkyl chloroformates) into RCl and CO_2.[212]

Nucleophilic Substitution at an Allylic Carbon: Allylic Rearrangements

Allylic substrates rapidly undergo nucleophilic substitution reactions (see p. 482), but we discuss them in a separate section because they are commonly accompanied by a certain kind of rearrangement known as an *allylic rearrangement*.[213] When allylic substrates are treated with nucleophiles under S_N1 conditions, two products are usually obtained: the normal one and a rearranged one.



Two products are formed because an allylic type of carbocation is a resonance hybrid



so that C-1 and C-3 each carry a partial positive charge and both are attacked by Y. Of course, an allylic rearrangement is undetectable in the case of symmetrical allylic cations, as in the case where R = H, unless isotopic labeling is used. This mechanism has been called the S_N1' mechanism. The IUPAC designation is $1/D_N + 3/A_N$, the numbers 1 and 3 signifying the *relative* positions where the nucleophile attacks and from which the nucleofuge leaves.

[211]Lewis, E.S.; Boozer, C.E. *J. Am. Chem. Soc.* ***1952***, *74*, 308.

[212]Lewis, E.S.; Herndon, W.C.; Duffey, D.C. *J. Am. Chem. Soc.* ***1961***, *83*, 1959; Lewis, E.S.; Witte, K. *J. Chem. Soc. B* ***1968***, 1198. For other examples, see Hart, H.; Elia, R.J. *J. Am. Chem. Soc.* ***1961***, *83*, 985; Stevens, C.L.; Dittmer, H.; Kovacs, J. *J. Am. Chem. Soc.* ***1963***, *85*, 3394; Kice, J.L.; Hanson, G.C. *J. Org. Chem.* ***1973***, *38*, 1410; Cohen, T.; Solash, J. *Tetrahedron Lett.* ***1973***, 2513; Verrinder, D.J.; Hourigan, M.J.; Prokipcak, J.M. *Can. J. Chem.* ***1978***, *56*, 2582.

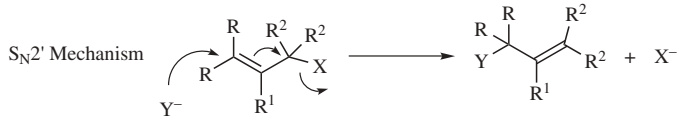
[213]For a review, see DeWolfe, R.H., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9, Elsevier, NY, ***1973***, pp. 417–437. For comprehensive older reviews, see DeWolfe, R.H.; Young, W.G. *Chem. Rev.* ***1956***, *56*, 753; in Patai, S. *The Chemistry of Alkenes*, Wiley, NY, **1964**, the sections by Mackenzie, K. pp. 436–453 and DeWolfe, R.H.; Young, W.G. pp. 681–738.

As with other S_N1 reactions, there is clear evidence that S_N1' reactions can involve ion pairs. If the intermediate attacked by the nucleophile is a completely free carbocation, then, say,

$$\underset{\mathbf{75}}{CH_3CH{=}CHCH_2Cl} \qquad \text{and} \qquad \underset{\mathbf{76}}{CH_3CHClCH{=}CH_2}$$

should give the same mixture of alcohols when reacting with hydroxide ion, since the carbocation from each should be the same. When treated with 0.8 *M* aq. NaOH at 25°C, **75** gave 60% $CH_3CH{=}CHCH_2OH$ and 40% $CH_3CHOHCH{=}CH_2$, while **76** gave the products in yields of 38 and 62%, respectively.[214] This phenomenon is called the *product spread*. In this case, and in most others, the product spread is in the direction of the starting compound. With increasing polarity of solvent,[215] the product spread decreases and in some cases is entirely absent. It is evident that in such cases the high polarity of the solvent stabilizes completely free carbocations. There is other evidence for the intervention of ion pairs in many of these reactions. When $H_2C{=}CHCMe_2Cl$ was treated with acetic acid, both acetates were obtained, but also some $ClCH_2CH{=}CMe_2$,[216] and the isomerization was faster than the acetate formation. This could not have arisen from a completely free Cl^- returning to the carbon, since the rate of formation of the rearranged chloride was unaffected by the addition of external Cl^-. All these facts indicate that the first step in these reactions is the formation of an unsymmetrical intimate ion pair that undergoes a considerable amount of internal return and in which the counterion remains close to the carbon from which it departed. Thus, **75** and **76**, for example, give rise to two *different* intimate ion pairs. The field of the anion polarizes the allylic cation, making the nearby carbon atom more electrophilic, so that it has a greater chance of attracting the nucleophile.[217]

Nucleophilic substitution at an allylic carbon can also take place by an S_N2 mechanism, in which case no allylic rearrangement usually takes place. However, allylic rearrangements can also take place under S_N2 conditions, by the following mechanism, in which the nucleophile attacks at the γ carbon rather than the usual position:[218]



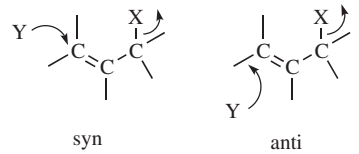
The IUPAC designation is $3/1/A_ND_N$. This mechanism is a second-order allylic rearrangement; it usually comes about where S_N2 conditions hold but where

[214]DeWolfe, R.H.; Young, W.G. *Chem. Rev.* ***1956***, *56*, 753 give several dozen such examples.
[215]Katritzky, A.R.; Fara, D.C.; Yang, H.; Tämm, K.; Tamm, T.; Karelson, M. *Chem. Rev.* ***2004***, *104*, 175.
[216]Young, W.G.; Winstein, S.; Goering, H.L. *J. Am. Chem. Soc.* ***1951***, *73*, 1958.
[217]For additional evidence for the involvement of ion pairs in S_N1' reactions, see Goering, H.L.; Linsay, E.C. *J. Am. Chem. Soc.* ***1969***, *91*, 7435; d'Incan, E.; Viout, P. *Bull. Soc. Chim. Fr.* ***1971***, 3312; Astin, K.B.; Whiting, M.C. *J. Chem. Soc. Perkin Trans. 2* ***1976***, 1157; Kantner, S.S.; Humski, K.; Goering, H.L. *J. Am. Chem. Soc.* ***1982***, *104*, 1693; Thibblin, A. *J. Chem. Soc. Perkin Trans. 2* ***1986***, 313; Ref. 77.
[218]For a review of the S_N2' mechanism, see Magid, R.M. *Tetrahedron* ***1980***, *36*, 1901, see pp. 1901–1910.

a substitution sterically retards the normal S_N2 mechanism. There are few well-established cases of the S_N2' mechanism on substrates of the type C=C–CH_2X, but compounds of the form C=C–CR_2X give the S_N2' rearrangement almost exclusively[219] when they give bimolecular reactions at all. Increasing the size of the nucleophile can also increase the extent of the S_N2' reaction at the expense of the S_N2.[219] In certain cases, the leaving group can also have an affect on whether the rearrangement occurs. Thus PhCH=$CHCH_2X$, treated with $LiAlH_4$, gave 100% S_N2 reaction (no rearrangement) when X = Br or Cl, but 100% S_N2' when $X = PPh_3^+ Br^-$.[220] The solvent also plays a role in some cases, with more polar solvents giving more S_N2' product.[221]

The S_N2' mechanism as shown above involves the simultaneous movement of three pairs of electrons. However, Bordwell has contended that there is no evidence that requires that this bond making and bond breaking be in fact concerted,[222] and that a true S_N2' mechanism is a myth. There is evidence both for[223] and against[224] this proposal. There is also a review of the S_N' reaction.[225]

The stereochemistry of S_N2' reactions has been investigated. It has been found that both syn[226] (the nucleophile enters on the side from which the leaving group departs) and anti[227] reactions can take place, depending on the nature of X and Y,[228] although the syn pathway predominates in most cases.



[219]Bordwell, F.G.; Clemens, A.H.; Cheng, J. *J. Am. Chem. Soc.* ***1987***, *109*, 1773. Also see, Young, J.-j; Jung, L.-j.; Cheng, K.-m. *Tetrahedron Lett.* ***2000***, *41*, 3411.

[220]Hirab, T.; Nojima, M.; Kusabayashi, S. *J. Org. Chem.* ***1984***, *49*, 4084.

[221]Hirashita, T.; Hayashi, Y.; Mitsui, K.; Araki, S. *Tetrahedron Lett.* ***2004***, *45*, 3225.

[222]Bordwell, F.G.; Mecca, T.G. *J. Am. Chem. Soc.* ***1972***, *94*, 5829; Bordwell, F.G. *Acc. Chem. Res.* ***1970***, *3*, 281, pp. 282–285. See also, de la Mare, P.B.D.; Vernon, C.A. *J. Chem. Soc. B* ***1971***, 1699; Dewar, M.J.S. *J. Am. Chem. Soc.* ***1984***, *106*, 209.

[223]See Uebel, J.J.; Milaszewski, R.F.; Arlt, R.E. *J. Org. Chem.* ***1977***, *42*, 585.

[224]See Fry, A. *Pure Appl. Chem.* ***1964***, *8*, 409; Georgoulis, C.; Ville, G. *J. Chem. Res. (S)* ***1978***, 248; *Bull. Soc. Chim. Fr.* ***1985***, 485; Meislich, H.; Jasne, S.J. *J. Org. Chem.* ***1982***, *47*, 2517.

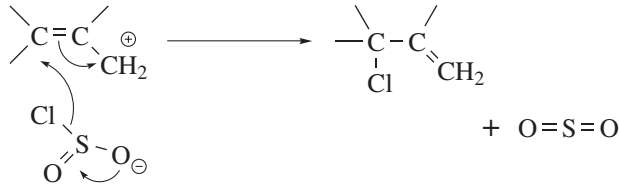
[225]Paquette, L.A.; Stirling, C.J.M. *Tetrahedron* ***1992***, *48*, 7383.

[226]See, for example, Stork, G.; White, W.N. *J. Am. Chem. Soc.* ***1956***, *78*, 4609; Jefford, C.W.; Sweeney, A.; Delay, F. *Helv. Chim. Acta* ***1972***, *55*, 2214; Kirmse, W.; Scheidt, F.; Vater, H. *J. Am. Chem. Soc.* ***1978***, *100*, 3945; Gallina, C.; Ciattini, P.G. *J. Am. Chem. Soc.* ***1979***, *101*, 1035; Magid, R.M.; Fruchey, O.S. *J. Am. Chem. Soc.* ***1979***, *101*, 2107; Bäckvall, J.E.; Vågberg, J.O.; Genêt, J.P. *J. Chem. Soc., Chem. Commun.* ***1987***, 159.

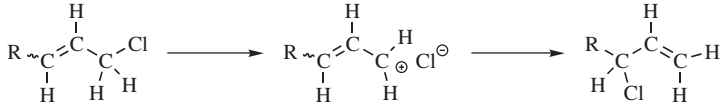
[227]See, for example, Borden, W.T.; Corey, E.J. *Tetrahedron Lett.* ***1969***, 313; Takahashi, T.T.; Satoh, J.Y. *Bull. Chem. Soc. Jpn.* ***1975***, *48*, 69; Staroscik, J.; Rickborn, B. *J. Am. Chem. Soc.* ***1971***, *93*, 3046; See also, Liotta, C. *Tetrahedron Lett.* ***1975***, 523; Stork, G.; Schoofs, A.R. *J. Am. Chem. Soc.* ***1979***, *101*, 5081.

[228]Stork, G.; Kreft III, A.F. *J. Am. Chem. Soc.* ***1977***, *99*, 3850, 3851; Oritani, T.; Overton, K.H. *J. Chem. Soc., Chem. Commun.* ***1978***, 454; Bach, R.D.; Wolber, G.J. *J. Am. Chem. Soc.* ***1985***, *107*, 1352. See also, Chapleo, C.B.; Finch, M.A.W.; Roberts, S.M.; Woolley, G.T.; Newton, R.F.; Selby, D.W. *J. Chem. Soc. Perkin Trans. 1* ***1980***, 1847; Stohrer, W. *Angew. Chem. Int. Ed.* ***1983***, *22*, 613.

When a molecule has in an allylic position a nucleofuge capable of giving the S_Ni reaction, it is possible for the nucleophile to attack at the γ position instead of the α position. This is called the S_Ni' mechanism and has been demonstrated on 2-buten-1-ol and 3-buten-2-ol, both of which gave 100% allylic rearrangement

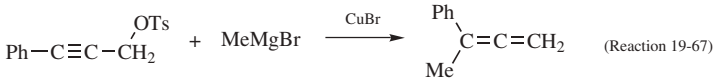


when treated with thionyl chloride in ether.[229] Ordinary allylic rearrangements (S_N1') or S_N2' mechanisms could not be expected to give 100% rearrangement in *both* cases. In the case shown, the nucleophile is only part of the leaving group, not the whole. But it is also possible to have reactions in which a simple leaving group, such as Cl, comes off to form an ion pair and then returns not to the position whence it came, but to the allylic position:



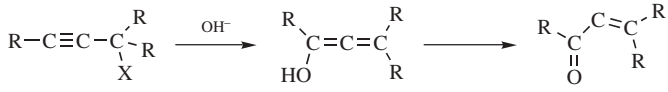
Most S_Ni' reactions are of this type.

Allylic rearrangements have also been demonstrated in propargyl systems, for example,[230]



(Reaction 19-67)

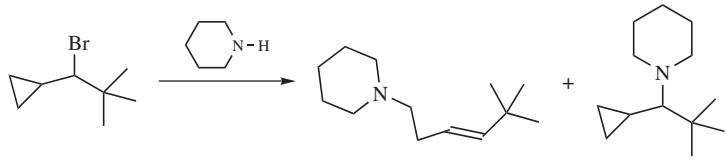
The product in this case is an allene,[231] but such shifts can also give triple-bond compounds or, if Y = OH, an enol will be obtained that tautomerizes to an α,β-unsaturated aldehyde or ketone.



[229]Young, W.G. *J. Chem. Educ.* ***1962***, *39*, 456. For other examples, see Mark, V. *Tetrahedron Lett.* ***1962***, 281; Czernecki, S.; Georgoulis, C.; Labertrande, J.; Prévost, C. *Bull. Soc. Chim. Fr.* ***1969***, 3568; Lewis, E.S.; Witte, K. *J. Chem. Soc. B* ***1968***, 1198; Corey, E.J.; Boaz, N.W. *Tetrahedron Lett.* ***1984***, *25*, 3055.
[230]Vermeer, P.; Meijer, J.; Brandsma, L. *Recl. Trav. Chim. Pays-Bas* ***1975***, *94*, 112.
[231]For reviews of such rearrangements, see Schuster, H.F.; Coppola, G.M. *Allenes in Organic Synthesis*, Wiley, NY, ***1984***, pp. 12–19, 26–30; Taylor, D.R. *Chem. Rev.* ***1967***, *67*, 317, pp. 324–328. For a palladium-catalyzed variation of this transformation see Larock, R.C.; Reddy, Ch.K. *Org. Lett.* ***2000***, *2*, 3325.

When X = OH, this conversion of acetylenic alcohols to unsaturated aldehydes or ketones is called the *Meyer–Schuster rearrangement*.[232] The propargyl rearrangement can also go the other way; that is, 1-haloalkenes, treated with organocopper compounds, give alkynes.[233]

The S_N2' reaction has been shown to predominate in reactions of mixed cuprates (**10-57**) with allylic mesylates,[234] and in ring opening reactions of aziridines.[235] A related reaction is the opening of cyclopropylcarbinyl halides with organocuprates where the cyclopropane ring reacts similarly to the C=C unit of an alkene to give a homoallylic substituted product.[236] This latter reaction is interesting since the reaction of **77** with piperidine leads to the S_N2' product (**78**) in ~87% yield, but there is ~8% of the direct substitution product, **79**. Since the carbon bearing the bromine is very hindered, formation of **72** is somewhat unusual under these conditions. As Bordwell has suggested (see above), this may not be a true S_N2 process.



77 **78** **79**

Nucleophilic Substitution at an Aliphatic Trigonal Carbon: The Tetrahedral Mechanism

All the mechanisms so far discussed take place at a saturated carbon atom. Nucleophilic substitution is also important at trigonal carbons, especially when the carbon is double bonded to an oxygen, a sulfur, or a nitrogen. These reactions are discussed in Chapter 16. Nucleophilic substitution at vinylic carbons is considered in the next section; at aromatic carbons in Chapter 13.

Nucleophilic Substitution at a Vinylic Carbon

Nucleophilic substitution at a vinylic carbon[237] is difficult (see p. 481), but many examples are known. The most common mechanisms are the tetrahedral mechanism

[232]For a review, see Swaminathan, S.; Narayanan, K.V. *Chem. Rev.* ***1971***, *71*, 429. For discussions of the mechanism, see Edens, M.; Boerner, D.; Chase, C.R.; Nass, D.; Schiavelli, M.D. *J. Org. Chem.* ***1977***, *42*, 3403; Andres, J.; Cardenas, R.; Silla, E.; Tapi, O. *J. Am. Chem. Soc.* ***1988***, *110*, 666.

[233]Corey, E.J.; Boaz, N.W. *Tetrahedron Lett.* ***1984***, *25*, 3059, 3063.

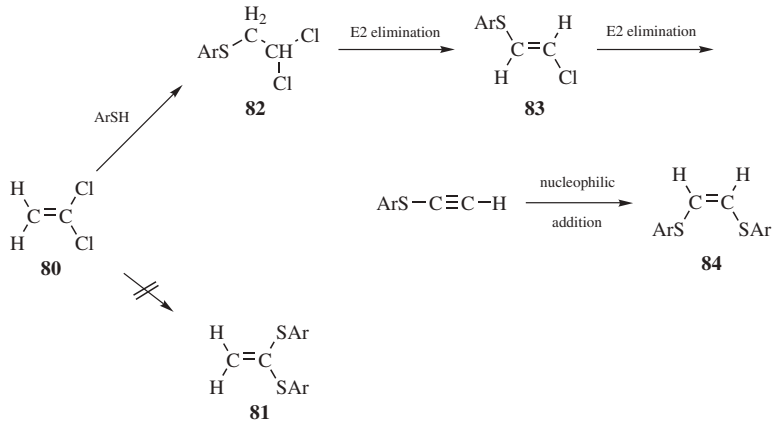
[234]Ibuka, T.; Taga, T.; Habashita, H.; Nakai, K.; Tamamura, H.; Fujii, N.; Chounan, Y.; Nemoto, H.; Yamamoto, Y. *J. Org. Chem.* ***1993***, *58*, 1207.

[235]Wipf, P.; Fritch, P.C. *J. Org. Chem.* ***1994***, *59*, 4875.

[236]Smith, M.B.; Hrubiec, R.T. *Tetrahedron* ***1984***, *40*, 1457; Hrubiec, R.T.; Smith, M.B. *J. Org. Chem.* ***1984***, *49*, 385; Hrubiec, R.T.; Smith, M.B. *Tetrahedron Lett.* ***1983***, *24*, 5031.

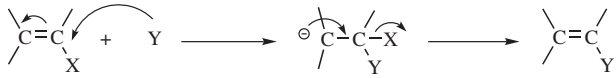
[237]For reviews, see Rappoport, Z. *Recl. Trav. Chim. Pays-Bas* ***1986***, *104*, 309; *React. Intermed. (Plenum)* ***1983***, *3*, 427, *Adv. Phys. Org. Chem.* ***1969***, *7*, 1; Shainyan, B.A. *Russ. Chem. Rev.* ***1986***, *55*, 511; Modena, G. *Acc. Chem. Res.* ***1971***, *4*, 73.

and the closely related *addition–elimination mechanism*. Both of these mechanisms are impossible at a saturated substrate. The addition–elimination mechanism

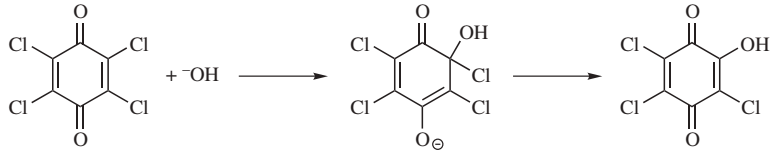


has been demonstrated for the reaction between 1,1-dichloroethene (**80**) and ArS^- catalyzed by ^-OEt.[238] The product was not the 1,1-dithiophenoxy compound **81** but the ''rearranged'' compound **84**. Isolation of **82** and **83** showed that an addition–elimination mechanism had taken place. In the first step, ArSH adds to the double bond (nucleophilic addition, p. 1007) to give the saturated **82**. The second step is an E2 elimination reaction (p. 1478) to give the alkene **83**. A second elimination and addition give **84**.

The tetrahedral mechanism, often also called addition–elimination (AdN-E), takes place with much less facility than with carbonyl groups, since the negative charge of the intermediate must be borne by a carbon, which is less electronegative than oxygen, sulfur, or nitrogen:



Such an intermediate can also stabilize itself by combining with a positive species. When it does, the reaction is nucleophilic addition to a C=C double bond (see Chapter 15). It is not surprising that with vinylic substrates addition and substitution often compete. For chloroquinones, where the charge is spread by resonance, tetrahedral intermediates have been isolated:[239]

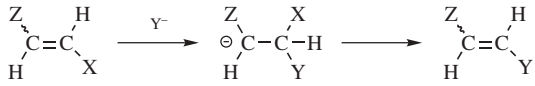


[238]Truce, W.E.; Boudakian, M.M. *J. Am. Chem. Soc.* ***1956***, *78*, 2748.
[239]Hancock, J.W.; Morrell, C.E.; Rhom, D. *Tetrahedron Lett.* ***1962***, 987.

In the case of $Ph(MeO)C{=}C(NO_2)Ph + RS^-$, the intermediate lived long enough to be detected by UV spectroscopy.[240]

Since both the tetrahedral and addition–elimination mechanisms begin the same way, it is usually difficult to tell them apart, and often no attempt is made to do so. The strongest kind of evidence for the addition–elimination sequence is the occurrence of a "rearrangement," but of course the mechanism could still take place even if no rearrangement is found. Evidence[241] that a tetrahedral or an addition–elimination mechanism takes place in certain cases (as opposed, e.g., to an S_N1 or S_N2 mechanism) is that the reaction rate increases when the leaving group is changed from Br to Cl to F (this is called the *element effect*).[242] This clearly demonstrates that the carbon–halogen bond does not break in the rate-determining step (as it would in both the S_N1 and S_N2 mechanisms), because fluorine is by far the poorest leaving group among the halogens in both the S_N1 and S_N2 reactions (p. 496). The rate is faster with fluorides in the cases cited, because the superior electron-withdrawing character of the fluorine makes the carbon of the C—F bond more positive, and hence more susceptible to nucleophilic attack.

Ordinary vinylic substrates react very poorly if at all by these mechanisms, but substitution is greatly enhanced in substrates of the type ZCH=CHX, where Z is an electron-withdrawing group, such as HCO, RCO,[243] EtOOC, $ArSO_2$, NC, and F, since these β groups stabilize the carbanion:



Many such examples are known. In most cases where the stereochemistry has been investigated, retention of configuration is observed,[244] but stereoconvergence [the same product mixture from an (*E*) or (*Z*) substrate] has also been observed,[245] especially where the carbanionic carbon bears two electron-withdrawing groups. Although rare, nucleophilic substitution with inversion has also been reported as in the intramolecular substitution of the C—Br bond of 2-bromobut-2-enylamines by the pendant nitrogen atom, giving 2-ethylene aziridines by way of stereochemical inversion.[246] It is not immediately apparent why the tetrahedral mechanism

[240]Bernasconi, C.F.; Fassberg, J.; Killion, Jr., R.B.; Rappoport, Z. *J. Am. Chem. Soc.* ***1989***, *112*, 3169; *J. Org. Chem.* ***1990***, *55*, 4568.

[241]Additional evidence comes from the pattern of catalysis by amines, similar to that discussed for aromatic substrates on p. 856. See Rappoport, Z.; Peled, P. *J. Am. Chem. Soc.* ***1979***, *101*, 2682, and references cited therein.

[242]Beltrame, P.; Favini, G.; Cattania, M.G.; Guella, F. *Gazz. Chim. Ital.* ***1968***, *98*, 380. See also, Solov'yanov, A.A.; Shtern, M.M.; Beletskaya, I.P.; Reutov, O.A. *J. Org. Chem. USSR* ***1983***, *19*, 1945; Avramovitch, B.; Weyerstahl, P.; Rappoport, Z. *J. Am. Chem. Soc.* ***1987***, *109*, 6687.

[243]For a review, see Rybinskaya, M.I.; Nesmeyanov, A.N.; Kochetkov, N.K. *Russ. Chem. Rev.* ***1969***, *38*, 433.

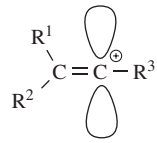
[244]Rappoport, Z. *Adv. Phys. Org. Chem.* ***1969***, *7*, see pp. 31–62; Shainyan, B.A. *Russ. Chem. Rev.* ***1986***, *55*, 516. See also, Rappoport, Z.; Gazit, A. *J. Am. Chem. Soc.* ***1987***, *109*, 6698.

[245]See Rappoport, Z.; Gazit, A. *J. Org. Chem.* ***1985***, *50*, 3184, *J. Am. Chem. Soc.* ***1986***, *51*, 4112; Park, K.P.; Ha, H. *Bull. Chem. Soc. Jpn.* ***1990***, *63*, 3006.

[246]Shiers, J.J.; Shipman, M.; Hayes, J.-F.; Slawin, A.M.Z. *J. Am. Chem. Soc.* ***2004***, *126*, 6868.

should lead to retention, but this behavior has been ascribed, on the basis of molecular orbital calculations, to hyperconjugation involving the carbanionic electron pair and the substituents on the adjacent carbon.[247]

Vinylic substrates are in general very reluctant to undergo S_N1 reactions, but they can be made to do so in two ways:[248] (*1*) By the use of an a group that stabilizes the vinylic cation. For example, α-aryl vinylic halides $ArCBr{=}CR'_2$ have often been shown to give S_N1 reactions.[249] The S_N1 reactions have also been demonstrated with other stabilizing groups: cyclopropyl,[250] vinylic,[251] alkynyl,[252] and an adjacent double bond ($R_2C{=}C{=}CR'X$).[253] (*2*) Even without a stabilization, by the use of a very good leaving group, OSO_2CF_3 (triflate).[254] The stereochemical outcome of S_N1 reactions at a vinylic substrate is often randomization,[255] that is, either a cis or a trans substrate gives a 1:1 mixture of cis and trans products, indicating that vinylic cations are linear. Another indication that vinylic cations prefer to be linear is the fact that reactivity in cycloalkenyl systems decreases with decreasing ring size.[256] However, a linear vinylic cation need not give random products.[257] The empty *p* orbital lies in the plane of the double bond,



so entry of the nucleophile can be and often is influenced by the relative size of R^1 and R^2.[258] It must be emphasized that even where vinylic substrates do give S_N1

[247]Apeloig, Y.; Rappoport, Z. *J. Am. Chem. Soc.* ***1979***, *101*, 5095.

[248]For reviews of the S_N1 mechanism at a vinylic substrate, see Stang, P.J.; Rappoport, Z.; Hanack, H.; Subramanian, L.R. *Vinyl Cations*, Chapt. 5; Academic Press, NY, ***1979***; Stang, P.J. *Acc. Chem. Res.* ***1978***, *11*, 107; Rappoport, Z. *Acc. Chem. Res.* ***1976***, *9*, 265; Subramanian, L.R.; Hanack, M. *J. Chem. Educ.* ***1975***, *52*, 80; Hanack, M. *Acc. Chem. Res.* ***1970***, *3*, 209; Modena, G.; Tonellato, U. *Adv. Phys. Org. Chem.* ***1971***, *9*, 185, 231–253; Grob, C.A. *Chimia* ***1971***, *25*, 87; Rappoport, Z.; Bässler, T.; Hanack, M. *J. Am. Chem. Soc.* ***1970***, *92*, 4985.

[249]For a review, see Stang, P.J.; Rappoport, Z.; Hanack, H.; Subramanian, L.R. *Vinyl Cations*, Chapt. 6, Academic Press, NY, ***1979***.

[250]Kelsey, D.R.; Bergman, R.G. *J. Am. Chem. Soc.* ***1970***, *92*, 238; ***1971***, *93*, 1941; Hanack, M.; Bässler, T.; Eymann, W.; Heyd, W.E.; Kopp, R. *J. Am. Chem. Soc.* ***1974***, *96*, 6686.

[251]Grob, C.A.; Spaar, R. *Tetrahedron Lett.* ***1969***, 1439; *Helv. Chim. Acta* ***1970***, *53*, 2119.

[252]Hassdenteufel, J.R.; Hanack, M. *Tetrahedron Lett.* ***1980***, 503. See also, Kobayashi, S.; Nishi, T.; Koyama, I.; Taniguchi, H. *J. Chem. Soc., Chem. Commun.* ***1980***, 103.

[253]Schiavelli, M.D.; Gilbert, R.P.; Boynton, W.A.; Boswell, C.J. *J. Am. Chem. Soc.* ***1972***, *94*, 5061.

[254]See, for example, Clarke, T.C.; Bergman, R.G. *J. Am. Chem. Soc.* ***1972***, *94*, 3627; ***1974***, *96*, 7934; Summerville, R.H.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1972***, *94*, 3629; ***1974***, *96*, 1110; Hanack, M.; Märkl, R.; Martinez, A.G. *Chem. Ber.* ***1982***, *115*, 772.

[255]Rappoport, Z.; Apeloig, Y. *J. Am. Chem. Soc.* ***1969***, *91*, 6734; Kelsey, D.R.; Bergman, R.G. *J. Am. Chem. Soc.* ***1970***, *92*, 238; ***1971***, *93*, 1941.

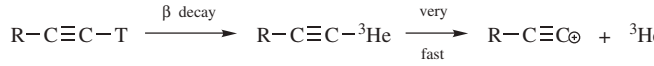
[256]Pfeifer, W.D.; Bahn, C.A.; Schleyer, P.v.R.; Bocher, S.; Harding, C.E.; Hummel, K.; Hanack, M.; Stang, P.J. *J. Am. Chem. Soc.* ***1971***, *93*, 1513.

[257]For examples of inversion, see Clarke, T.C.; Bergman, R.G. *J. Am. Chem. Soc.* ***1972***, *94*, 3627; ***1974***, *96*, 7934; Summerville, R.H.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1972***, *94*, 3629; ***1974***, *96*, 1110.

[258]Maroni, R.; Melloni, G.; Modena, G. *J. Chem. Soc., Chem. Commun.* ***1972***, 857.

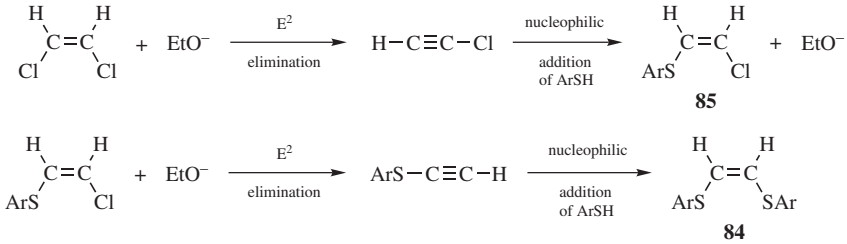
reactions, the rates are generally lower than those of the corresponding saturated compounds.

Alkynyl cations are so unstable that they cannot be generated even with very good leaving groups. However, one way in which they have been generated was by formation of a tritiated substrate.



When the tritium (half-life 12.26 years) decays it is converted to the helium-3 isotope, which, of course, does not form covalent bonds, and so immediately departs, leaving behind the alkynyl cation. When this was done in the presence of benzene, $RC{=}CC_6H_5$ was isolated.[259] The tritium-decay technique has also been used to generate vinylic and aryl cations.[260]

Besides the mechanisms already discussed, another mechanism, involving an *elimination–addition* sequence, has been observed in vinylic systems (a similar mechanism is known for aromatic substrates, p. 859). An example of a reaction involving this mechanism is the reaction of 1,2-dichloroethane with ArS^- and ^-OEt to produce **84**. The mechanism may be formulated as:



The steps are the same as in the addition–elimination mechanism, but in reverse order. Evidence for this sequence[261] is as follows: (*1*) The reaction does not proceed without ethoxide ion, and the rate is dependent on the concentration of this ion and not on that of ArS^-. (*2*) Under the same reaction conditions, chloroacetylene gave **85** and **84**. (*3*) Compound **85**, treated with ArS^-, gave no reaction but, when EtO^- was added, **84** was obtained. It is interesting that the elimination–addition mechanism has even been shown to occur in five- and six-membered cyclic systems, where triple bonds are greatly strained.[262] Note that both the addition–elimination and elimination–addition sequences, as shown above, lead to overall retention of configuration, since in each case both addition and elimination are anti.

[259]Angelini, G.; Hanack, M.; Vermehren, J.; Speranza, M. *J. Am. Chem. Soc.* ***1988***, *110*, 1298.

[260]For a review, see Cacace, F. *Adv. Phys. Org. Chem.* ***1970***, *8*, 79. See also, Fornarini, S.; Speranza, M. *J. Am. Chem. Soc.* ***1985***, *107*, 5358.

[261]Flynn, Jr., J.; Badiger, V.V.; Truce, W.E. *J. Org. Chem.* ***1963***, *28*, 2298. See also, Shainyan, B.A.; Mirskova, A.N. *J. Org. Chem. USSR* ***1984***, *20*, 885, 1989; ***1985***, *21*, 283.

[262]Montgomery, L.K.; Clouse, A.O.; Crelier, A.M.; Applegate, L.E. *J. Am. Chem. Soc.* ***1967***, *89*, 3453; Caubere, P.; Brunet, J. *Tetrahedron* ***1971***, *27*, 3515; Bottini, A.T.; Corson, F.P.; Fitzgerald, R.; Frost II, K.A. *Tetrahedron* ***1972***, *28*, 4883.

The elimination–addition sequence has also been demonstrated for certain reactions of saturated substrates, for example, $ArSO_2CH_2CH_2SO_2Ar$.[263] Treatment of this with ethoxide proceeds as follows:

$$ArSO_2CH_2CH_2SO_2Ar \xrightarrow[E^2 \text{ elimination}]{EtO^-} ArSO_2CH{=}CH_2 \xrightarrow[\text{addition}]{EtO^-} ArSO_2CH_2CH_2OEt$$

Mannich bases (see **16-19**) of the type $RCOCH_2CH_2NR_2$ similarly undergo nucleophilic substitution by the elimination–addition mechanism.[264] The nucleophile replaces the NR_2 group.

The simple S_N2 mechanism has never been convincingly demonstrated for vinylic substrates.[265]

Vinylic halides can react by a $S_{RN}1$ mechanism (p. 862) in some cases. An example is the $FeCl_2$-catalyzed reaction of 1-bromo-2-phenylethene and the enolate anion of pinacolone (t-$BuCOCH_2^-$), which gave a low yield of substitution products along with alkynes.[266]

REACTIVITY

A large amount of work has been done on this subject. although a great deal is known, much is still poorly understood, and many results are anomalous and hard to explain. In this section, only approximate generalizations are attempted. The work discussed here, and the conclusions reached, pertain to reactions taking place in solution. Some investigations have also been carried out in the gas phase.[267]

The Effect of Substrate Structure

The effect on the reactivity of a change in substrate structure depends on the mechanism.

1. *Branching at the* α *and* β *Carbons*. For the S_N2 mechanism, branching at either the α or the β carbon decreases the rate. Tertiary systems seldom[268]

[263]Kader, A.T.; Stirling, C.J.M. *J. Chem. Soc.* ***1962***, 3686. For another example, see Popov, A.F.; Piskunova, Z.; Matvienko, V.N. *J. Org. Chem. USSR* ***1986***, *22*, 1299.

[264]For an example, see Andrisano, R.; Angeloni, A.S.; De Maria, P.; Tramontini, M. *J. Chem. Soc. C* ***1967***, 2307.

[265]For discussions, see Miller, S.I. *Tetrahedron* ***1977***, *33*, 1211; Texier, F.; Henri-Rousseau, O.; Bourgois, J. *Bull. Soc. Chim. Fr.* ***1979***, II-11; Rappoport, Z. *Acc. Chem. Res.* ***1981***, *14*, 7; Rappoport, Z.; Avramovitch, B. *J. Org. Chem.* ***1982***, *47*, 1397.

[266]Galli, C.; Gentili, P.; Rappoport, Z. *J. Org. Chem.* ***1994***, *59*, 6786; Galli, C.; Gentili, P. *J. Chem. Soc., Chem. Commun.* ***1993***, 570.

[267]See, for example, DePuy, C.H.; Gronert, S.; Mullin, A.; Bierbaum, V.M. *J. Am. Chem. Soc.* ***1990***, *112*, 8650.

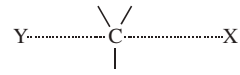
[268]For a reported example, see Edwards, O.E.; Grieco, C. *Can. J. Chem.* ***1974***, *52*, 3561.

TABLE 10.3. Average Relative S_N2 Rates for Some Alkyl Substrates[270]

R	Relative rate	R	Relative rate
Methyl	30	Isobutyl	0.03
Ethyl	1	Neopentyl	10^{-5}
Propyl	0.4	Allyl	40
Butyl	0.4	Benzyl	120
Isopropyl	0.025		

react by the S_N2 mechanism and neopentyl systems react so slowly as to make such reactions, in general, synthetically useless.[269] Table 10.3 shows average relative rates for some alkyl substrates.[270] The reason for these low rates is almost certainly steric.[271] The transition state **1** is more crowded when larger groups are close to the central carbon.

The tetrahedral mechanism for substitution at a carbonyl carbon is also slowed or blocked completely by α or β branching for similar reasons. Solvolysis in such systems is linked to relief of B-strain, but solvent participation can overshadow this as steric hindrance increases.[272] Severe steric strain can cause distortion from coplanarity in the carbocation intermediate,[273] although there seems to be no loss of resonance stability.[274] Adding electron-donating substituents to such molecules improves coplanarity in the cation.[275] For example, esters of the formula R_3CCOOR' cannot generally be hydrolyzed by the tetrahedral mechanism (see **16-59**), nor can acids R_3CCOOH be easily esterified.[276] Synthetic advantage can be taken of this fact, for example, when in a molecule containing two ester groups only the less hindered one is hydrolyzed.



1

[269]The S_N2 reactions on neopentyl tosylates have been conveniently carried out in the solvents HMPA and DMSO: Lewis, R.G.; Gustafson, D.H.; Erman, W.F. *Tetrahedron Lett.* ***1967***, 401; Paquette, L.A.; Philips, J.C. *Tetrahedron Lett.* ***1967***, 4645; Anderson, P.H.; Stephenson, B.; Mosher, H.S. *J. Am. Chem. Soc.* ***1974***, *96*, 3171.

[270]This table is from Streitwieser, A. *Solvolytic Displacement Reactions*, McGraw-Hill, NY, ***1962***, p. 13. Also see, Table 9.2.

[271]For evidence, see Caldwell, G.; Magnera, T.F.; Kebarle, P. *J. Am. Chem. Soc.* ***1984***, *106*, 959.

[272]Liu, K.-T.; Hou, S.-J.; Tsao, K.-L. *J. Org. Chem.* ***1998***, *63*, 1360.

[273]Fujio, M.; Nomura, H.; Nakata, K.; Saeki, Y.; Mishima, M.; Kobayashi, S.; Matsushita, T.; Nishimoto, K.; Tsuno, Y. *Tetrahedron Lett.* ***1994***, *35*, 5005.

[274]Fujio, M.; Nakata, K.; Kuwamura, T.; Nakamura, H.; Saeki, Y.; Mishima, M.; Kobayashi, S.; Tsuno, Y. *Tetrahedron Lett.* ***1992***, *34*, 8309.

[275]Liu, K.T.; Tsao, M.-L.; Chao, I. *Tetrahedron Lett.* ***1996***, *37*, 4173.

[276]For a molecular mechanics study of this phenomenon, see DeTar, D.F.; Binzet, S.; Darba, P. *J. Org. Chem.* ***1987***, *52*, 2074.

TABLE 10.4. Relative Rates of Solvolysis of RBr in Two Solvents[277]

RBr Substrate	In 60% Ethanol at 55°C	In Water at 50°C
MeBr	2.08	1.05
EtBr	1.00	1.00
*i*PrBr	1.78	11.6
t-BuBr	2.41×10^4	1.2×10^6

For the S_N1 mechanism, a branching increases the rate, as shown in Table 10.4.[277] We can explain this by the stability order of alkyl cations (tertiary > secondary > primary). Of course, the rates are not actually dependent on the stability of the ions, but on the difference in free energy between the starting compounds and the transition states. We use the Hammond postulate (p. 308) to make the assumption that the transition states resemble the cations and that anything (e.g., a branching) that lowers the free energy of the ions also lowers it for the transition states. For simple alkyl groups, the S_N1 mechanism is important under all conditions only for tertiary substrates.[278] As previously indicated (p. 440), secondary substrates generally react by the S_N2 mechanism,[279] except that the S_N1 mechanism may become important at high solvent polarities. Table 10.4 shows that isopropyl bromide reacts less than twice as fast as ethyl bromide in the relatively nonpolar 60% ethanol (compare this with the 10^4 ratio for *tert*-butylbromide, where the mechanism is certainly S_N1), but in the more polar water the rate ratio is 11.6. The 2-adamantyl system is an exception; it is a secondary system that reacts by the S_N1 mechanism because backside attack is hindered for steric reasons.[280] Because there is no S_N2 component, this system provides an opportunity for comparing the pure S_N1 reactivity of secondary and tertiary substrates. It has been found that substitution of a methyl group for the a

[277]These values are from Streitwieser, A. *Solvolytic Displacement Reactions*, McGraw-Hill, NY, ***1962***, p. 43, where values are also given for other conditions. Methyl bromide reacts faster than ethyl bromide (and in the case of 60% ethanol, ispropyl bromide) because most of it (probably all) reacts by the S_N2 mechanism.

[278]For a report of an S_N1 mechanism at a primary carbon, see Zamashchikov, V.V.; Bezbozhnaya, T.V.; Chanysheva, I.R. *J. Org. Chem. USSR* ***1986***, *22*, 1029.

[279]See Raber, D.J.; Harris, J.M. *J. Chem. Educ.* ***1972***, *49*, 60; Lambert, J.B.; Putz, G.J.; Mixan, C.E. *J. Am. Chem. Soc.* ***1972***, *94*, 5132; Nordlander, J.E.; McCrary, Jr., T.J. *J. Am. Chem. Soc.* ***1972***, *94*, 5133; Fry, J.L.; Lancelot, C.J.; Lam, L.K.M.; Harris, J.M.; Bingham, R.C.; Raber, D.J.; Hall, R.E.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1970***, *92*, 2538; Dietze, P.E.; Jencks, W.P. *J. Am. Chem. Soc.* ***1986***, *108*, 4549; Dietze, P.E.; Hariri, R.; Khattak, J. *J. Org. Chem.* ***1989***, *54*, 3317.

[280]Fry, J.L.; Harris, J.M.; Bingham, R.C.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1970***, *92*, 2540; Schleyer, P.v.R.; Fry, J.L.; Lam, L.K.M.; Lancelot, C.J. *J. Am. Chem. Soc.* ***1970***, *92*, 2542. See also, Pritt, J.R.; Whiting, M.C. *J. Chem. Soc. Perkin Trans. 2* ***1975***, 1458. For an *ab initio* molecular-orbital study of the 2-adamantyl cation, see Dutler, R.; Rauk, A.; Sorensen, T.S.; Whitworth, S.M. *J. Am. Chem. Soc.* ***1989***, *111*, 9024.

hydrogen of 2-adamantyl substrates (thus changing a secondary to a tertiary system) increases solvolysis rates by a factor of $\sim 10^8$.[281] Simple primary substrates react by the S_N2 mechanism (or with participation by neighboring alkyl or hydrogen), but not by the S_N1 mechanism, even when solvolyzed in solvents of very low nucleophilicity[282] (e.g., trifluoroacetic acid or trifluoroethanol[283]), and even when very good leaving groups (e.g., OSO_2F) are present[284] (see, however, p. 497).

For some tertiary substrates, the rate of S_N1 reactions is greatly increased by the relief of B strain in the formation of the carbocation (see p. 398). Except where B strain is involved, β branching has little effect on the S_N1 mechanism, except that carbocations with β branching undergo rearrangements readily. Of course, isobutyl and neopentyl are primary substrates, and for this reason react very slowly by the S_N1 mechanism, but not more slowly than the corresponding ethyl or propyl compounds.

To sum up, primary and secondary substrates generally react by the S_N2 mechanism and tertiary by the S_N1 mechanism. However, tertiary substrates seldom undergo nucleophilic substitution at all. Elimination is always a possible side reaction of nucleophilic substitutions (wherever a β hydrogen is present), and with tertiary substrates it usually predominates. With a few exceptions, nucleophilic substitutions at a tertiary carbon have little or no preparative value. However, tertiary substrates that can react by the SET mechanism (e.g., p-$NO_2C_6H_4CMe_2Cl$) give very good yields of substitution products when treated with a variety of nucleophiles.[285]

2. *Unsaturation at the α Carbon*. Vinylic, acetylenic,[286] and aryl substrates are very unreactive toward nucleophilic substitutions. For these systems, both the S_N1 and S_N2 mechanisms are greatly slowed or stopped altogether. One reason that has been suggested for this is that sp^2 (and even more, sp) carbon atoms have a higher electronegativity than sp^3 carbons and thus a greater attraction for the electrons of the bond. As we have seen (p. 388), an sp–H bond has a higher acidity than an sp^3—H bond, with that of an sp^2 H bond in

[281]Fry, J.L.; Engler, E.M.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1972***, *94*, 4628. See also, Gassman, P.G.; Pascone, J.M. *J. Am. Chem. Soc.* ***1973***, *95*, 7801.

[282]For discussions and attempts to develop quantitative scales of solvent nucleophilicity see Minegishi, S.; Kobayashi, S.; Mayr, H. *J. Am. Chem. Soc.* ***2004***, *126*, 5174; Catalan, J.; Diaz, C.; Garcia-Blanco, F. *J. Org. Chem.* ***1999***, *64*, 6512; Bentley, T.W.; Llewellyn, G. *Prog. Phys. Org. Chem.* ***1990***, *17*, 121; Kevill, D.N., in Charton, M. *Advances in Quantitative Structure-Property Relationships*, Vol. 1, JAI Press, Greenwich, CT, ***1996***, pp. 81–115; Grunwald, E.; Winstein, S. *J. Am. Chem. Soc.* ***1948***, *70*, 846; Winstein, S.; Fainberg, A.H.; Grunwald, E. *J. Am. Chem. Soc.* ***1957***, *79*, 4146; Peterson, P.E.; Waller, F.J. *J. Am. Chem. Soc.* ***1972***, *94*, 991; Schadt, F.L.; Bentley, T.W.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1976***, *98*, 7667.

[283]Dafforn, G.A.; Streitwieser, Jr., A. *Tetrahedron Lett.* ***1970***, 3159.

[284]Cafferata, L.F.R.; Desvard, O.E.; Sicre, J.E. *J. Chem. Soc. Perkin Trans. 2* ***1981***, 940.

[285]Kornblum, N.; Cheng, L.; Davies, T.M.; Earl, G.W.; Holy, N.L.; Kerber, R.C.; Kestner, M.M.; Manthey, J.W.; Musser, M.T.; Pinnick, H.W.; Snow, D.H.; Stuchal, F.W.; Swiger, R.T. *J. Org. Chem.* ***1987***, *52*, 196.

[286]For a discussion of S_N reactions at acetylenic substrates, see Miller, S.I.; Dickstein, J.I. *Acc. Chem. Res.* ***1976***, *9*, 358.

between. This is reasonable; the carbon retains the electrons when the proton is lost and an *sp* carbon, which has the greatest hold on the electrons, loses the proton most easily. But in nucleophilic substitution, the leaving group *carries off* the electron pair, so the situation is reversed and it is the sp^3 carbon that loses the leaving group and the electron pair most easily. It may be recalled (p. 24) that bond distances decrease with increasing *s* character. Thus the bond length for a vinylic or aryl C—Cl bond is 1.73 Å compared with 1.78 Å for a saturated C—Cl bond. Other things being equal, a shorter bond is a stronger bond.

Of course, we have seen (p. 476) that S_N1 reactions at vinylic substrates can be accelerated by α substituents that stabilize that cation, and that reactions by the tetrahedral mechanism can be accelerated by β substituents that stabilize the carbanion. Also, reactions at vinylic substrates can in certain cases proceed by addition–elimination or elimination–addition sequences (pp. 473, 476).

In contrast to such systems, substrates of the type RCOX are usually much *more* reactive than the corresponding RCH_2X. Of course, the mechanism here is almost always the tetrahedral one. Three reasons can be given for the enhanced reactivity of RCOX: (*1*) The carbonyl carbon has a sizable partial positive charge that makes it very attractive to nucleophiles. (*2*) In an S_N2 reaction, a σ bond must break in the rate-determining step, which requires more energy than the shift of a pair of π electrons, which is what happens in a tetrahedral mechanism. (*3*) A trigonal carbon offers less steric hindrance to a nucleophile than a tetrahedral carbon.

For reactivity in aryl systems, see Chapter 13.

3. *Unsaturation at the* β *Carbon*. The S_N1 rates are increased when there is a double bond in the β position, so that allylic and benzylic substrates react rapidly (Table 10.5).[287] The reason is that allylic (p. 239) and benzylic[288]

TABLE 10.5. Relative Rates for the S_N1 Reaction between ROTs and Ethanol at 25°C[285]

Group	Relative Rate
Et	0.26
*i*Pr	0.69
$CH_2{=}CHCH_2$	8.6
$PhCH_2$	100
Ph_2CH	$\sim 10^5$
Ph_3C	$\sim 10^{10}$

[287]Streitwieser, A. *Solvolytic Displacement Reactions*, McGraw-Hill, NY, ***1962***, p. 75. Actually, the figures for Ph_2CHOTs and Ph_3COTs are estimated from the general reactivity of these substrates.

[288]For a Grunwald-Winstein correlation analysis of the solvolysis of benzyl bromide, see Liu, K.-T.; Hou, I.-J. *Tetrahedron* ***2001***, *57*, 3343.

(p. 240) cations are stabilized by resonance. As shown in Table 10.5, a second and a third phenyl group increase the rate still more, because these carbocations are more stable yet. Remember that allylic rearrangements are possible with allylic systems.

In general, S_N1 rates at an allylic substrate are increased by any substituent in the 1 or 3 position that can stabilize the carbocation by resonance or hyperconjugation.[289] Among these are alkyl, aryl, and halo groups.

86

The S_N2 rates for allylic and benzylic systems are also increased (see Table 10.3), probably owing to resonance possibilities in the transition state. Evidence for this in benzylic systems is that the rate of the reaction was 8000 times slower than the rate with $(PhCH_2)_2SEt^+$.[290] The cyclic **86** does not have the proper geometry for conjugation in the transition state.

Triple bonds in the β position (in propargyl systems) have about the same effect as double bonds.[291] Alkyl, aryl, halo, and cyano groups, among others, in the 3 position of allylic substrates increase S_N2 rates, owing to increased resonance in the transition state, but alkyl and halo groups in the 1 position decrease the rates because of steric hindrance.

4. α *Substitution*. Compounds of the formula ZCH_2X, where Z = RO, RS, or R_2N undergo S_N1 reactions very rapidly,[292] because of the increased resonance in the carbocation. These groups have an unshared pair on an atom directly attached to the positive carbon, which stabilizes the carbocation (p. 242). The field effects of these groups would be expected to decrease S_N1 rates (see Section 6, p. 485), so the resonance effect is far more important.

When Z in ZCH_2X is RCO,[293] HCO, ROCO, NH_2CO, NC, or F_3C,[294] S_N1 rates are decreased compared to CH_3X, owing to the electron-withdrawing field

[289]For a discussion of the relative reactivities of different allylic substrates, see DeWolfe, R.H.; Young, W.G., in Patai, S. *The Chemistry of Alkenes*, Wiley, NY, **1964**, pp. 683–688, 695–697.

[290]King, J.F.; Tsang, G.T.Y.; Abdel-Malik, M.M.; Payne, N.C. *J. Am. Chem. Soc.* ***1985***, *107*, 3224.

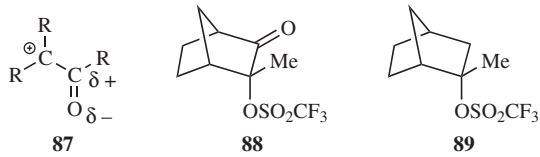
[291]Hatch, L.F.; Chiola, V. *J. Am. Chem. Soc.* ***1951***, *73*, 360; Jacobs, T.L.; Brill, W.F. *J. Am. Chem. Soc.* ***1953***, *75*, 1314.

[292]For a review of the reactions of α-haloamines, sulfides, and ethers, see Gross, H.; Höft, E. *Angew. Chem. Int. Ed.* ***1967***, *6*, 335.

[293]For a review of α-halo ketones, including reactivity, see Verhé, R.; De Kimpe, N., in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups*, *Supplement D*, pt. 1, Wiley, NY, ***1983***, pp. 813–931. This review has been reprinted, and new material added, in De Kimpe, N.; Verhé, R. *The Chemistry of α-Haloketones*, *α-Haloaldehydes*, *and α-Haloimines*, Wiley, NY, ***1988***, pp. 225–368.

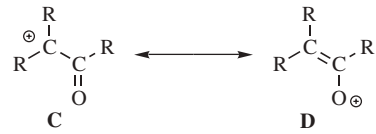
[294]Liu, K.; Kuo, M.; Shu, C. *J. Am. Chem. Soc.* ***1982***, *104*, 211; Gassman, P.G.; Harrington, C.K. *J. Org. Chem.* ***1984***, *49*, 2258; Allen, A.D.; Girdhar, R.; Jansen, M.P.; Mayo, J.D.; Tidwell, T.T. *J. Org. Chem.* ***1986***, *51*, 1324; Allen, A.D.; Kanagasabapathy, V.M.; Tidwell, T.T. *J. Am. Chem. Soc.* ***1986***, *108*, 3470; Richard, J.P. *J. Am. Chem. Soc.* ***1989***, *111*, 1455.

effects of these groups. Furthermore, carbocations[295] with an a CO or CN group are greatly destabilized because of the partial positive charge on the adjacent carbon (**87**). The S_N1 reactions have been carried out on such compounds,[296] but the rates are very low. For example, from a comparison of the solvolysis rates of **88** and **89**, a rate-retarding effect of 10^7.[3]



87 **88** **89**

was estimated for the C=O group.[297] However, when a different kind of comparison is made: $RCOCR'_2X$ versus HCR'_2X (where X = a leaving group), the RCO had only a small or negligible rate-retarding effect, indicating that resonance stabilization[298]



C **D**

may be offsetting the inductive destabilization for this group.[299] For a CN group also, the rate-retarding effect is reduced by this kind of resonance.[300] A carbocation with an a COR group has been isolated.[301]

When S_N2 reactions are carried out on these substrates, rates are greatly increased for certain nucleophiles (e.g., halide or halide-like ions), but decreased or essentially unaffected by others.[302] For example, α-chloroacetophenone ($PhCOCH_2Cl$) reacts with KI in acetone at 75°C ~32,000 times faster than 1-chlorobutane,[303] but α-bromoacetophenone reacts with the nucleophile triethylamine 0.14 times as fast as iodomethane.[302] The reasons

[295]For reviews of such carbocations, see Bégué, J.; CharpentierMorize, M. *Acc. Chem. Res.* ***1980***, *13*, 207; Charpentier-Morize, M. *Bull. Soc. Chim. Fr.* ***1974***, 343.

[296]For reviews, see Creary, X. *Acc. Chem. Res.* ***1985***, *18*, 3; Creary, X.; Hopkinson, A.C.; Lee-Ruff, E. *Adv. Carbocation Chem.* ***1989***, *1*, 45; Charpentier-Morize, M.; Bonnet-Delpon, D. *Adv. Carbocation Chem.* ***1989***, *1*, 219.

[297]Creary, X. *J. Org. Chem.* ***1979***, *44*, 3938.

[298]**D**, which has the positive charge on the more electronegative atom, is less stable than **C**, according to rule c on p. 47, but it nevertheless seems to be contributing in this case.

[299]Creary, X. *J. Am. Chem. Soc.* ***1984***, *106*, 5568. See, however, Takeuchi, K.; Yoshida, M.; Ohga,Y.; Tsugeno, A.; Kitagawa, T. *J. Org. Chem.* ***1990***, *55*, 6063.

[300]Gassman, P.G.; Saito, K.; Talley, J.J. *J. Am. Chem. Soc.* ***1980***, *102*, 7613.

[301]Takeuchi, K.; Kitagawa, T.; Okamoto, K. *J. Chem. Soc., Chem. Commun.* ***1983***, 7. See also, Dao, L.H.; Maleki, M.; Hopkinson, A.C.; Lee-Ruff, E. *J. Am. Chem. Soc.* ***1986***, *108*, 5237.

[302]Halvorsen, A.; Songstad, J. *J. Chem. Soc., Chem. Commun.* ***1978***, 327.

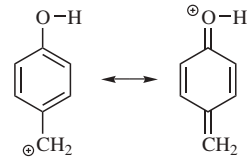
[303]Bordwell, F.G.; Brannen, Jr., W.T. *J. Am. Chem. Soc.* ***1964***, *86*, 4645. For some other examples, see Conant, J.B.; Kirner, W.R.; Hussey, R.E. *J. Am. Chem. Soc.* ***1925***, *47*, 488; Sisti, A.J.; Lowell, S. *Can. J. Chem.* ***1964***, *42*, 1896.

for this varying behavior are not clear, but those nucleophiles that form a "tight" transition state (one in which bond making and bond breaking have proceeded to about the same extent) are more likely to accelerate the reaction.[304]

When Z is SOR or SO_2R (e.g., α-halo sulfoxides and sulfones), nucleophilic substitution is retarded.[305] The S_N1 mechanism is slowed by the electron-withdrawing effect of the SOR or SO_2R group,[306] and the S_N2 mechanism presumably by the steric effect.

5. β *Substitution*. For compounds of the type ZCH_2CH_2X, where Z is any of the groups listed in the previous section as well as halogen[307] or phenyl, S_N1 rates are lower than for unsubstituted systems, because the resonance effects mentioned in Section 4 are absent, but the field effects are still there, although smaller. These groups in the β position do not have much effect on S_N2 rates unless they behave as neighboring groups and enhance the rate through anchimeric assistance,[308] or unless their size causes the rates to decrease for steric reasons.[309] It has been shown that silicon exerts a β-effect, and that tin exerts a γ-effect.[310] Silcon also exerts a γ-effect.[311]

6. *The Effect of Electron-Donating and Electron-Withdrawing Groups*. If substitution rates of series of compounds $p\text{-}ZC_6H_4CH_2X$ are measured, it is possible to study the electronic effects of groups Z on the reaction. Steric effects of Z are minimized or eliminated, because Z is so far from the reaction site. For S_N1 reactions electron-withdrawing Z decrease the rate and electron-donating Z increase it,[312] because the latter decrease the energy of the transition state (and of the carbocation) by spreading the positive charge, for example,



[304]For discussions of possible reasons, see McLennan, D.J.; Pross, A. *J. Chem. Soc. Perkin Trans. 2* ***1984***, 981; Yousaf, T.I.; Lewis, E.S. *J. Am. Chem. Soc.* ***1987***, *109*, 6137; Lee, I.; Shim, C.S.; Chung, S.Y.; Lee, I. *J. Chem. Soc. Perkin Trans. 2* ***1988***, 975; Yoh, S.; Lee, H.W. *Tetrahedron Lett.* ***1988***, *29*, 4431.

[305]Bordwell, F.G.; Jarvis, B.B. *J. Org. Chem.* ***1968***, *33*, 1182; Loeppky, R.N.; Chang, D.C.K. *Tetrahedron Lett.* ***1968***, 5414; Cinquini, M.; Colonna, S.; Landini, D.; Maia, A.M. *J. Chem. Soc. Perkin Trans. 2* ***1976***, 996.

[306]See, for example, Creary, X.; Mehrsheikh-Mohammadi, M.E.; Eggers, M.D. *J. Am. Chem. Soc.* ***1987***, *109*, 2435.

[307]See Gronert, S.; Pratt, L.M.; Mogali, S. *J. Am. Chem. Soc.* ***2001***, *123*, 3081.

[308]For example, substrates of the type $RSCH_2CH_2X$ are so prone to the neighboring-group mechanism that ordinary S_N2 reactions have only recently been observed: Sedaghat-Herati, M.R.; McManus, S.P.; Harris, J.M. *J. Org. Chem.* ***1988***, *53*, 2539.

[309]See, for example, Okamoto, K.; Kita, T.; Araki, K.; Shingu, H. *Bull. Chem. Soc. Jpn.* ***1967***, *40*, 1913.

[310]Sugawara, M.; Yoshida, J.-i. *Bull. Chem. Soc. Jpn.* ***2000***, *73*, 1253.

[311]Nakashima, T.; Fujiyama, R.; Fujio, M.; Tsuno, Y. *Bull. Chem. Soc. Jpn.* ***1999***, *72*, 741, 1043; Nakashima, T.; Fujiyama, R.; Kim, H.-J.; Fujio, M.; Tsuno, Y. *Bull. Chem. Soc. Jpn.* ***2000***, *73*, 429.

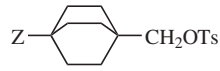
[312]Jorge, J.A.L.; Kiyan, N.Z.; Miyata, Y.; Miller, J. *J. Chem. Soc. Perkin Trans. 2* ***1981***, 100; Vitullo, V.P.; Grabowski, J.; Sridharan, S. *J. Chem. Soc., Chem. Commun.* ***1981***, 737.

while electron-withdrawing groups concentrate the charge. The Hammett $\sigma\rho$ relationship (p. 402) correlates fairly successfully the rates of many of these reactions (with σ^+ instead of σ). ρ values are generally about -4, which is expected for a reaction where a positive charge is created in the transition state.

For S_N2 reactions, no such simple correlations are found.[313] In this mechanism, bond breaking is about as important as bond making in the rate-determining step, and substituents have an effect on both processes, often in opposite directions. The unsubstituted benzyl chloride and bromide solvolyze by the S_N2 mechanism.[306]

For Z = alkyl, the Baker–Nathan order (p. 96) is usually observed both for S_N1 and S_N2 reactions.

In para-substituted benzyl systems, steric effects have been removed, but resonance and field effects are still present. However, Holtz and Stock studied a system that removes not only steric effects, but also resonance effects. This is the 4-substituted bicyclo[2.2.2]octylmethyl tosylate system (**90**).[314] In



90

this system, steric effects are completely absent owing to the rigidity of the molecules, and only field effects operate. By this means, Holtz and Stock showed that electron-withdrawing groups increase the rate of S_N2 reactions. This can be ascribed to stabilization of the transition state by withdrawal of some of the electron density.

For substrates that react by the tetrahedral mechanism, electron-withdrawing groups increase the rate and electron-donating groups decrease it.

7. *Cyclic Substrates*. Cyclopropyl substrates are extremely resistant to nucleophilic attack.[315] For example, cyclopropyl tosylate solvolyzes $\sim 10^6$ times more slowly than cyclobutyl tosylate in acetic acid at 60°C.[316] When such attack does take place, the result is generally not normal substitution (though exceptions are known,[317] especially when an a stabilizing group, such as aryl

[313]See Sugden, S.; Willis, J.B. *J. Chem. Soc.* ***1951***, 1360; Baker, J.W.; Nathan, W.S. *J. Chem. Soc.* ***1935***, 1840; Hayami, J.; Tanaka, N.; Kurabayashi, S.; Kotani, Y.; Kaji, A. *Bull. Chem. Soc. Jpn.* ***1971***, *44*, 3091; Westaway, K.C.; Waszczylo, Z. *Can. J. Chem.* ***1982***, *60*, 2500; Lee, I.; Sohn, S.C.; Oh, Y.J.; Lee, B.C. *Tetrahedron* ***1986***, *42*, 4713.

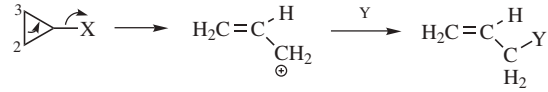
[314]Holtz, H.D.; Stock, L.M. *J. Am. Chem. Soc.* ***1965***, *87*, 2404.

[315]For reviews, see Friedrich, E.C., in Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, pt. 1; Wiley, NY, ***1987***, pp. 633–700; Aksenov, V.S.; Terent'eva, G.A.; Savinykh, Yu.V. *Russ. Chem. Rev.* ***1980***, *49*, 549.

[316]Roberts, J.D.; Chambers, V.C. *J. Am. Chem. Soc.* ***1951***, *73*, 5034.

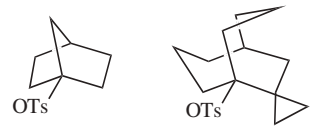
[317]For example, see Kirmse, W.; Schütte, H. *J. Am. Chem. Soc.* ***1967***, *89*, 1284; Landgrebe, J.A.; Becker, L.W. *J. Am. Chem. Soc.* ***1967***, *89*, 2505; Howell, B.A.; Jewett, J.G. *J. Am. Chem. Soc.* ***1971***, *93*, 798; van der Vecht, J.R.; Steinberg, H.; de Boer, T.J. *Recl. Trav. Chim. Pays-Bas* ***1978***, *96*, 313; Engbert, T.; Kirmse, W. *Liebigs Ann. Chem.* ***1980***, 1689; Turkenburg, L.A.M.; de Wolf, W.H.; Bickelhaupt, F.; Stam, C.H.; Konijn, M. *J. Am. Chem. Soc.* ***1982***, *104*, 3471; Banert, K. *Chem. Ber.* ***1985***, *118*, 1564; Vilsmaier, E.; Weber, S.; Weidner, J. *J. Org. Chem.* ***1987***, *52*, 4921.

or alkoxy is present), but ring opening:[310]



There is much evidence that the ring opening is usually concerted with the departure of the leaving group[318] (as in the similar case of cyclobutyl substrates, p. 465), from which we can conclude that if the 2,3 bond of the cyclopropane ring did not assist, the rates would be lower still. Strain plays a role in the ring-opening process.[319] It has been estimated[320] that without this assistance the rates of these already slow reactions would be further reduced by a factor of perhaps 10^{12}. For a discussion of the stereochemistry of the ring opening, see p. 1644. For larger rings, we have seen (p. 399) that, because of I strain, cyclohexyl substrates solvolyze slower than analogous compounds in which the leaving group is attached to a ring of 5 or of from 7 to 11 members.

8. *Bridgeheads*.[11] The S_N2 mechanism is impossible at most bridgehead compounds (p. 429). Nucleophilic attack in [1.1.1]-propellane has been reported, however.[321] In general, a relatively large ring is required for an S_N1 reaction to take place (p. 435).[322] The S_N1 reactions have been claimed to occur for 1-iodobicyclo[1.1.1]pentane via the bicyclo[1.1.1]pentyl cation,[323] but this has been disputed and the bicyclo[1.1.0]butyl carbinyl cation was calculated to be the real intermediate.[324] Solvolytic reactivity at bridgehead positions spans a wide range; for example, from $k = 4\times10^{-17}\ s^{-1}$



91 **92**

for **91** (very slow) to $3 \times 10^6\ s^{-1}$ for the [3.3.3] compound **92** (very fast);[325] a range of 22 orders of magnitude. Molecular mechanics calculations show that

[318]For example, see Schleyer, P.v.R.; Van Dine, G.W.; Schöllkopf, U.; Paust, J. *J. Am. Chem. Soc.* ***1966***, *88*, 2868; DePuy, C.H.; Schnack, L.G.; Hausser, J.W. *J. Am. Chem. Soc.* ***1966***, *88*, 3343; Jefford, C.W.; Wojnarowski, W. *Tetrahedron* ***1969***, *25*, 2089; Hausser, J.W.; Uchic, J.T. *J. Org. Chem.* ***1972***, *37*, 4087.

[319]See Wolk, J.L.; Hoz, T.; Basch, H.; Hoz, S. *J. Org. Chem.* ***2001***, *66*, 915.

[320]Sliwinski, W.F.; Su, T.M.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1972***, *94*, 133; Brown, H.C.; Rao, C.G.; Ravindranathan, M. *J. Am. Chem. Soc.* ***1978***, *100*, 7946.

[321]Sella, A.; Basch, H.; Hoz, S. *Tetrahedron Lett.* ***1996***, *37*, 5573.

[322]For a review of organic synthesis using bridgehead carbocations, see Kraus, G.A.; Hon, Y.; Thomas, P.J.; Laramay, S.; Liras, S.; Hanson, J. *Chem. Rev.* ***1989***, *89*, 1591.

[323]Adcock, J.L.; Gakh, A.A. *Tetrahedron Lett.* ***1992***, *33*, 4875.

[324]Wiberg, K.B.; McMurdie, N. *J. Org. Chem.* ***1993***, *58*, 5603.

[325]Bentley, T.W.; Roberts, K. *J. Org. Chem.* ***1988***, *50*, 5852.

TABLE 10.6. List of Groups in Approximately Descending Order of Reactivity Toward S_N1 and S_N2 Reactions[a]

S_N1 Reactivity	S_N2 Reactivity
Ar_3CX	Ar_3CX
Ar_2CHX	Ar_2CHX
$ROCH_2X$, $RSCH_2X$, R_2NCH_2X	$ArCH_2X$
R_3CX	ZCH_2X
$ArCH_2X$	$-\overset{\vert}{C}=\overset{\vert}{C}-CH_2X$
$-\overset{\vert}{C}=\overset{\vert}{C}-CH_2X$	$RCH_2X \sim RCHDX \sim RCHDCH_2X$
R_2CHX	R_2CHX
$RCH_2X \sim R_3CCH_2X$	R_3CX
$RCHDX$	ZCH_2CH_2X
$RCHDCH_2X$	R_3CCH_2X
$-\overset{\vert}{C}=\overset{\vert}{C}-X$	$-\overset{\vert}{C}=\overset{\vert}{C}-X$
ZCH_2X	
ZCH_2CH_2X	ArX
ArX	Bridgehead-X
[2.2.1] Bridgehead-X	

[a]The Z group is RCO, HCO, ROCO, NH_2CO, NC, or a similar one.

S_N1 bridgehead reactivity is determined by strain changes between the substrate and the carbocation intermediate.[326]

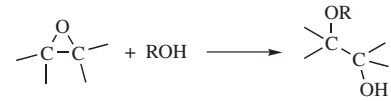
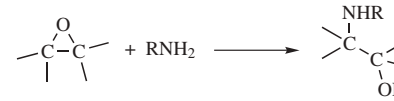
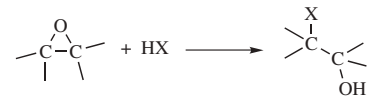
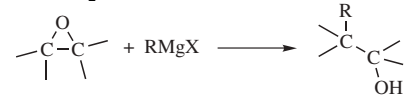
9. *Deuterium Substitution*. Both α and β secondary isotope effects affect the rate in various ways (p. 324). The measurement of a secondary isotope effects provides a means of distinguishing between S_N1 and S_N2 mechanisms, since for S_N2 reactions the values range from 0.95 to 1.06 per α D, while for S_N1 reactions the values are higher.[327] This method is especially good because it provides the minimum of perturbation of the system under study; changing from α H to α D hardly affects the reaction, while other probes, such as changing a substituent or the polarity of the solvent, may have a much more complex effect.

Table 10.6 is an approximate listing of groups in order of S_N1 and S_N2 reactivity. Table 10.7 shows the main reactions that proceed by the S_N2 mechanism (if R = primary or, often, secondary alkyl).

[326]Bingham, R.C.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1971***, *93*, 3189; Müller, P.; Blanc, J.; Mareda, J. *Chimia* ***1987***, *41*, 399; Müller, P.; Mareda, J. *Helv. Chim. Acta* ***1987***, *70*, 1017; Bentley, T.W.; Roberts, K. *J. Org. Chem.* ***1988***, *50*, 5852.

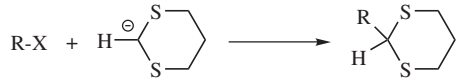
[327]Shiner, Jr., V.J.; Fisher, R.D. *J. Am. Chem. Soc.* ***1971***, *93*, 2553. For a review of secondary isotope effects in S_N2 reactions, see Westaway, K.C. *Isot. Org. Chem.* ***1987***, *7*, 275.

TABLE 10.7. The More Important Synthetic Reactions of Chapter 10 That Take Place by an S_N2 Mechanism.[a] Catalysts are not shown[b]

10-1	$RX + OH^- \longrightarrow ROH$
10-8	$RX + OR' \longrightarrow ROR'$
10-9	
10-10	$R{-}OSO_2OR'' + OR' \longrightarrow ROR'$
10-12	$2\ ROH \longrightarrow ROR$
10-14	
10-15	$R_3O^+ + R'OH \longrightarrow ROR'$
10-17	$RX + R'COO^- \longrightarrow R'COOR$
10-21	$RX + OOH^- \longrightarrow ROOH$
10-25	$RX + SH^- \longrightarrow RSH$
10-26	$RX + R'S^- \longrightarrow RSR'$
10-27	$RX + S_2{}^{2-} \longrightarrow RSSR$
10-30	$RX + SCN^- \longrightarrow RSCN$
10-31	$RX + R'_2NH \longrightarrow RR'_2N$
10-31	$RX + R'_3N \longrightarrow RR'_3N^+\ X^-$
10-35	
10-41	$RX + R'CONH^- \longrightarrow RNHCOR'$
10-42	$RX + NO_2^- \longrightarrow RNO_2 + RONO$
10-43	$RX + N_3^- \longrightarrow RN_3$
10-44	$RX + NCO^- \longrightarrow RNCO$
10-44	$RX + NCS^- \longrightarrow RNCS$
10-46	$RX + X' \longrightarrow RX'$
10-47	$R{-}OSO_2OR' + X^- \longrightarrow RX$
10-48	$ROH + PCl_5 \longrightarrow RCl$
10-49	$ROR' + 2HI \longrightarrow RI + R'I$
10-50	
10-51	$R{-}O{-}COR' + LiI \longrightarrow RI + R'COO^-$
10-57	$RX + R'_2CuLi \longrightarrow RR'$
10-65	
10-67	$RX + HC^-(CO_2R')_2 \longrightarrow RCH(CO_2R')_2$

(*continued*)

TABLE 10.7. (*Continued*)

10-68	$RX + R''\overset{\ominus}{C}H{-}COR' \longrightarrow RCR''{-}COR'$
10-70	$RX + R'\overset{\ominus}{C}HCOO^- \longrightarrow RR'CHCOO^-$
10-71	
10-74	$RX + RC{\equiv}C^{\ominus} \longrightarrow RC{\equiv}CR'$
10-75	$RX + CN^- \longrightarrow RCN$

[a](R = primary, often secondary, alkyl).
[b]This is a schematic list only. Some of these reactions may also take place by other mechanisms and the scope may vary greatly. See the discussion of each reaction for details.

The Effect of the Attacking Nucleophile[328]

Any species that has an unshared pair (i.e., any Lewis base) can be a nucleophile, whether it is neutral or has a negative charge. The rates of S_N1 reactions are independent of the identity of the nucleophile, since it does not appear in the rate-determining step.[329] This may be illustrated by the effect of changing the nucleophile from H_2O to ^-OH for a primary and a tertiary substrate. For methyl bromide, which reacts by an S_N2 mechanism, the rate is multiplied >5000 by the change to the more powerful nucleophile ^-OH, but for *tert*-butylbromide, which reacts by an S_N1 mechanism, the rate is unaffected.[330] A change in nucleophile can, however, change the *product* of an S_N1 reaction. Thus solvolysis of benzyl tosylate in methanol gives benzyl methyl ether (the nucleophile is the solvent methanol). If the more powerful nucleophile Br^- is added, the rate is unchanged, but the product is now benzyl bromide.

For S_N2 reactions in solution, there are four main principles that govern the effect of the nucleophile on the rate, although the nucleophilicity order is not invariant, but depends on substrate, solvent, leaving group, and so on.

1. A nucleophile with a negative charge is always a more powerful nucleophile than its conjugate acid (assuming the latter is also a nucleophile). Thus ^-OH is more powerful than H_2O, $^-NH_2$ more powerful than NH_3, and so on.
2. In comparing nucleophiles whose attacking atom is in the same row of the periodic table, nucleophilicity is approximately in order of basicity, although

[328]For a monograph, see Harris, J.M.; McManus, S.P. *Nucleophilicity*, American Chemical Society, Washington, DC, ***1987***. For reviews, see Klumpp, G.W. *Reactivity in Organic Chemistry*; Wiley, NY, ***1982***, pp. 145–167, 181–186; Hudson, R.F., in Klopman, G. *Chemical Reactivity and Reaction Paths*; Wiley, NY, ***1974***, pp. 167–252.
[329]It is, however, possible to measure the rates of reaction of nucleophiles with fairly stable carbocations: see Ritchie, C.D. *Acc. Chem. Res.* ***1972***, *5*, 348; Ritchie, C.D.; Minasz, R.J.; Kamego, A.A.; Sawada, M. *J. Am. Chem. Soc.* ***1977***, *99*, 3747; McClelland, R.A.; Banait, N.; Steenken, S. *J. Am. Chem. Soc.* ***1986***, *108*, 7023.
[330]Bateman, L.C.; Cooper, K.A.; Hughes, E.D.; Ingold, C.K. *J. Chem. Soc.* ***1940***, 925.

basicity is thermodynamically controlled and nucleophilicity is kinetically controlled. So an approximate order of nucleophilicity is $^{-}NH_2^- > RO^- > {}^{-}OH > R_2NH > ArO^- > NH_3 >$ pyridine $> F^- > H_2O > ClO_4^-$, and another is $R_3C^- > R_2N^- > RO^- > F^-$ (see Table 8.1). This type of correlation works best when the structures of the nucleophiles being compared are similar, as with a set of substituted phenoxides. Within such a series, linear relationships can often be established between nucleophilic rates and pK values.[331]

3. Going down the Periodic table, nucleophilicity increases, although basicity decreases. Thus the usual order of halide nucleophilicity is $I^- > Br^- > Cl^- > F^-$ (as we will see below, this order is solvent dependent). Similarly, any sulfur nucleophile is more powerful than its oxygen analog, and the same is true for phosphorus versus nitrogen. The main reason for this distinction between basicity and nucleophilic power is that the smaller negatively charged nucleophiles are more solvated by the usual polar protic solvents; that is, because the negative charge of Cl^- is more concentrated than the charge of I^-, the former is more tightly surrounded by a shell of solvent molecules that constitute a barrier between it and the substrate. This is most important for protic polar solvents in which the solvent may be hydrogen bonded to small nucleophiles. Evidence for this is that many nucleophilic substitutions with small negatively charged nucleophiles are much more rapid in aprotic polar solvents than in protic ones[332] and that, in DMF, an aprotic solvent, the order of nucleophilicity was $Cl^- > Br^- > I^-$.[333] Another experiment was the use of $Bu_4N^+ X^-$ and LiX as nucleophiles in acetone, where X^- was a halide ion. The halide ion in the former salt is much less associated than in LiX. The relative rates with LiX were Cl^-, 1; Br^-, 5.7; I^-, 6.2, which is in the normal order, while with $Bu_4N^+ X^-$, where X^- is much freer, the relative rates were Cl^-, 68; Br^-, 18; I^-, 3.7.[334] In a further experiment, halide ions were allowed to react with the molten salt $(n\text{-}C_5H_{11})_4N^+ X^-$ at 180°C in the absence of a solvent.[335] Under these conditions, where the ions are unsolvated and unassociated, the relative rates were Cl^-, 620; Br^-, 7.7; I^-, 1. In the gas phase, where no solvent is present, an approximate order of nucleophilicity was found to be $^{-}OH > F^- \approx MeO^- > MeS^- \gg Cl^- > CN^- > Br^-$,[336]

[331]See, for example, Jokinen, S.; Luukkonen, E.; Ruostesuo, J.; Virtanen, J.; Koskikallio, J. *Acta Chem. Scand.* ***1971***, *25*, 3367; Bordwell, F.G.; Hughes, D.L. *J. Org. Chem.* ***1983***, *48*, 2206; *J. Am. Chem. Soc.* ***1984***, *106*, 3234.

[332]Parker, A.J. *J. Chem. Soc.* ***1961***, 1328 has a list of ~20 such reactions.

[333]Weaver, W.M.; Hutchison, J.D. *J. Am. Chem. Soc.* ***1964***, *86*, 261; See also, Fuchs, R.; Mahendran, K. *J. Org. Chem.* ***1971***, *36*, 730; Müller, P.; Siegfried, B. *Helv. Chim. Acta* ***1971***, *54*, 2675; Liotta, C.; Grisdale, E.E.; Hopkins, Jr., H.P. *Tetrahedron Lett.* ***1975***, 4205; Bordwell, F.G.; Hughes, D.L. *J. Org. Chem.* ***1981***, *46*, 3570. For a contrary result in liquid SO_2, see Lichtin, N.N.; Puar, M.S.; Wasserman, B. *J. Am. Chem. Soc.* ***1967***, *89*, 6677.

[334]Winstein, S.; Savedoff, L.G.; Smith, S.G.; Stevens, I.D.R.; Gall, J.S. *Tetrahedron Lett.* ***1960***, no. 9, 24.

[335]Gordon, J.E.; Varughese, P. *Chem. Commun.* ***1971***, 1160. See also, Ford, W.T.; Hauri, R.J.; Smith, S.G. *J. Am. Chem. Soc.* ***1974***, *96*, 4316.

[336]Olmstead, W.N.; Brauman, J.I. *J. Am. Chem. Soc.* ***1977***, *99*, 4219. See also, Tanaka, K.; Mackay, G.I.; Payzant, J.D.; Bohme, D.K. *Can. J. Chem.* ***1976***, *54*, 1643.

providing further evidence that solvation[337] is responsible for the effect in solution.

However, solvation is not the entire answer since, even for *uncharged* nucleophiles, nucleophilicity increases going down a column in the periodic table. These nucleophiles are not so greatly solvated and changes in solvent do not greatly affect their nucleophilicity.[338] To explain these cases we may use the principle of hard and soft acids and bases (p. 375).[339] The proton is a hard acid, but an alkyl substrate (which may be considered to act as a Lewis acid toward the nucleophile considered as a base) is a good deal softer. According to the principle given on p. 380, we may then expect the alkyl group to prefer softer nucleophiles than the proton does. Thus the larger, more polarizable (softer) nucleophiles have a greater (relative) attraction toward an alkyl carbon than toward a proton.

4. The freer the nucleophile, the greater the rate.[340] We have already seen one instance of this.[334] Another is that the rate of attack by $(EtOOC)_2CBu^-\ Na^+$ in benzene was increased by the addition of substances (e.g., 1,2-dimethoxyethane, adipamide) that specifically solvated the Na^+ and thus left the anion freer.[341] In a nonpolar solvent, such as benzene, salts, such as $(EtOOC)_2CBu^-\ Na^+$, usually exist as ion-pair aggregations of large molecular weights.[342] Similarly, it was shown that the half-life of the reaction between $C_6H_5COCHEt^-$ and ethyl bromide depended on the positive ion: K^+, 4.5×10^{-3}; Na^+, 3.9×10^{-5}; Li^+, 3.1×10^{-7}.[343] Presumably, the potassium ion leaves the negative ion most free to attack most rapidly. Further evidence is that in the gas phase,[344] where nucleophilic ions are completely free, without solvent or counterion, reactions take place orders of magnitude faster than the same reactions in solution.[345] It has proven possible to measure the rates of reaction of ^-OH with methyl bromide in the gas phase, with ^-OH either unsolvated or solvated with one, two, or three molecules of water.[346] The rates were, with the number of water molecules

[337]See Kormos, B.L.; Cramer, C.J. *J. Org. Chem.* ***2003***, *68*, 6375.

[338]Parker, A.J. *J. Chem. Soc.* ***1961***, 4398.

[339]Pearson, R.G. *Surv. Prog. Chem.* ***1969***, *5*, 1, pp. 21–38.

[340]For a review of the effect of nucleophile association on nucleophilicity, see Guibe, F.; Bram, G. *Bull. Soc. Chim. Fr.* ***1975***, 933.

[341]Zaugg, H.E.; Leonard, J.E. *J. Org. Chem.* ***1972***, *37*, 2253. See also, Solov'yanov, A.A.; Ahmed, E.A.A.; Beletskaya, I.P.; Reutov, O.A. *J. Org. Chem. USSR* ***1987***, *23*, 1243; Jackman, L.M.; Lange, B.C. *J. Am. Chem. Soc.* ***1981***, *103*, 4494.

[342]See, for example Williard, P.G.; Carpenter, G.B. *J. Am. Chem. Soc.* ***1986***, *108*, 462.

[343]Zook, H.D.; Gumby, W.L. *J. Am. Chem. Soc.* ***1960***, *82*, 1386. See also, Cacciapaglia, R.; Mandolini, L. *J. Org. Chem.* ***1988***, *53*, 2579.

[344]For some other measurements of rates of S_N2 reactions in the gas phase, see Barlow, S.E.; Van Doren, J.M.; Bierbaum, V.M. *J. Am. Chem. Soc.* ***1988***, *110*, 7240; Merkel, A.; Havlas, Z.; Zahradník, R. *J. Am. Chem. Soc.* ***1988***, *110*, 8355.

[345]Olmstead, W.N.; Brauman, J.I. *J. Am. Chem. Soc.* ***1977***, *99*, 4219.

[346]Bohme, D.K.; Raksit, A.B. *J. Am. Chem. Soc.* ***1984***, *106*, 3447. See also, Hierl, P.M.; Ahrens, A.F.; Henchman, M.; Viggiano, A.A.; Paulson, J.F.; Clary, D.C. *J. Am. Chem. Soc.* ***1986***, *108*, 3142.

in parentheses: (0) 1.0×10^{-9}; (1) 6.3×10^{-10}; (2) 2×10^{-12}; (3) 2×10^{-13} cm^3 $molecule^{-1}$ s^{-1}. This provides graphic evidence that solvation of the nucleophile decreases the rate. The rate of this reaction in aqueous solution is 2.3×10^{-25} cm^3 $molecule^{-1}$ s^{-1}. Similar results were found for other nucleophiles and other solvents.[347] In solution too, studies have been made of the effect of solvation of the nucleophile by a specific number of water molecules. When the salt $(n\text{-}C_6H_{13})_4N^+$ F^- was allowed to react with *n*-octyl methanesulfonate, the relative rate fell from 822 for no water molecules to 96 for 1.5 water molecules to 1 for 6 water molecules.[348]

In Chapter 3, we saw that cryptands specifically solvate the alkali metal portion of salts like KF, KOAc, and so on. Synthetic advantage can be taken of this fact to allow anions to be freer, thus increasing the rates of nucleophilic substitutions and other reactions (see p. 509).

However, the four rules given above do not always hold. One reason is that steric influences often play a part. For example, the *tert*-butoxide ion Me_3CO^- is a stronger base than ^-OH or ^-OEt, but a much poorer nucleophile because its large bulk hinders it from closely approaching a substrate.

The following overall nucleophilicity order for S_N2 mechanisms (in protic solvents) was given by Edwards and Pearson:[349] $RS^- > ArS^- > I^- > CN^- > {}^-OH > N_3^- > Br^- > ArO^- > Cl^- >$ pyridine $> AcO^- > H_2O$. A quantitative relationship[350] (the *Swain–Scott equation*) has been worked out similar to the linear free-energy equations considered in Chapter 9:[351]

$$\log \frac{k}{k_0} = sn$$

where n is the nucleophilicity of a given group, s is the sensitivity of a substrate to nucleophilic attack, and k_0 is the rate for H_2O, which is taken as the standard and for which n is assigned a value of zero. The parameter s is defined as 1.0 for methyl bromide. Table 10.8 contains values of n for some common nucleophiles.[352] The order is similar to that of Edwards and Pearson. The Swain–Scott equation can be derived from Marcus theory.[353]

[347]Bohme, D.K.; Raksit, A.B. *Can. J. Chem.* ***1985***, *63*, 3007.
[348]Landini, D.; Maia, A.; Rampoldi, A. *J. Org. Chem.* ***1989***, *54*, 328.
[349]Edwards, J.O.; Pearson, R.G. *J. Am. Chem. Soc.* ***1962***, *84*, 16.
[350]Swain, C.G.; Scott, C.B. *J. Am. Chem. Soc.* ***1953***, *75*, 141.
[351]This is not the only equation that has been devised in an attempt to correlate nucleophilic reactivity. For reviews of attempts to express nucleophilic power quantitatively, see Ritchie, C.D. *Pure Appl. Chem.* ***1978***, *50*, 1281; Duboc, C., in Chapman, N.B.; Shorter, J. *Correlation Analysis in Chemistry: Recent Advances*, Plenum, NY, ***1978***, pp. 313–355; Ibne-Rasa, K.M. *J. Chem. Educ.* ***1967***, *44*, 89. See also, Hoz, S.; Speizman, D. *J. Org. Chem.* ***1983***, *48*, 2904; Kawazoe, Y.; Ninomiya, S.; Kohda, K.; Kimoto, H. *Tetrahedron Lett.* ***1986***, *27*, 2897; Kevill, D.N.; Fujimoto, E.K. *J. Chem. Res. (S)* ***1988***, 408.
[352]From Wells, P.R. *Chem. Rev.* ***1963***, *63*, 171, p. 212. See also, Koskikallio, J. *Acta Chem. Scand.* ***1969***, *23*, 1477, 1490.
[353]Albery, W.J.; Kreevoy, M.M. *Adv. Phys. Org. Chem.* ***1978***, *16*, 87, pp. 113–115.

TABLE 10.8. Nucleophilicities of Some Common Reagents[352]

Nucleophile	*n*	Nucleophile	*n*
^{-}SH	5.1	Br^{-}	3.5
^{-}CN	5.1	PhO^{-}	3.5
I^{-}	5.0	AcO^{-}	2.7
$PhNH_2$	4.5	Cl^{-}	2.7
^{-}OH	4.2	F^{-}	2.0
N_3^{-}	4.0	NO_3^{-}	1.0
Pyridine	3.6	H_2O	0.0

It is now evident that an absolute order of either nucleophilicity[354] or leaving-group ability, even in the gas phase where solvation is not a factor, does not exist, because they have an effect on each other. When the nucleophile and leaving group are both hard or both soft, the reaction rates are relatively high, but when one is hard and the other soft, rates are reduced.[344] Although this effect is smaller than the effects in paragraphs one and four above, it still prevents an absolute scale of either nucleophilicity or leaving-group ability.[355] There has been controversy as to whether the selectivity of a reaction should increase with decreasing reactivity of a series of nucleophiles, or whether the opposite holds. There is evidence for both views.[356]

For substitution at a carbonyl carbon, the nucleophilicity order is not the same as it is at a saturated carbon, but follows the basicity order more closely. The reason is presumably that the carbonyl carbon, with its partial positive charge, resembles a proton more than does the carbon at a saturated center. That is, a carbonyl carbon is a much harder acid than a saturated carbon. The following nucleophilicity order for these substrates has been determined:[357] $Me_2C{=}NO^{-} > EtO^{-} > MeO^{-} > {}^{-}OH > OAr^{-} > N_3^{-} > F^{-} > H_2O > Br^{-} \sim I^{-}$. Soft bases are ineffective at a carbonyl carbon.[358] In a reaction carried out in the gas phase with alkoxide nucleophiles OR^{-} solvated by only one molecule of an alcohol R′OH, it was found that both RO^{-} and $R'O^{-}$ attacked the formate substrate (HCOOR″) about equally, although in the unsolvated case, the more basic alkoxide is the better nucleophile.[359] In this study, the product ion R^2O^{-} was also solvated by one molecule of ROH or R′OH.

[354]However, for a general model of intrinsic nucleophilicity in the gas phase, see Pellerite, M.J.; Brauman, J.I. *J. Am. Chem. Soc.* ***1983***, *105*, 2672.

[355]For reference scales for the characterization of cationic electrophiles and neutral nucleophiles see Mayr, H.; Bug, T.; Gotta, M.F.; Hering, N.; Irrgang, B.; Janker, B.; Kempf, B.; Loos, R.; Ofial, A.R.; Remennikov, G.; Schimmel, H. *J. Am. Chem. Soc.* ***2001***, *123*, 9500.

[356]For discussions, see Dietze, P.; Jencks, W.P. *J. Am. Chem. Soc.* ***1989***, *111*, 5880.

[357]Hudson, R.F.; Green, M. *J. Chem. Soc.* ***1962***, 1055; Bender, M.L.; Glasson, W.A. *J. Am. Chem. Soc.* ***1959***, *81*, 1590; Jencks, W.P.; Gilchrist, M. *J. Am. Chem. Soc.* ***1968***, *90*, 2622.

[358]For theoretical treatments of nucleophilicity at a carbonyl carbon, see Buncel, E.; Shaik, S.S.; Um, I.; Wolfe, S. *J. Am. Chem. Soc.* ***1988***, *110*, 1275, and references cited therein.

[359]Baer, S.; Stoutland, P.O.; Brauman, J.I. *J. Am. Chem. Soc.* ***1989***, *111*, 4097.

If an atom containing one or more unshared pairs is adjacent to the attacking atom on the nucleophile, the nucleophilicity is enhanced.[360] Examples of such nucleophiles are HO_2^-, $Me_2C{=}NO^-$, NH_2NH_2, and so on. This is called the *alpha effect* (α-effect),[361] and a broader definition is a positive deviation exhibited by an α-nucleophile from a Brønsted type nucleophilicity plot, [362] where the reference (or normal) nucleophile is one that possesses the same basicity as the α-nucleophile, but does not deviate from the Brønsted-type plot. Several reviews of the α-effect have been published previously,[362,363]

Several possible explanations have been offered.[364] One is that the ground state of the nucleophile is destabilized by repulsion between the adjacent pairs of electrons;[365] another is that the transition state is stabilized by the extra pair of electrons;[366] a third is that the adjacent electron pair reduces solvation of the nucleophile.[367] Evidence supporting the third explanation is that there was no alpha effect in the reaction of HO_2^- with methyl formate in the gas phase,[368] although HO_2^- shows a strong alpha effect in solution. The α-effect has been demonstrated to be remarkably dependent on the nature of the solvent. [369] The α-effect is substantial for substitution at a carbonyl or other unsaturated carbon, at some inorganic atoms,[370] and for reactions of a nucleophile with a carbocation,[371] but is generally smaller or absent entirely for substitution at a saturated carbon.[372]

[360]Definition in the *Glossary of Terms used in Physical Organic Chemistry, Pure & Appl. Chem.* ***1979***, *51*, 1731.

[361]For reviews, see Grekov, A.P.; Veselov, V.Ya. *Russ. Chem. Rev.* ***1978***, *47*, 631; Fina, N.J.; Edwards, J.O. *Int. J. Chem. Kinet.* ***1973***, *5*, 1.

[362]Hoz, S.; Buncel, E. *Israel J. Chem.* ***1985***, *26*, 313.

[363]Grekov, A.P.; Veselov, V.Ya. *Russ. Chem. Rev.* ***1978***, *47*, 631; Fina, N.J.; Edwards, J.O. *Int. J. Chem. Kinet*. ***1973***, *5*, 1; Jencks, W.P. *Catalysis in Chemistry and Enzymology*, McGraw-Hill, New York, ***1969***; pp. 107–111.

[364]For discussions, see Wolfe, S.; Mitchell, D.J.; Schlegel, H.B.; Minot, C.; Eisenstein, O. *Tetrahedron Lett.* ***1982***, *23*, 615; Ho, S.; Buncel, E. *Isr. J. Chem.* ***1985***, *26*, 313.

[365]Buncel, E.; Hoz, S. *Tetrahedron Lett.* ***1983***, *24*, 4777. For evidence that this is not the sole cause, see Oae, S.; Kadoma, Y. *Can. J. Chem.* ***1986***, *64*, 1184.

[366]See Hoz, S. *J. Org. Chem.* ***1982***, *47*, 3545; Laloi-Diard, M.; Verchere, J.; Gosselin, P.; Terrier, F. *Tetrahedron Lett.* ***1984***, *25*, 1267.

[367]For other explanations, see Hudson, R.F.; Hansell, D.P.; Wolfe, S.; Mitchell, D.J. *J. Chem. Soc., Chem. Commun.* ***1985***, 1406; Shustov, G.V. *Doklad. Chem.* ***1985***, *280*, 80. For a discussion, see Herschlag, D.; Jencks, W.P. *J. Am. Chem. Soc.* ***1990***, *112*, 1951.

[368]DePuy, C.H.; Della, E.W.; Filley, J.; Grabowski, J.J.; Bierbaum, V.M. *J. Am. Chem. Soc.* ***1983***, *105*, 2481; Buncel, E.; Um, I. *J. Chem. Soc., Chem. Commun.* ***1986***, 595; Terrier, F.; Degorre, F.; Kiffer, D.; Laloi, M. *Bull. Soc. Chim. Fr.* ***1988***, 415. For some evidence against this explanation, see Moss, R.A.; Swarup, S.; Ganguli, S. *J. Chem. Soc., Chem. Commun.* ***1987***, 860.

[369]Buncel, E.; Um, I.-H. *Tetrahedron* ***2004***, *60*, 7801.

[370]For example, see Kice, J.L.; Legan, E. *J. Am. Chem. Soc.* ***1973***, *95*, 3912.

[371]Dixon, J.E.; Bruice, T.C. *J. Am. Chem. Soc.* ***1971***, *93*, 3248, 6592.

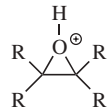
[372]Gregory, M.J.; Bruice, T.C. *J. Am. Chem. Soc.* ***1967***, *89*, 4400; Oae, S.; Kadoma, Y.; Yano, Y. *Bull. Chem. Soc. Jpn.* ***1969***, *42*, 1110; McIsaac, Jr., J.E.; Subbaraman, L.R.; Subbaraman, J.; Mulhausen, H.A.; Behrman, E.J. *J. Org. Chem.* ***1972***, *37*, 1037. See, however, Beale, J.H. *J. Org. Chem.* ***1972***, *37*, 3871; Buncel, E.; Wilson, H.; Chuaqui, C. *J. Am. Chem. Soc.* ***1982***, *104*, 4896; *Int. J. Chem. Kinet.* ***1982***, *14*, 823.

The Effect of the Leaving Group

1. *At a Saturated Carbon*. The leaving group comes off more easily the more stable it is as a free entity. This is usually inverse to its basicity, and the best leaving groups are the weakest bases. Thus iodide is the best leaving group among the halides and fluoride the poorest. Since XH is always a weaker base than X^-, nucleophilic substitution is always easier at a substrate RXH^+ than at RX. An example of this effect is that OH and OR are not leaving groups from ordinary alcohols and ethers, but can come off when the groups are protonated, that is, converted to ROH_2^+ or $RORH^+$.[373] Reactions in which the leaving group does not come off until it has been protonated have been called S_N1cA or S_N2cA, depending on whether after protonation the reaction is an S_N1 or S_N2 process (these designations are often shortened to A1 and A2). The cA stands for conjugate acid, since the substitution takes place on the conjugate acid of the substrate. The IUPAC designations for these mechanisms are, respectively, $A_h + D_N + A_N$ and $A_h + A_ND_N$; that is, the same designations as S_N1 and S_N2, with A_h to show the preliminary step. When another electrophile assumes the role of the proton, the symbol A_e is used instead. The ions ROH_2^+ and $RORH^+$ can be observed as stable entities at low temperatures in super acid solutions.[374] At higher temperatures they cleave to give carbocations.

It is obvious that the best nucleophiles (e.g., NH_2^-, ^-OH) cannot take part in S_N1cA or S_N2cA processes, because they would be converted to their conjugate acids under the acidic conditions necessary to protonate the leaving groups.[375] Because S_N1 reactions do not require powerful nucleophiles, but do require good leaving groups, most of them take place under acidic conditions. In contrast, S_N2 reactions, which do require powerful nucleophiles (which are generally strong bases), most often take place under basic or neutral conditions.


93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95


96

Another circumstance that increases leaving-group power is ring strain. Ordinary ethers do not cleave at all and protonated ethers only under

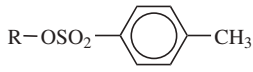
[373]For a review of ORH^+ as a leaving group, see Staude, E.; Patat, F., in Patai, S. *The Chemistry of the Ether Linkage*, Wiley, NY, ***1967***, pp. 22–46.

[374]Olah, G.A.; O'Brien, D.H. *J. Am. Chem. Soc.* ***1967***, *89*, 1725; Olah, G.A.; Sommer, J.; Namanworth, E. *J. Am. Chem. Soc.* ***1967***, *89*, 3576; Olah, J.A.; Olah, G.A., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1970***, pp. 743–747.

[375]Even in the gas phase, NH_3 takes a proton from $CH_3OH_2^+$ rather than acting as a nucleophile: Okada, S.; Abe, Y.; Taniguchi, S.; Yamabe, S. *J. Chem. Soc., Chem. Commun.* ***1989***, 610.

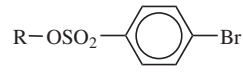
strenuous conditions, but epoxides[376] (**93**) are cleaved quite easily and protonated epoxides (**94**) even more easily. Aziridines (**95**)[377] and episulfides (**96**) are also easily cleaved (see p. 518).[378]

Although halides are common leaving groups in nucleophilic substitution for synthetic purposes, it is often more convenient to use alcohols. Since OH does not leave from ordinary alcohols, it must be converted to a group that does leave. One way is protonation, mentioned above. Another is conversion to a reactive ester, most commonly a sulfonic ester. The sulfonic ester groups *tosylate*, *brosylate*, *nosylate*, and *mesylate* are better leaving groups



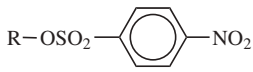
ROTs

p-Toluenesulfonates
Tosylates



ROBs

p-Bromobenzenesulfonates
Brosylates



RONs

p-Nitrobenzenesulfonates
Nosylates

ROMs

Methanesulfonates
Mesylates

than halides and are frequently used.[379] Other leaving groups are still better, and compounds containing these groups make powerful alkylating agents. Among them are oxonium ions (ROR_2^+),[380] and the fluorinated compounds

ROTf
Trifluoromethanesulfonates
Triflates

Nonafluorobutanesulfonates
Nonaflates

2,2,2-Trifluoroethanesulfonates
Tresylates

[376]For a review of the reactions of epoxides, see Smith, J.G. *Synthesis* ***1984***, 629. For a review of their synthesis and reactions, see Bartók, M.; Láng, K.L., in Patai, S. *The Chemistry of Functional Groups*, *Supplement E*, Wiley, NY, ***1980***, pp. 609–681.

[377]See Kametani, T.; Honda, T. *Adv. Heterocycl. Chem.* ***1986***, *39*, 181; Hu, X.E. *Tetrahedron* ***2004***, *60*, 2701.

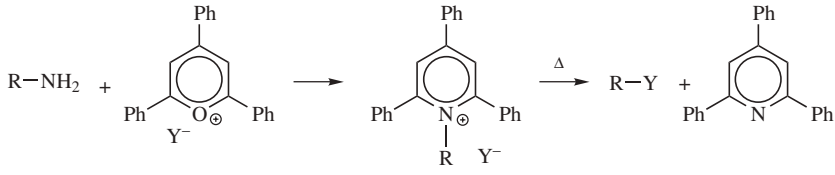
[378]There is evidence that relief of ring strain is not the only factor responsible for the high rates of ring opening of three-membered rings: Di Vona, M.L.; Illuminati, G.; Lillocci, C. *J. Chem. Soc. Perkin Trans. 2* ***1985***, 1943; Bury, A.; Earl, H.A.; Stirling, C.J.M. *J. Chem. Soc., Chem. Commun.* ***1985***, 393.

[379]Bentley, T.W.; Christl, M.; Kemmer, R.; Llewellyn, G.; Oakley, J.E. *J. Chem. Soc. Perkin Trans. 2* ***1994***, 2531.

[380]For a monograph, see Perst, H. *Oxonium Ions in Organic Chemistry*; Verlag Chemie: Deerfield Beach, FL, ***1971***, pp. 100–127. For reviews, see Perst, H., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 5, Wiley, NY, ***1976***, pp. 1961–2047; Granik, V.G.; Pyatin, B.M.; Glushkov, R.G. *Russ. Chem. Rev.* ***1971***, *40*, 747. For a discussion of their use, see Curphey, T.J. *Org. Synth.* ***VI***, 1021.

triflates[381] and *nonaflates*.[381] *Tresylates* are ~400 times less reactive than triflates, but still ~100 times more reactive than tosylates.[382] Halonium ions ($RClR^+$, $RBrR^+$, RIR^+), which can be prepared in super acid solutions (p. 236) and isolated as solid SbF_6^- salts, are also extremely reactive in nucleophilic substitution.[383] Of the above types of compound, the most important in organic synthesis are tosylates, mesylates, oxonium ions, and triflates. The others have been used mostly for mechanistic purposes.

The leaving group ability of NH_2, NHR, and NR_2 are extremely poor,[384] but the leaving-group ability of NH_2 can be greatly improved by converting a primary amine RNH_2 to the ditosylate $RNTs_2$. The NTs_2 group has been successfully replaced by a number of nucleophiles.[385] Another way of converting NH_2 into a good leaving group has been extensively developed by Katritzky and co-workers.[386] In this method the amine is converted to a



pyridinium compound (**98**) by treatment with a pyrylium salt (frequently a 2,4,6-triphenylpyrylium salt, **97**).[387] When the salt is heated, the counterion acts as a nucleophile. In some cases, a non-nucleophilic ion, such as BF_4^-, is used as the counterion for the conversion **97** → **98**, and then Y^- is added to **98**. Among the nucleophiles that have been used successfully in this reaction are I^-, Br^-, Cl^-, F^-, ^-OAc, N_3^-, NHR_2, and H^-. Ordinary NR_2 groups are good leaving groups when the substrate is a Mannich base (these are compounds of the form $RCOCH_2CH_2NR_2$; see reaction **16-19**).[388] The elimination–addition mechanism applies in this case.

[381]For reviews of triflates, nonaflates, and other fluorinated ester leaving groups, see Stang, P.J.; Hanack, M.; Subramanian, L.R. *Synthesis* ***1982***, 85; Howells, R.D.; McCown, J.D. *Chem. Rev.* ***1977***, *77*, 69, pp. 85–87.

[382]Crossland, R.K.; Wells, W.E.; Shiner, Jr., V.J. *J. Am. Chem. Soc.* ***1971***, *93*, 4217.

[383]Peterson, P.E.; Clifford, P.R.; Slama, F.J. *J. Am. Chem. Soc.* ***1970***, *92*, 2840; Peterson, P.E.; Waller, F.J. *J. Am. Chem. Soc.* ***1972***, *94*, 5024; Olah, G.A.; Mo, Y.K. *J. Am. Chem. Soc.* ***1974***, *96*, 3560.

[384]For a review of the deamination of amines, see Baumgarten, R.J.; Curtis, V.A., in Patai, S. *The Chemistry of Functional Groups*, *Supplement F*, pt. 2, Wiley, NY, ***1982***, pp. 929–997.

[385]For references, see Müller, P.; Thi, M.P.N. *Helv. Chim. Acta* ***1980***, *63*, 2168; Curtis, V.A.; Knutson, F.J.; Baumgarten, R.J. *Tetrahedron Lett.* ***1981***, *22*, 199.

[386]For reviews, see Katritzky, A.R.; Marson, C.M. *Angew. Chem. Int. Ed.* ***1984***, *23*, 420; Katritzky, A.R. *Tetrahedron* ***1980***, *36*, 679. For reviews of the use of such leaving groups to study mechanistic questions, see Katritzky, A.R.; Sakizadeh, K.; Musumarra, G. *Heterocycles* ***1985***, *23*, 1765; Katritzky, A.R.; Musumarra, G. *Chem. Soc. Rev.* ***1984***, *13*, 47.

[387]For discussions of the mechanism, see Katritzky, A.R.; Brycki, B. *J. Am. Chem. Soc.* ***1986***, *108*, 7295, and other papers in this series.

[388]For a review of Mannich bases, see Tramontini, M. *Synthesis* ***1973***, 703.

Probably the best leaving group is N_2 from the species RN_2^+, which can be generated in several ways,[389] of which the two most important are the treatment of primary amines with nitrous acid (see p. $$$ for this reaction)

$$RNH_2 + HONO \longrightarrow RN_2^+$$

and the protonation of diazo compounds[390]

$$R_2C{=}\overset{\oplus}{N}{=}\overset{\ominus}{N} + H^+ \longrightarrow R_2CHN_2^+$$

No matter how produced, RN_2^+ are usually too unstable to be isolable,[391] reacting presumably by the S_N1 or S_N2 mechanism.[392] Actually, the exact mechanisms are in doubt because the rate laws, stereochemistry, and products have proved difficult to interpret.[393] If there are free carbocations they should give the same ratio of substitution to elimination to rearrangements, and so on, as carbocations generated in other S_N1 reactions, but they often do not. ''Hot'' carbocations (unsolvated and/or chemically activated) that can hold their configuration have been postulated,[394] as have ion pairs, in which $^-$OH (or $^-$OAc, and so on, depending on how the diazonium ion is generated) is the counterion.[395] One class of aliphatic diazonium salts of which several

[389]For reviews, see Kirmse, W. *Angew. Chem. Int. Ed.* ***1976***, *15*, 251; Collins, C.J. *Acc. Chem. Res.* ***1971***, *4*, 315; Moss, R.A. *Chem. Eng. News* ***1971***, *49*, 28 (No. 48, Nov. 22).

[390]For a treatise, see Regitz, M.; Maas, G. *Diazo Compounds*, Academic Press, NY, ***1986***. For reviews of the reactions of aliphatic diazo compounds with acids, see Hegarty, A.F., in Patai, S. *The Chemistry of Diazonium and Diazo Groups*, pt. 2, Wiley, NY, 1978, pp. 511–591, 571–575; More O'Ferrall, R.A. *Adv. Phys. Org. Chem.* ***1967***, *5*, 331. For review of the structures of these compounds, see Studzinskii, O.P.; Korobitsyna, I.K. *Russ. Chem. Rev.* ***1970***, *39*, 834.

[391]Aromatic diazonium salts can, of course, be isolated (see Chapter 13), but only a few aliphatic diazonium salts have been prepared (see also, Weiss, R.; Wagner, K.; Priesner, C.; Macheleid, J. *J. Am. Chem. Soc.* ***1985***, *107*, 4491). For reviews see Laali, K.; Olah, G.A. *Rev. Chem. Intermed.* ***1985***, *6*, 237; Bott, K., in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups*, *Supplement C*, pt. 1, Wiley, NY, ***1983***, pp. 671–697; Bott, K. *Angew. Chem. Int. Ed.* ***1979***, *18*, 259. The simplest aliphatic diazonium ion $CH_3N_2^+$ has been prepared at $-120°C$ in superacid solution, where it lived long enough for an nmr spectrum to be taken: Berner, D.; McGarrity, J.F. *J. Am. Chem. Soc.* ***1979***, *101*, 3135.

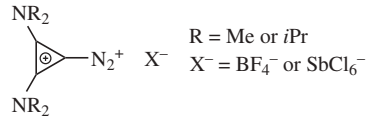
[392]For an example of a diazonium ion reacting by an S_N2 mechanism, see Mohrig, J.R.; Keegstra, K.; Maverick, A.; Roberts, R.; Wells, S. *J. Chem. Soc., Chem. Commun.* ***1974***, 780.

[393]For reviews of the mechanism, see Manuilov, A.V.; Barkhash, V.A. *Russ. Chem. Rev.* ***1990***, *59*, 179; Saunders, Jr., W.H.; Cockerill, A.F. *Mechanisms of Elimination Reactions*, Wiley, NY, ***1973***, pp. 280–317; in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1970***, the articles by Keating, J.T.; Skell, P.S. pp. 573–653; and by Friedman, L. pp. 655–713; White, E.H.; Woodcock, D.J., in Patai, S. *The Chemistry of the Amino Group*, Wiley, NY, ***1968***, pp. 440–483; Ref. 389.

[394]Semenow, D.; Shih, C.; Young, W.G. *J. Am. Chem. Soc.* ***1958***, *80*, 5472. For a review of ''hot'' or ''free'' carbocations, see Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1970***, the articles by Keating, J.T.; Skell, P.S. pp. 573–653.

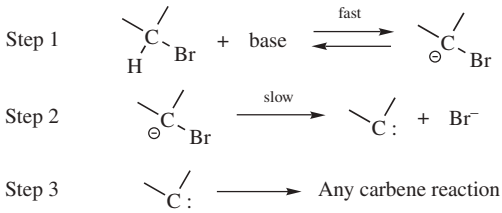
[395]Collins, C.J. *Acc. Chem. Res.* ***1971***, *4*, 315; Collins, C.J.; Benjamin, B.M. *J. Org. Chem.* ***1972***, *37*, 4358; White, E.H.; Field, K.W. *J. Am. Chem. Soc.* ***1975***, *97*, 2148; Cohen, T.; Daniewski, A.R.; Solash, J. *J. Org. Chem.* ***1980***, *45*, 2847; Maskill, H.; Thompson, J.T.; Wilson, A.A. *J. Chem. Soc. Perkin Trans. 2* ***1984***, 1693; Connor, J.K.; Maskill, H. *Bull. Soc. Chim. Fr.* ***1988***, 342.

members have been isolated as stable salts are the cyclopropeniumyldiazonium salts:[396]



Diazonium ions generated from ordinary aliphatic primary amines are usually useless for preparative purposes, since they lead to a mixture of products giving not only substitution by any nucleophile present, but also elimination and rearrangements if the substrate permits. For example, diazotization of *n*-butylamine gave 25% 1-butanol, 5.2% 1-chlorobutane, 13.2% 2-butanol, 36.5% butenes (consisting of 71% 1-butene, 20% *trans*-2-butene, and 9% *cis*-2-butene), and traces of butyl nitrites.[397]

In the S_N1cA and S_N2cA mechanisms (p. 496) there is a preliminary step, the addition of a proton, before the normal S_N1 or S_N2 process occurs. There are also reactions in which the substrate *loses* a proton in a preliminary step. In these reactions, there is a carbene intermediate.



Once formed by this process, the carbene may undergo any of the normal carbene reactions (see p. 287). When the net result is substitution, this mechanism has been called the S_N1cB (for conjugate base) mechanism.[398] Although the slow step is an S_N1 step, the reaction is second order; first order in substrate and first order in base.

Table 10.9 lists some leaving groups in approximate order of ability to leave. The order of leaving-group ability is about the same for S_N1 and S_N2 reactions.

2. *At a Carbonyl Carbon*. This reaction is discussed in Chapter 16.

[396]Weiss, R.; Wagner, K.; Priesner, C.; Macheleid, J. *J. Am. Chem. Soc.* ***1985***, *107*, 4491.
[397]Whitmore, F.C.; Langlois, D.P. *J. Am. Chem. Soc.* ***1932***, *54*, 3441; Streitwieser, Jr., A.; Schaeffer, W.D. *J. Am. Chem. Soc.* ***1957***, *79*, 2888.
[398]Pearson, R.G.; Edgington, D.N. *J. Am. Chem. Soc.* ***1962***, *84*, 4607.

TABLE 10.9. Leaving Groups Listed in Approximate Order of Decreasing Ability to Leave[a]

	Common Leaving Groups	
Substrate RX	At Saturated Carbon	At Carbonyl Carbon
RN_2^+	x	
ROR'^+_2		
$ROSO_2C_4F_9$		
$ROSO_2CF_3$	x	
$ROSO_2F$		
ROTs, etc.[b]	x	
RI	x	
RBr	x	
ROH_2^+	x (conjugate acid of alcohol)	
RCl	x	x (acyl halides)
$RORH^+$	x (conjugate acid of ether)	
$RONO_2$, etc.[b]		
RSR'^+_2[400]		
RNR'^+_3	x	
RF		
ROCOR′[401]	x	x (anhydrides)
RNH_3^+		
ROAr[402]		x (aryl esters)

(*continued*)

The Effect of the Reaction Medium[399]

The effect of solvent polarity[403] on the rate of S_N1 reactions depends on whether the substrate is neutral or positively charged.[404] For neutral substrates, which constitute the majority of cases, the more polar the solvent, the faster the reaction, since there is a greater charge in the transition state than in the starting compound (Table 10.10[405]) and the energy of an ionic transition state is reduced by polar solvents.

[399]For a monograph, see Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed., VCH, NY, ***1988***. For reviews, see Klumpp, G.W. *Reactivity in Organic Chemistry*, Wiley, NY, ***1982***, pp. 186–203; Bentley, T.W.; Schleyer, P.v.R. *Adv. Phys. Org. Chem.* ***1977***, *14*, 1.

[400]For a review of the reactions of sulfonium salts, see Knipe, A.C., in Stirling, C.J.M. *The Chemistry of the Sulphonium Group*, pt. 1, Wiley, NY, ***1981***, pp. 313–385. See also, Badet, B.; Julia, M.; Lefebvre, C. *Bull. Soc. Chim. Fr.* ***1984***, II-431.

[401]For a review of S_N2 reactions of carboxylic esters, where the leaving group is OCOR′, see McMurry, J.E. *Org. React.* ***1976***, *24*, 187.

[402]Nitro substitution increases the leaving-group ability of ArO groups, and alkyl picrates [2,4,6-$ROC_6H_2(NO_2)_3$] react at rates comparable to tosylates: Sinnott, M.L.; Whiting, M.C. *J. Chem. Soc. B* ***1971***, 965. See also, Page, I.D.; Pritt, J.R.; Whiting, M.C. *J. Chem. Soc. Perkin Trans. 2* ***1972***, 906.

[403]Mu, L.; Drago, R.S.; Richardson, D.E. *J. Chem. Soc. Perkin Trans. 2*, ***1998***, 159; Fujio, M.; Saeki, Y.; Nakamoto, K.; Kim, S.H.; Rappoport, Z.; Tsuno, Y. *Bull. Chem. Soc. Jpn.* ***1996***, *69*, 751.

[404]Mitsuhashi, T.; Hirota, H.; Yamamoto, G. *Bull. Chem. Soc. Jpn.* ***1994***, *67*, 824; Bentley, T.W.; Llewellyn, G.; Ryu, Z.H. *J. Org. Chem.* ***1998***, *63*, 4654.

[405]This analysis is due to Ingold, C.K. *Structure and Mechanism in Organic Chemistry*, 2nd ed., Cornell University Press, Ithaca, NY, ***1969***, pp. 457–463.

TABLE 10.9. (*Continued*)

	Common Leaving Groups	
Substrate RX	At Saturated Carbon	At Carbonyl Carbon
ROH		x (carboxylic acids)
ROR		x (alkyl esters)
RH		
RNH_2		x (amides)
RAr		
RR		

[a]Groups that are common leaving groups at saturated and carbonyl carbons are indicated.
[b]The substrates ROTs, and so on, includes esters of sulfuric and sulfonic acids in general, for example, $ROSO_2OH$, $ROSO_2OR$, $ROSO_2R$. The substrate $RONO_2$, and so on, includes inorganic ester leaving groups, such as $ROPO(OH)_2$ and $ROB(OH)_2$.

TABLE 10.10. Transition States for S_N1 Reactions of Charged and Uncharged Substrates, and for S_N2 Reactions of the Four Charge Types[405]

Reactants and Transition States		Charge in the Transition State Relative to Starting Materials	How an Increase in Solvent Polarity Affects the Rate
S_N2	Type I $RX + Y^- \rightarrow Y^{\delta-}\bullet\bullet\bullet R\bullet\bullet\bullet X^{\delta-}$	Dispersed	Small decrease
	Type II $RX + Y^- \rightarrow Y^{\delta+}\bullet\bullet\bullet R\bullet\bullet\bullet X^{\delta-}$	Increased	Large increase
	Type III $RX + Y^- \rightarrow Y^{\delta-}\bullet\bullet\bullet R\bullet\bullet\bullet X^{\delta+}$	Decreased	Large decrease
	Type IV $RX + Y^- \rightarrow Y^{\delta+}\bullet\bullet\bullet R\bullet\bullet\bullet X^{\delta+}$	Dispersed	Small decrease
S_N1	$RX \rightarrow R^{\delta+}\bullet\bullet\bullet X^{\delta-}$	Increased	Large increase
	$RX^- \rightarrow R^{\delta-}\bullet\bullet\bullet X^{\delta-}$	Dispersed	Small decrease

However, when the substrate is positively charged, the charge is more spread out in the transition state than in the starting ion, and a greater solvent polarity slows the reaction. Even for solvents with about the same polarity, there is a difference between protic and aprotic solvents.[406] The S_N1 reactions of un-ionized substrates are more rapid in protic solvents, which can form hydrogen bonds with the leaving group. Examples of protic solvents are water,[407] alcohols, and carboxylic acids, while some polar aprotic solvents are DMF, dimethyl sulfoxide (DMSO),[408] acetonitrile, acetone, sulfur dioxide, and

[406]See, for example, Ponomareva, E.A.; Dvorko, G.F.; Kulik, N.I.; Evtushenko, N.Yu. *Doklad. Chem.* ***1983***, *272*, 291.
[407]For a study of nucleophilic reactivities in water, see Bug, T.; Mayr, H. *J. Am. Chem. Soc.* ***2003***, *125*, 12980. For a correlation of the Hammett equation and micellar effects see Brinchi, L.; DiProfio, P.; Germani, R.; Savelli, G.; Spreti, N.; Bunton, L.A. *Eur. J. Org. Chem.* ***2000***, 3849.
[408]For reviews of reactions in dimethyl sulfoxide, see Buncel, E.; Wilson, H. *Adv. Phys. Org. Chem.* ***1977***, *14*, 133; Martin, D.; Weise, A.; Niclas, H. *Angew. Chem. Int. Ed.* ***1967***, *6*, 318.

hexamethylphosphoramide [$(Me_2N)_3PO$], HMPA.[409] An algorithm has been developed to accurately calculate dielectric screening effects in solvents.[410] S_N2 reactions have been done in ionic liquids (see p. 415),[411] and in supercritical carbon dioxide (see p. 414).[412]

For S_N2 reactions, the effect of the solvent[413] depends on which of the four charge types the reaction belongs to (p. 425). In types I and IV, an initial charge is dispersed in the transition state, so the reaction is hindered by polar solvents. In type III, initial charges are *decreased* in the transition state, so that the reaction is even more hindered by polar solvents. Only type II, where the reactants are uncharged but the transition state has built up a charge, is aided by polar solvents. These effects are summarized in Table 10.10.[405] Westaway has proposed a ''solvation rule'' for S_N2 reactions, which states that changing the solvent will not change the structure of the transition state for type I reactions, but will change it for type II reactions.[414] For S_N2 reactions also, the difference between protic and aprotic solvents must be considered.[415] For reactions of types I and III the transition state is more solvated in polar aprotic solvents than in protic ones,[416] while (as we saw on p. 490) the original charged nucleophile is less solvated in aprotic solvents[417] (the second factor is generally much greater than the first[418]). So the change from, say, methanol to DMSO should greatly increase the rate. As an example, the relative rates at 25°C for the reaction between MeI and Cl^- were[332] in MeOH, 1; in $HCONH_2$ (still protic although a weaker acid), 12.5; in HCONHMe, 45.3; and $HCONMe_2$, 1.2×10^6. The change in rate in going from a protic to an aprotic solvent is also related to the *size* of the attacking anion. Small ions are solvated best in protic solvents, since hydrogen bonding is most important for them, while large anions are solvated best in aprotic solvents (protic solvents have highly developed structures held together by hydrogen bonds; aprotic solvents have much looser structures, and it is easier for a large anion to be fitted in). So the rate of attack by small anions is most greatly increased by the change from a protic to an aprotic solvent. This may have preparative significance. The review articles in Ref. 400 have lists of several dozen reactions of charge types I and III in which

[409]For reviews of HMPA, see Normant, H. *Russ. Chem. Rev.* ***1970***, *39*, 457; *Bull. Soc. Chim. Fr.* ***1968***, 791; *Angew. Chem. Int. Ed.* ***1967***, *6*, 1046.

[410]Klamt, A.; Schüürmann, G. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 799.

[411]Wheeler, C.; West, K.N.; Liotta, C.L.; Eckert, C.A. *Chem. Commun.* ***2001***, 887; Kim, D.W.; Song, C.E.; Chi, D.Y. *J. Org. Chem.* ***2003***, *68*, 4281; Chiappe, C.; Pieraccini, D.; Saullo, P. *J. Org. Chem.* ***2003***, *68*, 6710.

[412]DeSimone, J.; Selva, M.; Tundo, P. *J. Org. Chem.* ***2001***, *66*, 4047.

[413]For microsolvation of S_N2 transition states see Craig, S.L.; Brauman, J.I. *J. Am. Chem. Soc.* ***1999***, *121*, 6690.

[414]Westaway, K.C. *Can. J. Chem.* ***1978***, *56*, 2691; Westaway, K.C.; Lai, Z. *Can. J. Chem.* ***1989***, *67*, 345.

[415]For reviews of the effects of protic and aprotic solvents, see Parker, A.J. *Chem. Rev.* ***1969***, *69*, 1; *Adv. Phys. Org. Chem.* ***1967***, *5*, 173; *Adv. Org. Chem.* ***1965***, *5*, 1; Madaule-Aubry, F. *Bull. Soc. Chim. Fr.* ***1966***, 1456.

[416]However, even in aprotic solvents, the transition state is less solvated than the charged nucleophile: Magnera, T.F.; Caldwell, G.; Sunner, J.; Ikuta, S.; Kebarle, P. *J. Am. Chem. Soc.* ***1984***, *106*, 6140.

[417]See, for example, Fuchs, R.; Cole, L.L. *J. Am. Chem. Soc.* ***1973***, *95*, 3194.

[418]See, however, Haberfield, P.; Clayman, L.; Cooper, J.S. *J. Am. Chem. Soc.* ***1969***, *91*, 787.

TABLE 10.11. Relative Rates of Ionization of *p*-Methoxyneophyl Toluenesulfonate in Various Solvents[419]

Solvent	Relative Rate	Solvent	Relative Rate
HCOOH	153	Ac_2O	0.020
H_2O	39	Pyridine	0.013
80% EtOH–H_2O	1.85	Acetone	0.0051
AcOH	1.00	EtOAc	6.7×10^{-4}
MeOH	0.947	THF	5.0×10^{-4}
EtOH	0.370	Et_2O	3×10^{-5}
Me_2SO	0.108	$CHCl_3$	
Octanoic acid	0.043	Benzene	Lower still
MeCN	0.036	Alkanes	
$HCONMe_2$	0.029		

yields are improved and reaction times reduced in polar aprotic solvents. Reaction types II and IV are much less susceptible to the difference between protic and aprotic solvents.

Since for most reactions S_N1 rates go up and S_N2 rates go down in solvents of increasing polarity, it is quite possible for the same reaction to go by the S_N1 mechanism in one solvent and the S_N2 in another. Table 10.11 is a list of solvents in order of ionizing power;[419] a solvent high on the list is a good solvent for S_N1 reactions. Trifluoroacetic acid, which was not studied by Smith, Fainberg, and Winstein, has greater ionizing power than any solvent listed in Table 10.11.[420] Because it also has very low nucleophilicity, it is an excellent solvent for S_N1 solvolyses. Other good solvents for this purpose are 1,1,1-trifluoroethanol CF_3CH_2OH, and 1,1,1,3,3,3-hexafluoro-2-propanol, $(F_3C)_2CHOH$.[421]

We have seen how the polarity of the solvent influences the rates of S_N1 and S_N2 reactions. The ionic strength of the medium has similar effects. In general, the addition of an external salt affects the rates of S_N1 and S_N2 reactions in the same way as an increase in solvent polarity, although this is not quantitative; different salts have different effects.[422] However, there are exceptions: although the rates of S_N1 reactions are usually increased by the addition of salts (this is called the *salt effect*), addition of the leaving-group ion often decreases the rate (the common-ion effect, p. 434). There is also the special salt effect of $LiClO_4$, mentioned on p. 439. In addition to these effects, S_N1 rates are also greatly accelerated when there are ions present that specifically help in pulling off the leaving group.[423] Especially

[419]Smith, S.G.; Fainberg, A.H.; Winstein, S. *J. Am. Chem. Soc.* ***1961***, *83*, 618.
[420]Capon, B.; McManus, S. *Neighboring Group Participation*, Vol. 1; Plenum, NY, ***1976***; Haywood-Farmer, J. *Chem. Rev.* ***1974***, *74*, 315; Streitwieser, Jr., A.; Dafforn, G.A. *Tetrahedron Lett.* ***1969***, 1263.
[421]Schadt, F.L.; Schleyer, P.v.R.; Bentley, T.W. *Tetrahedron Lett.* ***1974***, 2335.
[422]See, for example, Duynstee, E.F.J.; Grunwald, E.; Kaplan, M.L. *J. Am. Chem. Soc.* ***1960***, *82*, 5654; Bunton, C.A.; Robinson, L. *J. Am. Chem. Soc.* ***1968***, *90*, 5965.
[423]For a review, see Kevill, D.N., in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups*, *Supplement D*, pt. 2, Wiley, NY, ***1983***, pp. 933–984.

important are Ag^+, Hg^{2+}, and Hg_2^{2+}, but H^+ helps to pull off F (hydrogen bonding).[424] Even primary halides have been reported to undergo S_N1 reactions when assisted by metal ions.[425] This does not mean, however, that reactions in the presence of metallic ions invariably proceed by the S_N1 mechanism. It has been shown that alkyl halides can react with $AgNO_2$ and $AgNO_3$ by the S_N1 or S_N2 mechanism, depending on the reaction conditions.[426]

The effect of solvent has been treated quantitatively (for S_N1 mechanisms, in which the solvent pulls off the leaving group) by a linear free-energy relationship[427]

$$\log \frac{k}{k_0} = m\,Y$$

where m is characteristic of the substrate (defined as 1.00 for *t*-BuCl) and is usually near unity, Y is characteristic of the solvent and measures its ''ionizing power,'' and k_0 is the rate in a standard solvent, 80% aqueous ethanol at 25°C. This is known as the Grunwald–Winstein equation, and its utility is at best limited. The Y values can of course be measured for solvent *mixtures* too, and this is one of the principal advantages of the treatment, since it is not easy otherwise to assign a polarity arbitrarily to a given mixture of solvents.[428] The treatment is most satisfactory for different proportions of a given solvent pair. For wider comparisons, the treatment is not so good quantitatively, although the Y values do give a reasonably good idea of solvolyzing power.[429] Table 10.12 contains a list of some Y values.[430]

Ideally, Y should measure only the ionizing power of the solvent, and should not reflect any backside attack by a solvent molecule in helping the nucleofuge

[424]For a review of assistance by metallic ions, see Rudakov, E.S.; Kozhevnikov, I.V.; Zamashchikov, V.V. *Russ. Chem. Rev.* ***1974***, *43*, 305. For an example of assistance in removal of F by H^+, see Coverdale, A.K.; Kohnstam, G. *J. Chem. Soc.* ***1960***, 3906.

[425]Zamashchikov, V.V.; Rudakov, E.S.; Bezbozhnaya, T.V.; Matveev, A.A. *J. Org. Chem. USSR* ***1984***, *20*, 424. See, however, Kevill, D.N.; Fujimoto, E.K. *J. Chem. Soc., Chem. Commun.* ***1983***, 1149.

[426]Kornblum, N.; Jones, W.J.; Hardies, D.E. *J. Am. Chem. Soc.* ***1966***, *88*, 1704; Kornblum, N.; Hardies, D.E. *J. Am. Chem. Soc.* ***1966***, *88*, 1707.

[427]Grunwald, E.; Winstein, S. *J. Am. Chem. Soc.* ***1948***, *70*, 846.

[428]For reviews of polarity scales of solvent mixtures, see Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed., VCH, NY, ***1988***, pp. 339–405; Langhals, H. *Angew. Chem. Int. Ed.* ***1982***, *21*, 724.

[429]For a criticism of the Y scale, see Abraham, M.H.; Doherty, R.M.; Kamlet, M.J.; Harris, J.M.; Taft, R.W. *J. Chem. Soc. Perkin Trans. 2* ***1987***, 1097.

[430]Y values are from Fainberg, A.H.; Winstein, S. *J. Am. Chem. Soc.* ***1956***, *78*, 2770, except for the value for CF_3CH_2OH, which is from Shiner, Jr., V.J.; Dowd, W.; Fisher, R.D.; Hartshorn, S.R.; Kessick, M.A.; Milakofsky, L.; Rapp, M.W. *J. Am. Chem. Soc.* ***1969***, *91*, 4838. Y_{OTs} values are from Bentley, T.W.; Llewellyn, G. *Prog. Phys. Org. Chem.* ***1990***, *17*, 143–144. Z values are from Kosower, E.M.; Wu, G.; Sorensen, T.S. *J. Am. Chem. Soc.* ***1961***, *83*, 3147. See also, Larsen, J.W.; Edwards, A.G.; Dobi, P. *J. Am. Chem. Soc.* ***1980***, *102*, 6780. $E_T(30)$ values are from Reichardt, C.; Dimroth, K. *Fortschr. Chem. Forsch.* ***1969***, *11*, 1; Reichardt, C. *Angew. Chem. Int. Ed.* ***1979***, *18*, 98; Laurence, C.; Nicolet, P.; Reichardt, C. *Bull. Soc. Chim. Fr.* ***1987***, 125; Laurence, C.; Nicolet, P.; Lucon, M.; Reichardt, C. *Bull. Soc. Chim. Fr.* ***1987***, 1001; Reichardt, C.; Eschner, M.; Schäfer, G. *Liebigs Ann. Chem.* ***1990***, 57. Values for many additional solvents are given, in the last five papers. Many values from all of these scales are given, in Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed.; VCH, NY, ***1988***.

TABLE 10.12. The Y, Y_{OTs}, Z, and E_T (30) Values for Some Solvents[430]

Solvent	Y	Y_{OTs}	Z	E_T (30)
CF_3COOH		4.57		
H_2O	3.5	4.1	94.6	63.1
$(CF_3)_2CHOH$		3.82		65.3
HCOOH	2.1	3.04		
H_2O–EtOH (1:1)	1.7	1.29	90	55.6
CF_3CH_2OH	1.0	1.77		59.8
$HCONH_2$	0.6		83.3	56.6
80% EtOH	0.0	0.0	84.8	53.7
MeOH	−1.1	−0.92	83.6	55.4
AcOH	−1.6	−0.9	79.2	51.7
EtOH	−2.0	−1.96	79.6	51.9
90% dioxane	−2.0	−2.41	76.7	46.7
*i*PrOH	−2.7	−2.83	76.3	48.4
95% acetone	−2.8	−2.95	72.9	48.3
t-BuOH	−3.3	−3.74	71.3	43.9
MeCN		−3.21	71.3	45.6
Me_2SO			71.1	45.1
$HCONMe_2$		−4.14	68.5	43.8
Acetone			65.7	42.2
HMPA				40.9
CH_2Cl_2				40.7
Pyridine			64.0	40.5
$CHCl_3$			63.2	39.1
PhCl				37.5
THF				37.4
Dioxane				36.0
Et_2O				34.5
C_6H_6			54	34.3
PhMe				33.9
CCl_4				32.4
n-Octane				31.1
n-Hexane				31.0
Cyclohexane				30.9

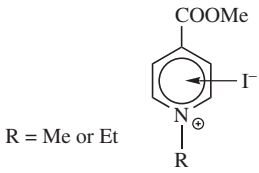
to leave (nucleophilic assistance; k_s, p. 456). Actually, there is evidence that many solvents do lend some nucleophilic assistance,[431] even with tertiary substrates.[432] It was proposed that a better measure of solvent ''ionizing power'' would be a relationship based on 2-adamantyl substrates, rather than *t*-BuCl, since the structure of this system completely prevents backside nucleophilic assistance (p. 480). Such a

[431]A scale of solvent nucleophilicity (as opposed to ionizing power), called the N_T scale, has been developed: Kevill, D.N.; Anderson, S.W. *J. Org. Chem.* ***1991***, *56*, 1845.

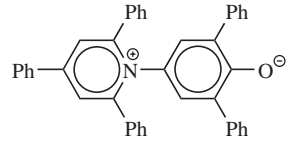
[432]For discussions, with references, see Kevill, D.N.; Anderson, S.W. *J. Am. Chem. Soc.* ***1986***, *108*, 1579; McManus, S.P.; Neamati-Mazreah, N.; Karaman, R.; Harris, J.M. *J. Org. Chem.* ***1986***, *51*, 4876; Abraham, M.H.; Doherty, R.M.; Kamlet, M.J.; Harris, J.M.; Taft, R.W. *J. Chem. Soc. Perkin Trans. 2* ***1987***, 913.

scale, called Y_{OTs}, was developed, with *m* defined as 1.00 for 2-adamantyl tosylate.[433] Some values of Y_{OTs} are given in Table 10.12. These values, which are actually based on both 1- and 2-adamantyl tosylates (both are equally impervious to nucleophilic assistance and show almost identical responses to solvent ionizing power[434]) are called Y_{OTs} because they apply only to tosylates. It has been found that solvent "ionizing power" depends on the leaving group, so separate scales[435] have been set up for OTf,[436] Cl,[402] Br,[437] I,[438] and other nucleofuges,[439] all based on the corresponding adamantyl compounds. A new Y scale has been established based on benzylic bromides.[440] In part, this was done because benzylic tosylates did not give a linear correlation with the 2-adamantyl Y_{OTs} parameter.[441] This is substrate dependent, since solvolysis of 2,2,-dimethyl-1-phenyl-1-propanol tosylate showed no nucleophilic solvent participation.[442]

In order to include a wider range of solvents than those in which any of the *Y* values can be conveniently measured, other attempts have been made at correlating solvent polarities.[443] Kosower found that the position of the charge-transfer peak (see p. 115) in the UV spectrum of the complex (**99**) between iodide ion and



99



100

[433]Schadt, F.L.; Bentley, T.W.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1976***, *98*, 7667.
[434]Bentley, T.W.; Carter, G.E. *J. Org. Chem.* ***1983***, *48*, 579.
[435]For a review of these scales, see Bentley, T.W.; Llewellyn, G. *Prog. Phys. Org. Chem.* ***1990***, *17*, 121.
[436]Kevill, D.N.; Anderson, S.W. *J. Org. Chem.* ***1985***, *50*, 3330. See also, Creary, X.; McDonald, S.R. *J. Org. Chem.* ***1985***, *50*, 474.
[437]Bentley, T.W.; Carter, G.E. *J. Am. Chem. Soc.* ***1982***, *104*, 5741. See also, Liu, K.; Sheu, H. *J. Org. Chem.* ***1991***, *56*, 3021.
[438]Bentley, T.W.; Carter, G.E.; Roberts, K. *J. Org. Chem.* ***1984***, *49*, 5183.
[439]See Bentley, T.W.; Roberts, K. *J. Org. Chem.* ***1985***, *50*, 4821; Takeuchi, K.; Ikai, K.; Shibata, T.; Tsugeno, A. *J. Org. Chem.* ***1988***, *53*, 2852; Kevill, D.N.; Hawkinson, D.C. *J. Org. Chem.* ***1990***, *55*, 5394 and references cited therein.
[440]Fujio, M.; Saeki, Y.; Nakamoto, K.; Yatsugi, K.-i.; Goto, N.; Kim, S.H.; Tsuji, Y.; Rappoport, Z.; Tsuno, Y. *Bull. Chem. Soc. Jpn.* ***1995***, *68*, 2603; Liu, K.-T.; Chin, C.-P.; Lin, Y.-S.; Tsao, M.-L. *J. Chem. Res. (S)* ***1997***, 18.
[441]Fujio, M.; Susuki, T.; Goto, M.; Tsuji, Y.; Yatsugi, K.; Saeki, Y.; Kim, S.H.; Tsuno, Y. *Bull. Chem. Soc. Jpn.* ***1994***, *67*, 2233.
[442]Tsuji, Y.; Fujio, M.; Tsuno, Y. *Tetrahedron Lett.* ***1992***, *33*, 349.
[443]For reviews of solvent polarity scales, see Abraham, M.H.; Grellier, P.L.; Abboud, J.M.; Doherty, R.M.; Taft, R.W. *Can. J. Chem.* ***1988***, *66*, 2673; Kamlet, M.J.; Abboud, J.M.; Taft, R.W. *Prog. Phys. Org. Chem.* ***1981***, *13*, 485; Shorter, J. *Correlation Analysis of Organic Reactivity*, Wiley, NY, ***1982***, pp. 127–172; Reichardt, C.; Dimroth, K. *Fortschr. Chem. Forsch.* ***1969***, *11*, 1; Reichardt, C. *Angew. Chem. Int. Ed.* ***1979***, *18*, 98; Abraham, M.H. *Prog. Phys. Org. Chem.* ***1974***, *11*, 1; Koppel, I.A.; Palm, V.A., in Chapman, N.B.; Shorter, J. *Advances in Linear Free Energy Relationships*, Plenum, NY, ***1972***, pp. 203–280; Ref. 443. See also, Chastrette, M.; Rajzmann, M.; Chanon, M.; Purcell, K.F. *J. Am. Chem. Soc.* ***1985***, *107*, 1.

1-methyl- or 1-ethyl-4-carbomethoxypyridinium ion was dependent on the polarity of the solvent.[444] From these peaks, which are very easy to measure, Kosower calculated transition energies that he called *Z* values. These values are thus measures of solvent polarity analogous to *Y* values. Another scale is based on the position of electronic spectra peaks of the pyridinium-*N*-phenolbetaine (**100**) in various solvents.[445] Solvent polarity values on this scale are called $E_T(30)$[446] values. The $E_T(30)$ values are related to *Z* values by the expression[447]

$$Z = 1.41\,E_T(30) + 6.92$$

Table 10.12 shows that *Z* and $E_T(30)$ values are generally in the same order as *Y* values. Other scales, the π* scale,[448] the π^*_{azo} scale,[449] and the Py scale,[450] are also based on spectral data.[451]

Carbon dioxide can be liquefied under high pressure (supercritical CO_2). Several reactions have been done using supercritical CO_2 as the medium, but special apparatus is required. This medium offers many advantages,[452] and some disadvantages, but is an interesting new area of research.

The effect of solvent on nucleophilicity has already been discussed (pp. 490–495).

Phase-Transfer Catalysis

A difficulty that occasionally arises when carrying out nucleophilic substitution reactions is that the reactants do not mix. For a reaction to take place the reacting molecules must collide. In nucleophilic substitutions the substrate is usually insoluble in water and other polar solvents, while the nucleophile is often an anion, which is soluble in water but not in the substrate or other organic solvents. Consequently, when the two reactants are brought together, their concentrations in the same phase are too low for convenient reaction rates. One way to overcome this

[444]Kosower, E.M.; Wu, G.; Sorensen, T.S. *J. Am. Chem. Soc.* ***1961***, *83*, 3147. See also, Larsen, J.W.; Edwards, A.G.; Dobi, P. *J. Am. Chem. Soc.* ***1980***, *102*, 6780.

[445]Dimroth, K.; Reichardt, C. *Liebigs Ann. Chem.* ***1969***, *727*, 93. See also, Haak, J.R.; Engberts, J.B.F.N. *Recl. Trav. Chim. Pays-Bas* ***1986***, *105*, 307.

[446]The symbol E_T comes from *energy*, *transition*. The (30) is used because the ion **100** bore this number in Dimroth, K.; Reichardt, C. *Liebigs Ann. Chem.* ***1969***, *727*, 93. Values based on other ions have also been reported: See, for example, Reichardt, C.; Harbusch-Görnert, E.; Schäfer, G. *Liebigs Ann. Chem.* ***1988***, 839.

[447]Reichardt, C.; Dimroth, K. *Fortschr. Chem. Forsch.* ***1969***, *11*, p. 32.

[448]Kamlet, M.J.; Abboud, J.M.; Taft, R.W. *J. Am. Chem. Soc.* ***1977***, *99*, 6027; Doherty, R.M.; Abraham, M.H.; Harris, J.M.; Taft, R.W.; Kamlet, M.J. *J. Org. Chem.* ***1986***, *51*, 4872; Kamlet, M.J.; Doherty, R.M.; Abboud, J.M.; Abraham, M.H.; Taft, R.W. *CHEMTECH* ***1986***, 566, and other papers in this series. See also, Doan, P.E.; Drago, R.S. *J. Am. Chem. Soc.* ***1982***, *104*, 4524; Kamlet, M.J.; Abboud, J.M.; Taft, R.W. *Prog. Phys. Org. Chem.* ***1981***, *13*, 485; Bekárek, V. *J. Chem. Soc. Perkin Trans. 2* ***1986***, 1425; Abe, T. *Bull. Chem. Soc. Jpn.* ***1990***, *63*, 2328.

[449]Buncel, E.; Rajagopal, S. *J. Org. Chem.* ***1989***, *54*, 798.

[450]Dong, D.C.; Winnik, M.A. *Can. J. Chem.* ***1984***, *62*, 2560.

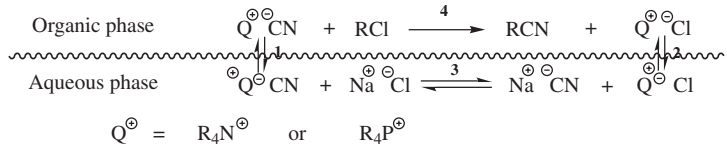
[451]For a review of such scales, see Buncel, E.; Rajagopal, S. *Acc. Chem. Res.* ***1990***, *23*, 226.

[452]Kaupp, G. *Angew. Chem. Int. Ed.* ***1994***, *33*, 1452.

difficulty is to use a solvent that will dissolve both species. As we saw on p. 501, a dipolar aprotic solvent may serve this purpose. Another way, which is used very often, is *phase-transfer catalysis*.[453]

In this method, a catalyst is used to carry the nucleophile from the aqueous into the organic phase. As an example, simply heating and stirring a two-phase mixture of 1-chlorooctane for several days with aqueous NaCN gives essentially no yield of 1-cyanooctane. But if a small amount of an appropriate quaternary ammonium salt is added, the product is quantitatively formed in ~2 h.[454] There are two principal types of phase-transfer catalyst, although the action of the two types is somewhat different, the effects are the same. Both get the anion into the organic phase and allow it to be relatively free to react with the substrate.

1. *Quaternary Ammonium or Phosphonium Salts*. In the above-mentioned case of NaCN, the uncatalyzed reaction does not take place because the $^-$CN ions cannot cross the interface between the two phases, except in very low concentration. The reason is that the Na^+ ions are solvated by the water, and this solvation energy would not be present in the organic phase. The CN^- ions cannot cross without the Na^+ ions because that would destroy the electrical neutrality of each phase. In contrast to Na^+ ions, quaternary ammonium (R_4N^+)[455] and phosphonium (R_4P^+) ions with sufficiently large R groups are poorly solvated in water and prefer organic solvents. If a small amount of such a salt is added, three equilibria are set up:



The Na^+ ions remain in the aqueous phase; they cannot cross. The Q^+ ions do cross the interface and carry an anion with them. At the beginning of the reaction the chief anion present is $^-$CN. This gets carried into the organic phase (equilibrium 1) where it reacts with RCl to produce RCN and Cl^-. The Cl^- then gets carried into the aqueous phase (equilibrium 2). Equilibrium 3, taking place entirely in the aqueous phase, allows Q^{+-}CN to be regenerated.

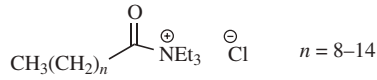
[453]For monographs, see Dehmlow, E.V.; Dehmlow, S.S. *Phase Transfer Catalysis*, 2nd ed., Verlag Chemie, Deerfield Beach, FL, ***1983***; Starks, C.M.; Liotta, C. *Phase Transfer Catalysis*, Academic Press, NY, ***1978***; Weber, W.P.; Gokel, G.W. *Phase Transfer Catalysis in Organic Synthesis*, Springer, NY, ***1977***. For reviews, see Makosza, M. *Pure Appl. Chem.* ***2000***, *72*, 1399; Montanari, F.; Landini, D.; Rolla, F. *Top. Curr. Chem.* ***1982***, *101*, 147; Alper, H. *Adv. Organomet. Chem.* ***1981***, *19*, 183; Dehmlow, E.V. *Chimia* ***1980***, *34*, 12; Makosza, M. *Surv. Prog. Chem.* ***1980***, *9*, 1; Sjöberg, K. *Aldrichimica Acta* ***1980***, *13*, 55; Brändström, A. *Adv. Phys. Org. Chem.* ***1977***, *15*, 267; Dockx, J. *Synthesis* ***1973***, 441.

[454]Starks, C.M.; Liotta, C. *Phase Transfer Catalysis*, Academic Press, NY, ***1978***, p. 2.

[455]Bis-quaternary ammonium salts have also been used: Lissel, M.; Feldman, D.; Nir, M.; Rabinovitz, M. *Tetrahedron Lett.* ***1989***, *30*, 1683.

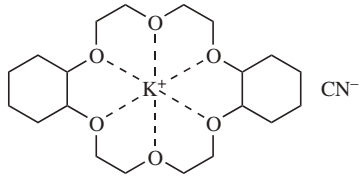
All the equilibria are normally reached much faster than the actual conversion of RCl to RCN, so the latter is the rate-determining step.

In some cases, the Q^+ ions have such a low solubility in water that virtually all remain in the organic phase.[456] In such cases the exchange of ions (equilibrium 3) takes place across the interface. Still another mechanism (*the interfacial mechanism*) can operate where $^-$OH extracts a proton from an organic substrate.[457] In this mechanism, the $^-$OH ions remain in the aqueous phase and the substrate in the organic phase; the deprotonation takes place at the interface.[458] Thermal stability of the quaternary ammonium salt is a problem, limiting the use of some catalysts. The trialkylacyl ammonium halide **101** is thermally stable, however, even at high reaction temperatures.[459] The use of molten quaternary ammonium salts as ionic reaction media for substitution reactions has also been reported.[460]

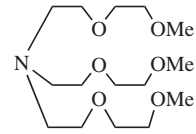


101

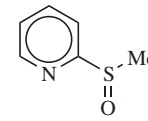
2. *Crown Ethers and Other Cryptands*.[461] We saw in Chapter 3 that certain cryptands are able to surround certain cations. In effect, a salt-like KCN is converted by dicyclohexano-18-crown-6 into a new salt (**102**) whose anion is the same, but whose cation is now a much larger species with the positive



102



103



104

charge spread over a large volume and hence much less concentrated. This larger cation is much less solubilized by water than K^+ and much more attracted to organic solvents, although KCN is generally insoluble in organic solvents, the cryptate salt is soluble in many of them. In these cases we do not need an aqueous phase at all but simply add the salt to the organic phase.

[456]Landini, D.; Maia, A.; Montanari, F. *J. Chem. Soc., Chem. Commun.* ***1977***, 112; *J. Am. Chem. Soc.* ***1978***, *100*, 2796.

[457]For a review, see Rabinovitz, M.; Cohen, Y.; Halpern, M. *Angew. Chem. Int. Ed.* ***1986***, *25*, 960.

[458]This mechanism was proposed by Makosza, M. *Pure Appl. Chem.* ***1975***, *43*, 439. See also, Dehmlow, E.V.; Thieser, R.; Sasson, Y.; Pross, E. *Tetrahedron* ***1985***, *41*, 2927; Mason, D.; Magdassi, S.; Sasson, Y. *J. Org. Chem.* ***1990***, *55*, 2714.

[459]Bhalerao, U.T.; Mathur, S.N.; Rao, S.N. *Synth. Commun.* ***1992***, *22*, 1645.

[460]Badri, M.; Brunet, J.-J.; Perron, R. *Tetrahedron Lett.* ***1992***, *33*, 4435.

[461]For a review of this type of phase-transfer catalysis, see Liotta, C., in Patai, S. *The Chemistry of Functional Groups*, *Supplement E*, Wiley, NY, ***1980***, pp. 157–174.

Suitable cryptands have been used to increase greatly the rates of reactions where F^-, Br^-, I^-, ^-OAc, and ^-CN are nucleophiles.[462] Certain compounds that are not cryptands can act in a similar manner. One example is the podand tris(3,6-dioxaheptyl)amine (**103**), also called TDA-1.[463] Another, not related to the crown ethers, is the pyridyl sulfoxide **104**.[464]

Both of the above-mentioned catalyst types get the anions into the organic phase, but there is another factor as well. There is evidence that sodium and potassium salts of many anions, even if they could be dissolved in organic solvents, would undergo reactions very slowly (dipolar aprotic solvents are exceptions) because in these solvents the anions exist as ion pairs with Na^+ or K^+ and are not free to attack the substrate (p. 492). Fortunately, ion pairing is usually much less with the quaternary ions and with the positive cryptate ions, so the anions in these cases are quite free to attack. Such anions are sometimes referred to as ''naked'' anions.

Not all quaternary salts and cryptands work equally well in all situations. Some experimentation is often required to find the optimum catalyst.

Although phase-transfer catalysis has been most often used for nucleophilic substitutions, it is not confined to these reactions. Any reaction that needs an insoluble anion dissolved in an organic solvent can be accelerated by an appropriate phase-transfer catalyst. We will see some examples in later chapters. In fact, in principle, the method is not even limited to anions, and a small amount of work has been done in transferring cations,[465] radicals, and molecules.[466] The reverse type of phase-transfer catalysis has also been reported: transport into the aqueous phase of a reactant that is soluble in organic solvents.[467] Microwave activated phase-transfer catalysis has been reported.[468]

The catalysts mentioned above are soluble. Certain cross-linked polystyrene resins, as well as alumina[469] and silica gel, have been used as insoluble phase-transfer catalysts. These, called *triphase catalysts*,[470] have the advantage of

[462]See, for example, Liotta, C.; Harris, H.P.; McDermott, M.; Gonzalez, T.; Smith, K. *Tetrahedron Lett.* ***1974***, 2417; Sam, D.J.; Simmons, H.E. *J. Am. Chem. Soc.* ***1974***, *96*, 2252; Durst, H.D. *Tetrahedron Lett.* ***1974***, 2421.

[463]Soula, G. *J. Org. Chem.* ***1985***, *50*, 3717.

[464]Furukawa, N.; Ogawa, S.; Kawai, T.; Oae, S. *J. Chem. Soc. Perkin Trans. 1* ***1984***, 1833. See also, Fujihara, H.; Imaoka, K.; Furukawa, N.; Oae, S. *J. Chem. Soc. Perkin Trans. 1* ***1986***, 333.

[465]See Armstrong, D.W.; Godat, M. *J. Am. Chem. Soc.* ***1979***, *101*, 2489; Iwamoto, H.; Yoshimura, M.; Sonoda, T.; Kobayashi, H. *Bull. Chem. Soc. Jpn.* ***1983***, *56*, 796.

[466]See, for example, Dehmlow, E.V.; Slopianka, M. *Chem. Ber.* ***1979***, *112*, 2765.

[467]Mathias, L.J.; Vaidya, R.A. *J. Am. Chem. Soc.* ***1986***, *108*, 1093; Fife, W.K.; Xin, Y. *J. Am. Chem. Soc.* ***1987***, *109*, 1278.

[468]Deshayes, S.; Liagre, M.; Loupy, A.; Luche, J.-L.; Petit, A. *Tetrahedron* ***1999***, *55*, 10851.

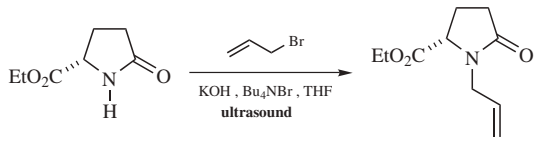
[469]Quici, S.; Regen, S.L. *J. Org. Chem.* ***1979***, *44*, 3436.

[470]For reviews, see Regen, S.L. *Nouv. J. Chim.* ***1982***, *6*, 629; *Angew. Chem. Int. Ed.* ***1979***, *18*, 421. See also, Molinari, H.; Montanari, F.; Quici, S.; Tundo, P. *J. Am. Chem. Soc.* ***1979***, *101*, 3920; Bogatskii, A.V.; Luk'yanenko, N.G.; Pastushok, V.N.; Parfenova, M.N. *Doklad. Chem.* ***1985***, *283*, 210; Pugia, M.J.; Czech, B.P.; Czech, B.P.; Bartsch, R.A. *J. Org. Chem.* ***1986***, *51*, 2945.

simplified product work-up and easy and quantitative catalyst recovery, since the catalyst can easily be separated from the product by filtration.

Influencing Reactivity by External Means

In many cases, reactions are slow. This is sometimes due to poor mixing or the aggregation state of one or more reactants. A powerful technique used to increase reaction rates is *ultrasound* (see p. 349). In this technique, the reaction mixture is subjected to high-energy sound waves, most often 20 KHz, but sometimes higher (a frequency of 20 KHz is about the upper limit of human hearing). When these waves are passed through a mixture, small bubbles form (*cavitation*). Collapse of these bubbles produces powerful shock waves that greatly increase the temperatures and pressures within these tiny regions, resulting in an increased reaction rate.[471] In the common instance where a metal, as a reactant or catalyst, is in contact with a liquid phase, a further effect is that the surface of the metal is cleaned and/or eroded by the ultrasound, allowing the liquid-phase molecules to come into closer contact with the metal atoms. Among the advantages of ultrasound is that it may increase yields, reduce side reactions, and permit the use of lower temperatures and/or pressures. The reaction of pyrrolidinone **105** with allyl bromide, under phase-transfer conditions, gave <10% of the *N*-allyl product, **106**. When the reaction was done under identical conditions, but with exposure to ultrasound (in an ultrasonic bath), the yield of **106** was 78%.[472] It has been postulated that ultrasound has its best results with reactions that proceed, at least partially, through free-radical intermediates.[473]



105 **106**

As noted in Chapter 7 (see p. 352), microwave irradiation is used extensively. Reaction times are greatly accelerated in many reactions, and reactions that took hours to be complete in refluxing solvents are done in minutes. Benzyl alcohol was converted to benzyl bromide, for example, using microwave irradiation (650 W) in only 9 min on a doped K10 Montmorillonite clay.[474] This is a growing and very useful technique.

The rate of many reactions can be increased by application of high pressure.[475] In solution, the rate of a reaction can be expressed in terms of the activation

[471]Reaction rates can also be increased by running reactions in a microwave oven. For reviews, see Mingos, D.M.P.; Baghurst, D.R. *Chem. Soc. Rev.* ***1991***, *20*, 1; Giguere, R.J. *Org. Synth. Theory Appl.* ***1989***, *1*, 103.

[472]Keusenkothen, P.F.; Smith, M.B. *Tetrahedron Lett.* ***1989***, *30*, 3369.

[473]See Einhorn, C.; Einhorn, J.; Dickens, M.J.; Luche, J. *Tetrahedron Lett.* ***1990***, *31*, 4129.

[474]Kad, G.-L.; Singh, V.; Kuar, K.P.; Singh, J. *Tetrahedron Lett.* ***1997***, *38*, 1079.

[475]Matsumoto, K.; Morris, A.R. *Organic Synthesis at High Pressure*, Wiley, NY, ***1991***; Matsumoto, K.; Sera, A.; Uchida, T. *Synthesis* ***1985***, 1; Matsumoto, K.; Sera, A. *Ibid.*, ***1985***, 999.

volume, $\Delta V^{\ddagger}$.[476]

$$\frac{\delta \ln k}{\delta p} = \frac{\Delta V^{\ddagger}}{RT}$$

The value of $\Delta V^{\ddagger}$ is the difference in partial molal volume between the transition state and the initial state, but it can be approximated by the molar volume.[476] Increasing pressure decreases the value of $\Delta V^{\ddagger}$ decreases and it $\Delta V^{\ddagger}$ is negative the reaction rate is accelerated. This equation is not strictly obeyed above 10 kbar. If the transition state of a reaction involves bond formation, concentration of charge, or ionization, a negative volume of activation often results. Cleavage of a bond, dispersal of charge, neutralization of the transition state and diffusion control lead to a positive volume of activation. Reactions for which rate enhancement is expected at high pressure include:[476]

1. Reactions in which the number of molecules decreases when starting materials are converted to products: cycloadditions, such as the Diels–Alder (**15-60**); condensations, such as the Knoevenagel condensation (**16-38**).
2. Reactions that proceed via cyclic transition states: Claisen (**18-33**) and Cope (**18-32**) rearrangements.
3. Reactions that take place through dipolar transition states: Menschutkin reaction (**10-31**), electrophilic aromatic substitution.
4. Reactions with steric hindrance.

Many high pressure reactions are done neat, but if a solvent is used, the influence of pressure on that solvent is important. The melting point generally increases at elevated pressures, which influences the viscosity of the medium (viscosity of liquids increases approximately two times per kilobar increase in pressure). Controlling the rate of diffusion of reactants in the medium is also important.[477] In most reactions, pressure is applied (5–20 kbar) at room temperature and then the temperature is increased until reaction takes place.

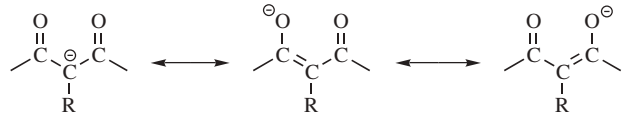
Ambident (Bidentant) Nucleophiles: Regioselectivity

Some nucleophiles have a pair of electrons on each of two or more atoms, or canonical forms can be drawn in which two or more atoms bear an unshared pair. In these cases, the nucleophile may attack in two or more different ways to give different products. Such reagents are called *ambident nucleophiles*.[478] In most cases, a nucleophile with two potentially attacking atoms can attack with either of them,

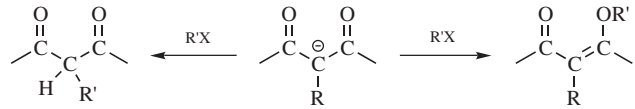
[476]le Noble, W.J. *Progr. Phys. Org. Chem.* ***1967***, *5*, 207; Isaacs, N.S. *Liquid Phase High Pressure Chemistry*, Wiley, Chichester, ***1981***; Asano, T.; le Noble, W.J. *Chem. Rev.* ***1978***, *78*, 407.
[477]Firestone, R.A.; Vitale, M.A. *J. Org. Chem.* ***1981***, *46*, 2160.
[478]For a monograph, see Reutov, O.A.; Beletskaya, I.P.; Kurts, A.L. *Ambident Anions*, Plenum, NY, ***1983***. For a review, see Black, T.H. *Org. Prep. Proced. Int.* ***1989***, *21*, 179.

depending on conditions, and mixtures are often obtained, although this is not always the case. For example, the nucleophile NCO^- usually gives only isocyanates RNCO and not the isomeric cyanates ROCN.[479] When a reaction can potentially give rise to two or more structural isomers (e.g., ROCN or RNCO), but actually produces only one, the reaction is said to be *regioselective*[480] (cf. the definitions of stereoselective, p. 194 and enantioselective, p. 171). Some important ambident nucleophiles are

1. *Ions of the Type* $\text{——CO—}\overset{\ominus}{\text{C}}\text{R—CO——}$. These ions, which are derived by removal of a proton from malonic esters, β-keto esters, β-diketones, and so on, are resonance hybrids:



They can thus attack a saturated carbon with their carbon atoms (*C*-alkylation) or with their oxygen atoms (*O*-alkylation):



With unsymmetrical ions, three products are possible, since either oxygen can attack. With a carbonyl substrate the ion can analogously undergo *C*-acylation or *O*-acylation.

2. *Compounds of the Type* $CH_3CO—CH_2—CO—$ *Can Give Up Two Protons*, if treated with 2 equivalents of a strong enough base, to give dicarbanions:

$$CH_3—CO—CH_2—CO— \xrightarrow{\text{2 equivalents of base}} \overset{\ominus}{C}H_2—CO—\overset{\ominus}{C}H—CO—$$

107

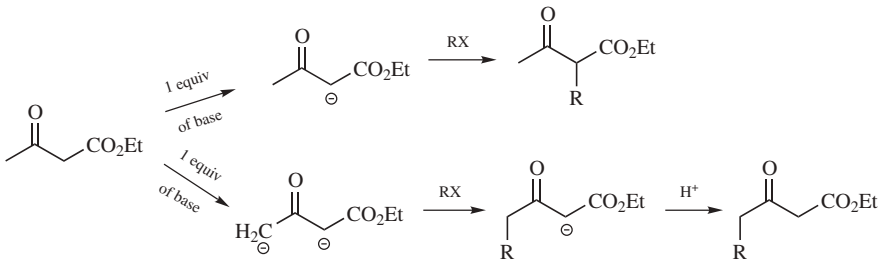
Such ions are ambident nucleophiles, since they have two possible attacking carbon atoms, aside from the possibility of attack by oxygen. In such cases, the attack is virtually always by the more basic carbon.[481] Since the hydrogen of a carbon bonded to two carbonyl groups is more acidic than that of a carbon bonded to just one (see Chapter 8), the CH group of **107** is less basic than the CH_2 group, so the latter attacks the substrate. This gives rise to a useful general principle: whenever we desire to remove a proton at a given

[479]Both cyanates and isocyanates have been isolated in treatment of secondary alkyl iodides with NCO^-: Holm, A.; Wentrup, C. *Acta Chem. Scand.* ***1966***, *20*, 2123.

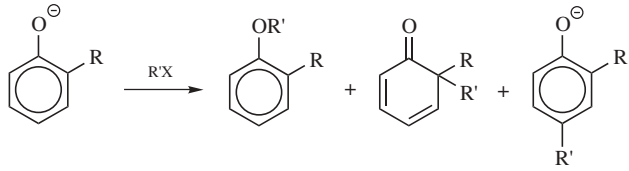
[480]This term was introduced by Hassner, A. *J. Org. Chem.* ***1968***, *33*, 2684.

[481]For an exception, see Trimitsis, G.B.; Hinkley, J.M.; TenBrink, R.; Faburada, A.L.; Anderson, R.; Poli, M.; Christian, B.; Gustafson, G.; Erdman, J.; Rop, D. *J. Org. Chem.* ***1983***, *48*, 2957.

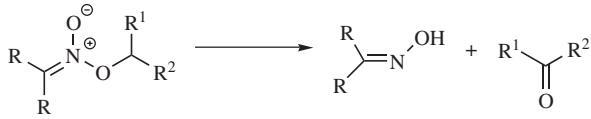
position for use as a nucleophile, but there is a stronger acidic group in the molecule, it may be possible to take off both protons; if it is, then attack is always by the desired position since it is the ion of the weaker acid. On the other hand, if it is desired to attack with the more acidic position, all that is necessary is to remove just one proton.[482] For example, ethyl acetoacetate can be alkylated at either the methyl or the methylene group (**10-67**):



3. *The CN^- Ion*. This nucleophile can give nitriles RCN (**10-75**) or isocyanides RN≡C.
4. *The Nitrite Ion*. This ion can give nitrite esters R—O—N=O (**10-22**) or nitro compounds RNO_2 (**10-76**), which are not esters.
5. Phenoxide ions (which are analogous to enolate anions) can undergo *C*-alkylation or *O*-alkylation:



6. Removal of a proton from an aliphatic nitro compound gives a carbanion ($R_2\bar{C}^{\ominus}—NO_2$) that can be alkylated at oxygen or carbon.[483] *O*-Alkylation gives nitronic esters, which are generally unstable to heat but break down to give an oxime and an aldehyde or ketone.



There are many other ambident nucleophiles.

[482]The use of this principle was first reported by Hauser, C.R.; Harris, C.M. *J. Am. Chem. Soc.* ***1958***, *80*, 6360. It has since been applied many times. For reviews, see Thompson, C.M.; Green, D.L.C. *Tetrahedron* ***1991***, *47*, 4223; Kaiser, E.M.; Petty, J.D.; Knutson, P.L.A. *Synthesis* ***1977***, 509; Harris, T.M.; Harris, C.M. *Org. React.* ***1969***, *17*, 155.

[483]For a review, see Erashko, V.I.; Shevelev, S.A.; Fainzil'berg, A.A. *Russ. Chem. Rev.* ***1966***, *35*, 719.

It would be useful to have general rules as to which atom of an ambident nucleophile will attack a given substrate under a given set of conditions.[484] Unfortunately, the situation is complicated by the large number of variables. It might be expected that the more electronegative atom would always attack, but this is often not the case. Where the products are determined by thermodynamic control (p. 307), the principal product is usually the one in which the atom of higher basicity has attacked (i.e., C > N > O > S).[485] However, in most reactions, the products are kinetically controlled and matters are much less simple. Nevertheless, the following generalizations can be made, while recognizing that there are many exceptions and unexplained results. As in the discussion of nucleophilicity in general (p. 490), there are two major factors: the polarizability (hard–soft character) of the nucleophile and solvation effects.

1. The principle of hard and soft acids and bases states that hard acids prefer hard bases and soft acids prefer soft bases (p. 375). In an S_N1 mechanism, the nucleophile attacks a carbocation, which is a hard acid. In an S_N2 mechanism, the nucleophile attacks the carbon atom of a molecule, which is a softer acid. The more electronegative atom of an ambident nucleophile is a harder base than the less electronegative atom. We may thus make the statement: As the character of a given reaction changes from S_N1- to S_N2-like, an ambident nucleophile becomes more likely to attack with its less electronegative atom.[486] Therefore, changing from S_N1 to S_N2 conditions should favor C attack by ^-CN, N attack by NO_2^-, C attack by enolate or phenoxide ions, etc. As an example, primary alkyl halides are attacked (in protic solvents) by the carbon atom of the anion of CH_3COCH_2COOEt, while α-chloro ethers, which react by the S_N1 mechanism, are attacked by the oxygen atom. However, this does not mean that attack is by the less electronegative atom in all S_N2 reactions and by the more electronegative atom in all S_N1 reactions. The position of attack also depends on the nature of the nucleophile, the solvent, the leaving group, and other conditions. The rule merely states that increasing the S_N2 character of the transition state makes attack by the less electronegative atom more likely.
2. All negatively charged nucleophiles must of course have a positive counterion. If this ion is Ag^+ (or some other ion that specifically helps in removing the leaving group, p. 504), rather than the more usual Na^+ or K^+, then the transition state is more S_N1-like. Therefore the use of Ag^+ promotes attack at the more electronegative atom. For example, alkyl halides treated with NaCN

[484]For reviews, see Jackman, L.M.; Lange, B.C. *Tetrahedron* ***1977***, *33*, 2737; Reutov, O.A.; Kurts, A.L. *Russ. Chem. Rev.* ***1977***, *46*, 1040; Gompper, R.; Wagner, H. *Angew. Chem. Int. Ed.* ***1976***, *15*, 321.
[485]For an example, see Bégué, J.; Charpentier-Morize, M.; Née, G. *J. Chem. Soc., Chem. Commun.* ***1989***, 83.
[486]This principle, sometimes called *Kornblum's rule*, was first stated by Kornblum, N.; Smiley, R.A.; Blackwood, R.K.; Iffland, D.C. *J. Am. Chem. Soc.* ***1955***, *77*, 6269.

generally give mostly RCN, but the use of AgCN increases the yield of isocyanides RNC.[487]

3. In many cases, the solvent influences the position of attack. The freer the nucleophile, the more likely it is to attack with its more electronegative atom, but the more this atom is encumbered by either solvent molecules or positive counterions, the more likely is attack by the less electronegative atom. In protic solvents, the more electronegative atom is better solvated by hydrogen bonds than the less electronegative atom. In polar aprotic solvents, neither atom of the nucleophile is greatly solvated, but these solvents are very effective in solvating cations. Thus in a polar aprotic solvent the more electronegative end of the nucleophile is freer from entanglement by both the solvent and the cation, so that a change from a protic to a polar aprotic solvent often increases the extent of attack by the more electronegative atom. An example is attack by sodium β-naphthoxide on benzyl bromide, which resulted in 95% *O*-alkylation in dimethyl sulfoxide and 85% *C*-alkylation in 2,2,2-trifluoroethanol.[488] Changing the cation from Li^+ to Na^+ to K^+ (in nonpolar solvents) also favors *O*- over *C*-alkylation[489] for similar reasons (K^+ leaves the nucleophile much freer than Li^+), as does the use of crown ethers, which are good at solvating cations (p. 119).[490] Alkylation of the enolate anion of cyclohexanone in the gas phase, where the nucleophile is completely free, showed only *O*-alkylation and no *C*-alkylation.[491]
4. In extreme cases, steric effects can govern the regioselectivity.[492]

Ambident Substrates

Some substrates (e.g., 1,3-dichlorobutane) can be attacked at two or more positions. We may call these *ambident substrates*. In the example given, there happen to be

[487]Actually, this reaction is more complicated than it seems on the surface; see Austad, T.; Songstad, J.; Stangeland, L.J. *Acta Chem. Scand.* ***1971***, *25*, 2327; Carretero, J.C.; García Ruano, J.L. *Tetrahedron Lett.* ***1985***, *26*, 3381.

[488]Kornblum, N.; Berrigan, P.J.; le Noble, W.J. *J. Chem. Soc.* ***1963***, *85*, 1141; Kornblum, N.; Seltzer, R.; Haberfield, P. *J. Am. Chem. Soc.* ***1963***, *85*, 1148. For other examples, see le Noble, W.J.; Puerta, J.E. *Tetrahedron Lett.* ***1966***, 1087; Brieger, G.; Pelletier, W.M. *Tetrahedron Lett.* ***1965***, 3555; Heiszwolf, G.J.; Kloosterziel, H. *Recl. Trav. Chim. Pays-Bas* ***1970***, *89*, 1153, 1217; Kurts, A.L.; Masias, A.; Beletskaya, I.P.; Reutov, O.A. *J. Org. Chem. USSR* ***1971***, *7*, 2323; Schick, H.; Schwarz, H.; Finger, A.; Schwarz, S. *Tetrahedron* ***1982***, *38*, 1279.

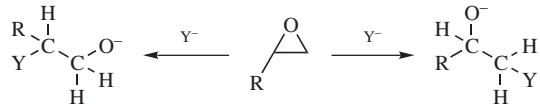
[489]Kornblum, N.; Seltzer, R.; Haberfield, P. *J. Am. Chem. Soc.* ***1963***, *85*, 1148; Kurts, A.L.; Beletskaya, I.P.; Masias, A.; Reutov, O.A. *Tetrahedron Lett.* ***1968***, 3679. See, however, Sarthou, P.; Bram, G.; Guibe, F. *Can. J. Chem.* ***1980***, *58*, 786.

[490]Smith, S.G.; Hanson, M.P. *J. Org. Chem.* ***1971***, *36*, 1931; Kurts, A.L.; Dem'yanov, P.I.; Beletskaya, I.P.; Reutov, O.A. *J. Org. Chem. USSR* ***1973***, *9*, 1341; Cambillau, C.; Sarthou, P.; Bram, G. *Tetrahedron Lett.* ***1976***, 281; Akabori, S.; Tuji, H. *Bull. Chem. Soc. Jpn.* ***1978***, *51*, 1197. See also, Zook, H.D.; Russo, T.J.; Ferrand, E.F.; Stotz, D.S. *J. Org. Chem.* ***1968***, *33*, 2222; le Noble, W.J.; Palit, S.K. *Tetrahedron Lett.* ***1972***, 493.

[491]Jones, M.E.; Kass, S.R.; Filley, J.; Barkley, R.M.; Ellison, G.B. *J. Am. Chem. Soc.* ***1985***, *107*, 109.

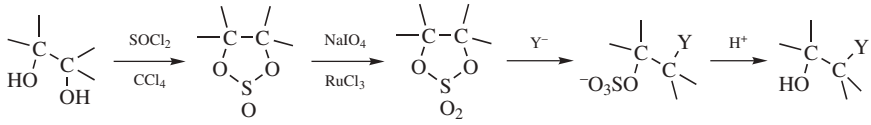
[492]See, for example, O'Neill, P.; Hegarty, A.F. *J. Org. Chem.* ***1987***, *52*, 2113.

two leaving groups in the molecule, but there are two kinds of substrates that are inherently ambident (unless symmetrical). One of these, the allylic type, has already been discussed (p. 469). The other is the epoxy (or the similar aziridine[493] or episulfide) substrate.[494]



Substitution of the free epoxide, which generally occurs under basic or neutral conditions, usually involves an S_N2 mechanism. Since primary substrates undergo S_N2 attack more readily than secondary, unsymmetrical epoxides are attacked in neutral or basic solution at the less highly substituted carbon, and stereospecifically, with inversion at that carbon. Under acidic conditions, it is the protonated epoxide that undergoes the reaction. Under these conditions the mechanism can be either S_N1 or S_N2. In S_N1 mechanisms, which favor tertiary carbons, we might expect that attack would be at the more highly substituted carbon, and this is indeed the case. However, even when protonated epoxides react by the S_N2 mechanism, attack is usually at the more highly substituted position.[495] Thus, it is often possible to change the direction of ring opening by changing the conditions from basic to acidic or vice versa. In the ring opening of 2,3-epoxy alcohols, the presence of Ti(*O*-*i*Pr)$_4$ increases both the rate and the regioselectivity, favoring attack at C-3 rather than C-2.[496] When an epoxide ring is fused to a cyclohexane ring, S_N2 ring opening invariably gives diaxial rather than diequatorial ring opening.[497]

Cyclic sulfates (**108**), prepared from 1,2-diols, react in the same manner as epoxides, but usually more rapidly:[498]



108

[493]Chechik, V.O.; Bobylev, V.A. *Acta Chem. Scand. B* ***1994***, *48*, 837.

[494]For reviews of S_N reactions at such substrates, see Rao, A.S.; Paknikar, S.K.; Kirtane, J.G. *Tetrahedron* ***1983***, *39*, 2323; Behrens, C.H.; Sharpless, K.B. *Aldrichimica Acta* ***1983***, *16*, 67; Enikolopiyan, N.S. *Pure Appl. Chem.* ***1976***, *48*, 317; Fokin, A.V.; Kolomiets, A.F. *Russ. Chem. Rev.* ***1976***, *45*, 25; Dermer, O.C.; Ham, G.E. *Ethylenimine and Other Aziridines*; Academic Press, NY, ***1969***, pp. 206–273; Akhrem, A.A.; Moiseenkov, A.M.; Dobrynin, V.N. *Russ. Chem. Rev.* ***1968***, *37*, 448; Gritter, R.J., in Patai, S. *The Chemistry of the Ether Linkage*, Wiley, NY, ***1967***, pp. 390–400.

[495]Addy, J.K.; Parker, R.E. *J. Chem. Soc.* ***1963***, 915; Biggs, J.; Chapman, N.B.; Finch, A.F.; Wray, V. *J. Chem. Soc. B* ***1971***, 55.

[496]Caron M.; Sharpless, K.B. *J. Org. Chem.* ***1985***, *50*, 1557. See also, Chong, J.M.; Sharpless, K.B. *J. Org. Chem.* ***1985***, *50*, 1560; Behrens, C.H.; Sharpless, K.B. *J. Org. Chem.* ***1985***, *50*, 5696.

[497]Murphy, D.K.; Alumbaugh, R.L.; Rickborn, B. *J. Am. Chem. Soc.* ***1969***, *91*, 2649. For a method of overriding this preference, see McKittrick, B.A.; Ganem, B. *J. Org. Chem.* ***1985***, *50*, 5897.

[498]Gao, Y.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1988***, *110*, 7538; Kim, B.M.; Sharpless, K.B. *Tetrahedron Lett.* ***1989***, *30*, 655.

Reactions

The reactions in this chapter are classified according to the attacking atom of the nucleophile in the order O, S, N, halogen, H, C. For a given nucleophile, reactions are classified by the substrate and leaving group, with alkyl substrates usually considered before acyl ones. Nucleophilic substitutions at a sulfur atom are treated at the end.

Not all the reactions in this chapter are actually nucleophilic substitutions. In some cases, the mechanisms are not known with enough certainty even to decide whether a nucleophile, an electrophile, or a free radical is attacking. In other cases, conversion of one compound to another can occur by two or even all three of these possibilities, depending on the reagent and the reaction conditions. However, one or more of the nucleophilic mechanisms previously discussed do hold for the overwhelming majority of the reactions in this chapter. For the alkylations, the S_N2 is by far the most common mechanism, as long as R is primary or secondary alkyl. For the acylations, the tetrahedral mechanism is the most common.

OXYGEN NUCLEOPHILES

A. Attack by OH at an Alkyl Carbon

10-1 Hydrolysis of Alkyl Halides

Hydroxy-de-halogenation

$$RX + H_2O \longrightarrow ROH_2^+ \xrightarrow{-H^+} ROH + H^+$$

$$RX + OH^- \longrightarrow ROH$$

Alkyl halides can be hydrolyzed to alcohols. Hydroxide ion is usually required, although particularly active substrates such as allylic or benzylic alcohols can be hydrolyzed by water. Ordinary halides can also be hydrolyzed by water,[499] if the solvent is HMPA or *N*-methyl-2-pyrrolidinone,[500] or if the reaction is done in an ionic solvent.[501] In contrast to most nucleophilic substitutions at saturated carbons, this reaction can be performed on tertiary substrates without significant interference from elimination side reactions. Tertiary alkyl α-halocarbonyl compounds can be converted to the corresponding alcohol with silver oxide in aqueous acetonitrile.[502] The

[499]It has been proposed that the mechanism of the reaction of primary halides with water is not the ordinary S_N2 mechanism, but that the rate-determining process involves a fluctuation of solvent configuration: Kurz, J.L.; Kurz, L.C. *Isr. J. Chem.* ***1985***, *26*, 339; Kurz, J.L.; Lee, J.; Love, M.E.; Rhodes, S. *J. Am. Chem. Soc.* ***1986***, *108*, 2960.

[500]Hutchins, R.O.; Taffer, I.M. *J. Org. Chem.* ***1983***, *48*, 1360.

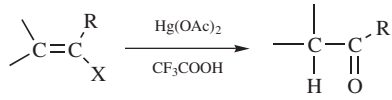
[501]Kim, D.W.; Hong, D.J.; Seo, J.W.; Kim, H.S.; Kim, H.K.; Song, C.E.; Chi, D.Y. *J. Org. Chem.* ***2004***, *69*, 3186.

[502]Cavicchioni, G. *Synth. Commun.* ***1994***, *24*, 2223.

reaction is not frequently used for synthetic purposes, because alkyl halides are usually obtained from alcohols.

An indirect conversion of halides to alcohols involved triethylborane. The reaction of an α-iodo ester with BEt_3, followed by reaction with dimethyl sulfide in methanol, gave an α-hydroxy ester.[503]

Vinylic halides are unreactive (p. 473), but they can be hydrolyzed to ketones at room temperature with mercuric trifluoroacetate, or with mercuric acetate in either

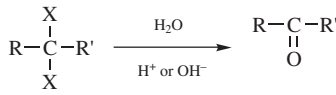


trifluoroacetic acid or acetic acid containing BF_3 etherate.[504] Primary bromides and iodides give alcohols when treated with bis(tributyltin)oxide $Bu_3Sn{-}O{-}SnBu_3$ in the presence of silver salts.[505]

OS **II**, 408; **III**, 434; **IV**, 128; **VI**, 142, 1037.

10-2 Hydrolysis of *gem*-Dihalides

Oxo-de-dihalo-bisubstitution



gem-Dihalides can be hydrolyzed with either acid or basic catalysis to give aldehydes or ketones.[506] Formally, the reaction may be regarded as giving R–C(OH)XR′, which is unstable and loses HX to give the carbonyl compound. For aldehydes derived from $RCHX_2$, strong bases cannot be used, because the product undergoes the aldol reaction (**16-34**) or the Cannizzaro reaction (**19-81**). A mixture of calcium carbonate and sodium acetate is effective,[507] and heating to 100°C in DMSO gives good yields.[508] Heating 1,1-dihaloalkenes ($C{=}CX_2$) with zinc and water leads to the corresponding methyl ketone.[509]

OS **I**, 95; **II**, 89, 133, 244, 549; **III**, 538, 788; **IV**, 110, 423, 807. Also see, OS **III**, 737.

[503]Kihara, N.; Ollivier, C.; Renaud, P. *Org. Lett.* ***1999***, *1*, 1419.
[504]Martin, S.F.; Chou, T. *Tetrahedron Lett.* ***1978***, 1943; Yoshioka, H.; Takasaki, K.; Kobayashi, M.; Matsumoto, T. *Tetrahedron Lett.* ***1979***, 3489.
[505]Gingras, M.; Chan, T.H. *Tetrahedron Lett.* ***1989***, *30*, 279.
[506]For a review, see Salomaa, P., in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***, pp. 177–210.
[507]Mataka, S.; Liu, G.-B.; Sawada, T.; Tori-i, A.; Tashiro, M. *J. Chem. Res. (S)* ***1995***, 410.
[508]Li, W.; Li, J.; DeVincentis, D.; Masour, T.S. *Tetrahedron Lett.* ***2004***, *45*, 1071.
[509]Wang, L.; Li, P.; Yan, J.; Wu, Z. *Tetrahedron Lett.* ***2003***, *44*, 4685.

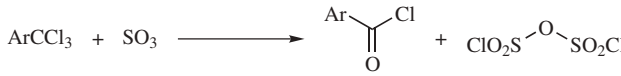
10-3 Hydrolysis of 1,1,1-Trihalides

Hydroxy,oxo-de-trihalo-tersubstitution

$$RCX_3 + H_2O \longrightarrow RCOOH$$

This reaction is similar to the previous one. The utility of the method is limited by the lack of availability of trihalides, although these compounds can be prepared by addition of CCl_4 and similar compounds to double bonds (**15-38**) and by the free-radical halogenation of methyl groups on aromatic rings (**14-1**). When the hydrolysis is carried out in the presence of an alcohol, a carboxylic ester can be obtained directly.[510] 1,1-Dichloroalkenes can also be hydrolyzed to carboxylic acids, by treatment with H_2SO_4. In general 1,1,1-trifluorides do not undergo this reaction,[511] although exceptions are known.[512]

Aryl 1,1,1-trihalomethanes can be converted to acyl halides by treatment with sulfur trioxide.[513]



Chloroform is more rapidly hydrolyzed with base than dichloromethane or carbon tetrachloride and gives not only formic acid, but also carbon monoxide.[514] Hine[515] has shown that the mechanism of chloroform hydrolysis is quite different from that of dichloromethane or carbon tetrachloride, although superficially the three reactions appear similar. The first step is the loss of a proton to give CCl_3^-, which then loses Cl^- to give dichlorocarbene CCl_2, which is hydrolyzed to formic acid or carbon monoxide.

This is an example of an S_N1cB mechanism (p. 500). The other two compounds react by the normal mechanisms. Carbon tetrachloride cannot give up a proton and dichloromethane is not acidic enough.

OS **III**, 270; **V**, 93. Also see, OS **I**, 327.

[510]See, for example, Le Fave, G.M.; Scheurer, P.G. *J. Am. Chem. Soc.* ***1950***, *72*, 2464.
[511]Sheppard, W.A.; Sharts, C.M. *Organic Fluorine Chemistry*, W.A. Benjamin, NY, ***1969***, pp. 410–411; Hudlický, M. *Chemistry of Organic Fluorine Compounds*, 2nd ed., Ellis Horwood, Chichester, ***1976***, pp. 273–274.
[512]See, for example, Kobayashi, Y.; Kumadaki, I. *Acc. Chem. Res.* ***1978***, *11*, 197.
[513]Rondestvedt Jr., C.S. *J. Org. Chem.* ***1976***, *41*, 3569, 3574, 3576. For another method, see Nakano, T.; Ohkawa, K.; Matsumoto, H.; Nagai, Y. *J. Chem. Soc., Chem. Commun.* ***1977***, 808.
[514]For a review, see Kirmse, W. *Carbene Chemistry*, 2nd ed., Academic Press, NY, ***1971***, pp. 129–141.
[515]Hine, J. *J. Am. Chem. Soc.* ***1950***, *72*, 2438. Also, see le Noble, W.J. *J. Am. Chem. Soc.* ***1965***, *87*, 2434.

10-4 Hydrolysis of Alkyl Esters of Inorganic Acids

Hydroxy-de-sulfonyloxy-substitution, and so on.

$$\mathbf{R{-}X \longrightarrow R{-}OH}$$

$$\mathbf{X = OSO_2R' , OSO_2OH , OSO_2OR , OSO_2R' , OSOR'}$$
$$\mathbf{= ONO_2 , ONO , OPO(OH)_2 , OPO(OR')_2 , OB(OH)_2 \quad and\ others}$$

Esters of inorganic acids, including those given above and others, can be hydrolyzed to alcohols. The reactions are most successful when the ester is that of a strong acid, but it can be done for esters of weaker acids by the use of hydroxide ion (a more powerful nucleophile) or acidic conditions (which make the leaving group come off more easily). When vinylic substrates are hydrolyzed, the products are aldehydes or ketones.

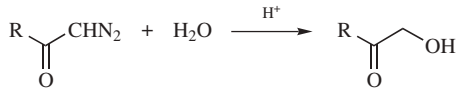
$$R_2C{=}CH{-}X \xrightarrow{H_2O} R_2C{=}CH{-}OH \rightleftharpoons R_2CH{-}CHO$$

These reactions are all considered at one place because they are formally similar, but although some of them involve R—O cleavage and are thus nucleophilic substitutions at a saturated carbon, others involve cleavage of the bond between the inorganic atom and oxygen and are thus nucleophilic substitutions at a sulfur, nitrogen, etc. It is even possible for the same ester to be cleaved at either position, depending on the conditions. Thus benzhydryl *p*-toluenesulfinate ($Ph_2CHOSOC_6H_4CH_3$) was found to undergo C—O cleavage in $HClO_4$ solutions and S—O cleavage in alkaline media.[516] In general, the weaker the corresponding acid, the less likely is C—O cleavage. Thus, sulfonic acid esters $ROSO_2R'$ generally give C—O cleavage,[517] while nitrous acid esters RONO usually give N—O cleavage.[518] Esters of sulfonic acids that are frequently hydrolyzed are mentioned on p. 497. For hydrolysis of sulfonic acid esters, see also **16-100**.

OS **VI**, 852. See also, **VIII**, 50.

10-5 Hydrolysis of Diazoketones

Hydro,hydroxy-de-diazo-bisubstitution



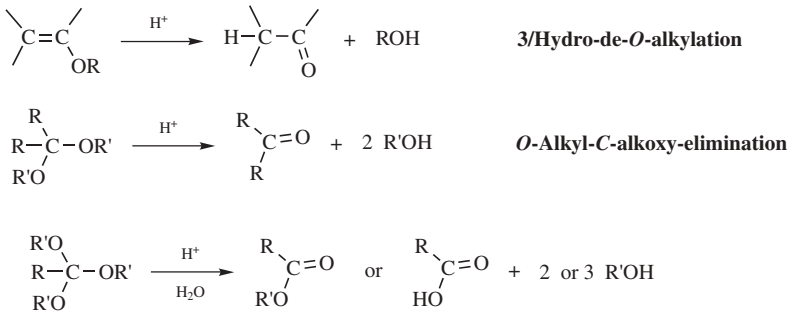
[516]Bunton, C.A.; Hendy, B.N. *J. Chem. Soc.* ***1963***, 627. For another example, see Batts, B.D. *J. Chem. Soc. B* ***1966***, 551.

[517]Barnard, P.W.C.; Robertson, R.E. *Can. J. Chem.* ***1961***, *39*, 881. See also, Drabicky, M.J.; Myhre, P.C.; Reich, C.J.; Schmittou, E.R. *J. Org. Chem.* ***1976***, *41*, 1472.

[518]For a discussion of the mechanism of hydrolysis of alkyl nitrites, see Williams, D.L.H. *Nitrosation*, Cambridge University Press, Cambridge, ***1988***, pp. 162–163.

Diazoketones are relatively easy to prepare (see **16-89**). When treated with acid, they add a proton to give α-keto diazonium salts, which are hydrolyzed to the alcohols by the S_N1 or S_N2 mechanism.[519] Relatively good yields of α-hydroxy ketones can be prepared in this way, since the diazonium ion is somewhat stabilized by the presence of the carbonyl group, which discourages N_2 from leaving because that would result in an unstable α-carbonyl carbocation.

10-6 Hydrolysis of Acetals, Enol Ethers, and Similar Compounds[520]



The alkoxyl group OR is not a leaving group, so these compounds must be converted to the conjugate acids before they can be hydrolyzed. Although 100% sulfuric acid and other concentrated strong acids readily cleave simple ethers,[521] the only acids used preparatively for this purpose are HBr and HI (**10-49**). However, acetals, ketals, and ortho esters[522] are easily cleaved by dilute acids. These compounds are hydrolyzed with greater facility because carbocations of the type RO—$\overset{|}{\text{C}}$H— are greatly stabilized by resonance (p. 242). The reactions therefore

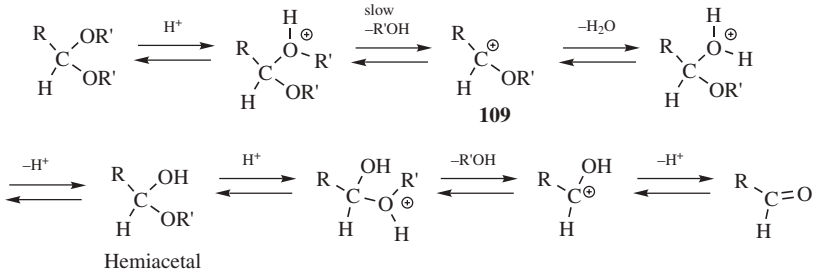
[519]Dahn, H.; Gold, H. *Helv. Chim. Acta* ***1963***, *46*, 983; Thomas, C.W.; Leveson, L.L. *Int. J. Chem. Kinet.*, ***1983***, *15*, 25. For a review of the acidpromoted decomposition of diazoketones, see Smith III, A.B; Dieter, R.K. *Tetrahedron* ***1981***, *37*, 2407.

[520]For reviews, see Bergstrom, R.G., in Patai, S. *The Chemistry of Functional Groups, Supplement E*, Wiley, NY, ***1980***, pp. 881–902; Cockerill, A.F.; Harrison, R.G., in Patai, S. *The Chemistry of Functional Groups*, *Supplement A*, pt. 1, Wiley, NY, ***1977***, pp. 149–329; Cordes, E.H.; Bull, H.G. *Chem. Rev.* ***1974***, *74*, 581; Cordes, E.H. *Prog. Phys. Org. Chem.* ***1967***, *4*, 1; Salomaa, P., in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***, pp. 184–198; Pindur, U.; Müller, J.; Flo, C.; Witzel, H. *Chem. Soc. Rev.* ***1987***, *16*, 75 (ortho esters); Cordes, E.H., in Patai, S. *The Chemistry of Carboxylic Acids and Esters*, Wiley, NY, ***1969***, pp. 632–656 (ortho esters); DeWolfe, R.H. *Carboxylic Ortho Acid Derivatives*, Academic Press, NY, ***1970***, pp. 134–146 (ortho esters); Rekasheva, A.F. *Russ. Chem. Rev.* ***1968***, *37*, 1009 (enol ethers).

[521]Jaques, D.; Leisten, J.A. *J. Chem. Soc.* ***1964***, 2683. See also, Olah, G.A.; O'Brien, D.H. *J. Am. Chem. Soc.* ***1967***, *89*, 1725.

[522]For a review of the reactions of ortho esters, see Pavlova, L.A.; Davidovich, Yu.A.; Rogozhin, S.V. *Russ. Chem. Rev.* ***1986***, *55*, 1026.

proceed by the S_N1 mechanism,[523] as shown for acetals:[524]



This mechanism (which is an S_N1cA or A1 mechanism) is the reverse of that for acetal formation by reaction of an aldehyde and an alcohol (**16-5**). Among the facts supporting the mechanism are[525] (*1*) The reaction proceeds with *specific* H_3O^+ catalysis (see p. 373). (*2*) It is faster in D_2O. (*3*) Optically active ROH are not racemized. (*4*) Even with *tert*-butylalcohol the R—O bond does not cleave, as shown by ^{18}O labeling.[526] (*5*) In the case of acetophenone ketals, the intermediate corresponding to **109** [$ArCMe(OR)_2$] could be trapped with sulfite ions (SO_3^{2-}).[527] (*6*) Trapping of this ion did not affect the hydrolysis rate,[527] so the rate-determining step must come earlier. (*7*) In the case of 1,1-dialkoxyalkanes, intermediates corresponding to **109** were isolated as stable ions in super acid solution at −75°C, where their spectra could be studied.[528] (*8*) Hydrolysis rates greatly increase in the order $CH_2(OR')_2 < RCH(OR')_2 < R_2C(OR')_2 < RC(OR')_3$, as would be expected for a carbocation intermediate.[529] Formation of **109** is usually the rate-determining step (as marked above), but there is evidence that at least in some cases this step is fast, and the rate-determining step is loss of R′OH from the protonated hemiacetal.[530] Rate-determining addition of water to **109** has also been reported.[531]

[523]For a review of the mechanisms of hydrolysis of acetals and thioacetals, see Satchell, D.P.N.; Satchell, R.S. *Chem. Soc. Rev.* ***1990***, *19*, 55.

[524]Kreevoy, M.M.; Taft, R.W. *J. Am. Chem. Soc.* ***1955***, *77*, 3146, 5590.

[525]For a discussion of these, and of other evidence, see Cordes, E.H. *Prog. Phys. Org. Chem.* ***1967***, *4*, 1.

[526]Cawley, J.J.; Westheimer, F.H. *Chem. Ind. (London)* ***1960***, 656.

[527]Young, P.R.; Jencks, W.P. *J. Am. Chem. Soc.* ***1977***, *99*, 8238. See also, Jencks, W.P. *Acc. Chem. Res.* ***1980***, *13*, 161; McClelland, R.A.; Ahmad, M. *J. Am. Chem. Soc.* ***1978***, *100*, 7027, 7031; Young, P.R.; Bogseth, R.C.; Rietz, E.G. *J. Am. Chem. Soc.* ***1980***, *102*, 6268. However, in the case of simple aliphatic acetals, **103** could not be trapped: Amyes, T.L.; Jencks, W.P. *J. Am. Chem. Soc.* ***1988***, *110*, 3677.

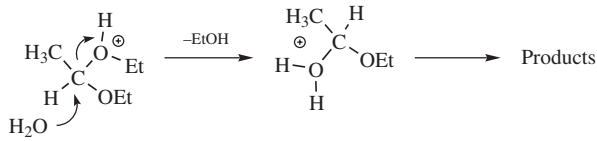
[528]See White, A.M.; Olah, G.A. *J. Am. Chem. Soc.* ***1969***, *91*, 2943; Akhmatdinov, R.T.; Kantor, E.A.; Imashev, U.B.; Yasman, Ya.B.; Rakhmankulov, D.L. *J. Org. Chem. USSR* ***1981***, *17*, 626.

[529]For the influence of alkyl group size on the mechanism see Belarmino, A.T.N.; Froehner, S.; Zanette, D.; Farah, J.P.S.; Bunton, C.A.; Romsted, L.S. *J. Org. Chem.* ***2003***, *68*, 706.

[530]Jensen, J.L.; Lenz, P.A. *J. Am. Chem. Soc.* ***1978***, *100*, 1291; Finley, R.L.; Kubler, D.G.; McClelland, R.A. *J. Org. Chem.* ***1980***, *45*, 644; Przystas, T.J.; Fife, T.H. *J. Am. Chem. Soc.* ***1981***, *103*, 4884; Chiang, Y.; Kresge, A.J. *J. Org. Chem.* ***1985***, *50*, 5038; Fife, T.H.; Natarajan, R. *J. Am. Chem. Soc.* ***1986***, *108*, 2425, 8050; McClelland, R.A.; Sørensen, P.E. *Acta Chem. Scand.* ***1990***, *44*, 1082.

[531]Toullec, J.; El-Alaoui, M. *J. Org. Chem.* ***1985***, *50*, 4928; Fife, T.H.; Natarajan, R. *J. Am. Chem. Soc.* ***1986***, *108*, 2425, 8050.

While the A1 mechanism shown above operates in most acetal hydrolyses, it has been shown that at least two other mechanisms can take place with suitable substrates.[532] In one of these mechanisms the second and third of the above steps are concerted, so that the mechanism is S_N2cA (or A2). This has been shown, for example, in the hydrolysis of 1,1-diethoxyethane, by isotope effect studies:[533]



In the second mechanism, the first and second steps are concerted. In the case of hydrolysis of 2-(*p*-nitrophenoxy)tetrahydropyran, *general* acid catalysis was shown[534] demonstrating that the substrate is protonated in the rate-determining step (p. 373). Reactions in which a substrate is protonated in the rate-determining step are called AS_E2 reactions.[535] However, if protonation of the substrate were all that happens in the slow step, then the proton in the transition state would be expected to lie closer to the weaker base (p. 373). Because the substrate is a much weaker base than water, the proton should be largely transferred. Since the Brønsted coefficient was found to be 0.5, the proton was actually transferred only about halfway. This can be explained if the basicity of the substrate is increased by partial breaking of the C—O bond. The conclusion drawn is that steps 1 and 2 are concerted. The hydrolysis of ortho esters in most cases is also subject to general acid catalysis.[536]

The hydrolysis of acetals and ortho esters is governed by the stereoelectronic control factor discussed on p. 1258,[537] although the effect can generally be seen only in systems where conformational mobility is limited, especially in cyclic systems. There is evidence for synplanar stereoselection in the acid hydrolysis of

[532]For a review, see Fife, T.H. *Acc. Chem. Res.* ***1972***, *5*, 264. For a discussion, see Wann, S.R.; Kreevoy, M.M. *J. Org. Chem.* ***1981***, *46*, 419.

[533]Kresge, A.J.; Weeks, D.P. *J. Am. Chem. Soc.* ***1984***, *106*, 7140. See also, Fife, T.H. *J. Am. Chem. Soc.* ***1967***, *89*, 3228; Craze, G.; Kirby, A.J.; Osborne, R. *J. Chem. Soc. Perkin Trans. 2* ***1978***, 357; Amyes, T.L.; Jencks, W.P. *J. Am. Chem. Soc.* ***1989***, *111*, 7888, 7900.

[534]Fife, T.H.; Brod, L.H. *J. Am. Chem. Soc.* ***1970***, *92*, 1681. For other examples, see Kankaanperä, A.; Lahti, M. *Acta Chem. Scand.* ***1969***, *23*, 2465; Mori, A.L.; Schaleger, L.L. *J. Am. Chem. Soc.* ***1972***, *94*, 5039; Capon, B.; Nimmo, K. *J. Chem. Soc. Perkin Trans. 2* ***1975***, 1113; Eliason, R.; Kreevoy, M.M. *J. Am. Chem. Soc.* ***1978***, *100*, 7037; Jensen, J.L.; Herold, L.R.; Lenz, P.A.; Trusty, S.; Sergi, V.; Bell, K.; Rogers, P. *J. Am. Chem. Soc.* ***1979***, *101*, 4672.

[535]For a review of A-S_E2 reactions, see Williams Jr., J.M.; Kreevoy, M.M. *Adv. Phys. Org. Chem.* ***1968***, *6*, 63.

[536]Chiang, Y.; Kresge, A.J.; Lahti, M.O.; Weeks, D.P. *J. Am. Chem. Soc.* ***1983***, *105*, 6852, and references cited therein; Santry, L.J.; McClelland, R.A. *J. Am. Chem. Soc.* ***1983***, *105*, 6138; Fife, T.H.; Przystas, T.J. *J. Chem. Soc. Perkin Trans. 2* ***1987***, 143.

[537]See, for example, Kirby, A.J. *Acc. Chem. Res.* ***1984***, *17*, 305; Bouab, O.; Lamaty, G.; Moreau, C. *Can. J. Chem.* ***1985***, *63*, 816. See, however, Ratcliffe, A.J.; Mootoo, D.R.; Andrews, C.W.; Fraser-Reid, B. *J. Am. Chem. Soc.* ***1989***, *111*, 7661.

acetals.[538] The mechanism of Lewis acid-mediated cleavage of chiral acetals is also known.[539]

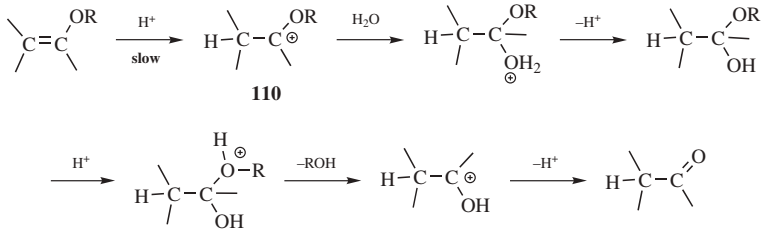
Convenient reagents for acetals are wet silica gel[540] and Amberlyst-15 (a sulfonic acid-based polystyrene cation exchange resin).[541] Both cyclic and acyclic acetals and ketals can be converted to aldehydes or ketones under nonaqueous conditions by treatment with Montmorillonite K10 clay in various solvents,[542] with Lewis acids, such as $FeCl_3 \bullet 6\ H_2O$ in chloroform,[543] $Bi(OTf)_3 \bullet xH_2O$,[544] or 5% $Ce(OTf)_3$ in wet nitromethane.[545] Hydrolysis techniques include treatment with β-cyclodextrin in water,[546] Me_3SiI in CH_2Cl_2, or $CHCl_3$,[547] $LiBF_4$,[548] ceric ammonium nitirate in aqueous acetonitrile,[549] DDQ[550] in wet MeCN, or Magtrieve in chloroform.[551]

Although acetals, ketals, and ortho esters are easily hydrolyzed by acids, they are extremely resistant to hydrolysis by bases. An aldehyde or ketone can therefore be protected from attack by a base by conversion to the acetal or ketal (**16-5**), and then can be cleaved with acid. Pyridine–HF has also been used for this conversion.[552] Thioacetals, thioketals, *gem*-diamines, and other compounds that contain any two of the groups OR, OCOR, NR_2, NHCOR, SR, and halogen on the same carbon can also be hydrolyzed to aldehydes or ketones, in most cases, by acid treatment. Several $ArCH(OAc)_2$ derivatives were hydrolyzed to the aldehyde using Montmorillonite K10,[553] alumina with microwaves,[554] ceric ammonium nitrate on silica gel,[555] or by heating with CBr_4 in acetonitirle.[556] Thioacetals $RCH(SR')_2$ and thioketals

[538]Li, S.; Kirby, A.J.; Deslongchamps, P. *Tetrahedron Lett.* ***1993***, *34*, 7757.
[539]Sammakia, T.; Smith, R.S. *J. Org. Chem.* ***1992***, *57*, 2997.
[540]Huet, F.; Lechevallier, A.; Pellet, M.; Conia, J.M. *Synthesis* ***1978***, 63. See Caballero, G.M.; Gros, E.G. *Synth. Commun.* ***1995***, *25*, 395 for hydrolysis of hindered ketals with $CuSO_4$ on silica gel.
[541]Coppola, G.M. *Synthesis* ***1984***, 1021.
[542]Li, T.-S.; Li, S.-H. *Synth. Commun.* ***1997***, *27*, 2299; Gautier, E.C.L.; Graham, A.E.; McKillop, A.; Standen, S.T.; Taylor, R.J.K. *Tetrahedron Lett.* ***1997***, *38*, 1881.
[543]Sen, S.E.; Roach, S.L.; Boggs, J.K.; Ewing, G.J.; Magrath, J. *J. Org. Chem.* ***1997***, *62*, 6684.
[544]Carringan, M.D.; Sarapa, D.; Smith, R.C.; Wieland, L.C.; Mohan, R.S. *J. Org. Chem.* ***2002***, *67*, 1027.
[545]Dalpozzo, R.; De Nino, A.; Maiuolo, L.; Procopio, A.; Tagarelli, A.; Sindona, G.; Bartoli, G. *J. Org. Chem.* ***2002***, *67*, 9093.
[546]Krishnaveni, N. S.; Surendra, K.; Reddy, M. A.; Nageswar, Y. V. D.; Rao, K. R. *J. Org. Chem.* ***2003***, *68*, 2018.
[547]Jung, M.E.; Andrus, W.A.; Ornstein, P.L. *Tetrahedron Lett.* ***1977***, 4175. See also, Balme, G.; Goré, J. *J. Org. Chem.* ***1983***, *48*, 3336.
[548]Lipshutz, B.H.; Harvey, D.F. *Synth. Commun.* ***1982***, *12*, 267.
[549]Ates, A.; Gautier, A.; Leroy, B.; Plancher, J.M.; Quesnel, Y.; Markó, I.E. *Tetrahedron Lett.* ***1999***, *40*, 1799.
[550]Tanemura, K.; Suzuki, T.; Horaguchi, T. *J. Chem. Soc., Chem. Commun.* ***1992***, 979.
[551]Ko, J.-y.; Park, S.-T. *Tetrahedron Lett.* ***1999***, *40*, 6025.
[552]Watanabe, Y.; Kiyosawa, Y.; Tatsukawa, A.; Hayashi, M. *Tetrahedron Lett.* ***2001***, *42*, 4641.
[553]Li, T.-S.; Zhang, Z.-H.; Fu, C.-G. *Tetrahedron Lett.* ***1997***, *38*, 3285.
[554]Varma, R.S.; Chatterjee, A.K.; Varma, M. *Tetrahedron Lett*, ***1993***, *34*, 3207.
[555]Cotelle, P.; Catteau, J.-P. *Tetrahedron Lett.* ***1992***, *33*, 3855.
[556]Ramalingam, T.; Srinivas, R.; Reddy, B.V.S.; Yadav, J.S. *Synth. Commun.* ***2001***, *31*, 1091.

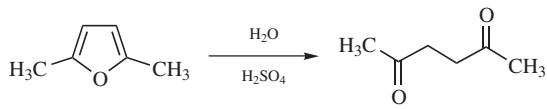
$R_2C(SR')_2$ are among those compounds generally resistant to acid hydrolysis.[557] Because conversion to these compounds (**16-11**) serves as an important method for protection of aldehydes and ketones, many methods have been devised to cleave them to the parent carbonyl compounds. Among reagents[558] used for this purpose are $HgCl_2$,[559] $FeCl_3$•6 H_2O,[560] cetyltrimethylammonium tribromide in dichloromethane,[561] *m*-chloroperoxybenzoic acid, and CF_3COOH in CH_2Cl_2,[562] Oxone® on wet alumina,[563] the Dess–Martin periodinane,[564] and DDQ in water under photolysis conditions,[565] and sodium nitrite in aqueous acetyl chloride.[566] Electrochemical methods have also been used.[567] Mixed acetals and ketals (RO—C—SR) can be hydrolyzed with most of the reagents mentioned above, including *N*-bromosuccinimide (NBS) in aqueous acetone,[568] and glyoxylic acid on Amberlyst 15 with microwave irradiation.[569]

Enol ethers are readily hydrolyzed by acids; the rate-determining step is protonation of the substrate.[570] However, protonation does not take place at the oxygen, but at the β carbon,[571] because that gives rise to the stable carbocation **110**.[572] After that the mechanism is similar to the A1 mechanism given above for the hydrolysis of acetals.



[557]Ali, M.; Satchell, D.P.N. *J. Chem. Soc. Perkin Trans. 2* ***1992***, 219; ***1993***, 1825; Ali, M.; Satchell, D.P.N.; Le, V.T. *J. Chem. Soc. Perkin Trans. 2* ***1993***, 917.
[558]For references to other reagents, see Gröbel, B.; Seebach, D. *Synthesis* ***1977***, 357, see pp. 359–367; Cussans, N.J.; Ley, S.V.; Barton, D.H.R. *J. Chem. Soc. Perkin Trans. 1* ***1980***, 1654.
[559]Corey, E.J.; Erickson, B.W. *J. Org. Chem.* ***1971***, *36*, 3553. For a mechanistic study, see Satchell, D.P.N.; Satchell, R.S. *J. Chem. Soc. Perkin Trans. 2* ***1987***, 513.
[560]Kamal, A.; Laxman, E.; Reddy, P.S.M.M. *Synlett* ***2000***, 1476.
[561]Mondal, E.; Bose, G.; Khan, A.T. *Synlett* ***2001***, 785.
[562]Cossy, J. *Synthesis* ***1987***, 1113.
[563]Ceccherelli, P.; Curini, M.; Marcotullio, M.C.; Epifano, F.; Rosati, O. *Synlett*, ***1996***, 767.
[564]Langille, N.F.; Dakin, L.A.; Panek, J.S. *Org. Lett.* ***2003***, *5*, 575. See also, Stork, G.; Zhao, K. *Tetrahedron Lett.* ***1989***, *30*, 287.
[565]Mathew, L.; Sankararaman, S. *J. Org. Chem.* ***1993***, *58*, 7576.
[566]Khan, A.T.; Mondal, E.; Sahu, P.R. *Synlett* ***2003***, 377.
[567]See Schulz-von Itter, N.; Steckhan, E. *Tetrahedron* ***1987***, *43*, 2475; Suda, K.; Watanabe, J.; Takanami, T. *Tetrahedron Lett.* ***1992***, *33*, 1355.
[568]Karimi, B.; Seradj, H.; Tabaei, M.H. *Synlett* ***2000***, 1798.
[569]Chavan, S.P.; Soni, P.; Kamat, S.K. *Synlett* ***2001***, 1251.
[570]Jones, J.; Kresge, A. J. *Can. J. Chem.* ***1993***, *71*, 38.
[571]Jones, D.M.; Wood, N.F. *J. Chem. Soc.* ***1964***, 5400; Okuyama, T.; Fueno, T.; Furukawa, J. *Bull. Chem. Soc. Jpn.* ***1970***, *43*, 3256; Kreevoy, M.M.; Eliason, R. *J. Phys. Chem.* ***1969***, *72*, 1313; Lienhard, G.; Wang, T.C. *J. Am. Chem. Soc.* ***1969***, *91*, 1146; Burt, R.A.; Chiang, Y.; Kresge, A.J.; Szilagyi, S. *Can. J. Chem.* ***1984***, *62*, 74.
[572]See Chwang, W.K.; Kresge, A.J.; Wiseman, J.R. *J. Am. Chem. Soc.* ***1979***, *101*, 6972.

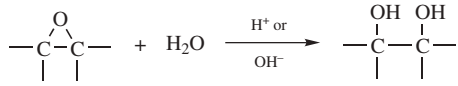
Among the facts supporting this mechanism (which is an A-S_E2 mechanism because the substrate is protonated in the rate-determining step) are (*1*) the ^{18}O labeling shows that in $ROCH{=}CH_2$ it is the vinyl–oxygen bond and not the RO bond that cleaves;[573] (*2*) the reaction is subject to general acid catalysis;[574] (*3*) there is a solvent isotope effect when D_2O is used.[574] Enamines are also hydrolyzed by acids (see **16-2**); the mechanism is similar. Ketene dithioacetals $R_2C{=}C(SR')_2$ also hydrolyze by a similar mechanism, except that the initial protonation step is partially reversible.[575] Furans represent a special case of enol ethers that are cleaved by acid to give 1,4-diones.[576] Thus oxonium ions are cleaved by water to give an alcohol and an ether:



OS **I**, 67, 205; **II**, 302, 305, 323; **III**, 37, 127, 465, 470, 536, 541, 641, 701, 731, 800; **IV**, 302, 499, 660, 816, 903; **V**, 91, 292, 294, 703, 716, 937, 967, 1088; **VI**, 64, 109, 312, 316, 361, 448, 496, 683, 869, 893, 905, 996; **VII**, 12, 162, 241, 249, 251, 263, 271, 287, 381, 495; **VIII**, 19, 155, 241, 353, 373

10-7 Hydrolysis of Epoxides

(3)*OC-seco*-hydroxy-de-alkoxy-substitution



The hydrolysis of epoxides is a convenient method for the preparation of *vic*-diols. The reaction is catalyzed by acids or bases (see discussion of the mechanism on p. 518). Among acid catalysts, perchloric acid leads to minimal side reactions,[577] and 10% Bu_4NHSO_4 in water is effective.[578] Water reacts with epoxides in the presence of β-cyclodextrin to give the corresponding diol.[579] Dimethyl sulfoxide is a superior solvent for the alkaline hydrolysis of epoxides.[580] Water at 10 kbar and 60°C opens epoxides with high stereoselectivity,[581] and epoxide hydrolase

[573]Kiprianova, L.A.; Rekasheva, A.F. *Dokl. Akad. Nauk SSSR*, ***1962***, *142*, 589.
[574]Fife, T.H. *J. Am. Chem. Soc.* ***1965***, *87*, 1084; Salomaa, P.; Kankaanperä, A.; Lajunen, M. *Acta Chem. Scand.* ***1966***, *20*, 1790; Kresge, A.J.; Yin, Y. *Can. J. Chem.* ***1987***, *65*, 1753.
[575]For a review, see Okuyama, T. *Acc. Chem. Res.* ***1986***, *19*, 370.
[576]Enzymatic hydrolysis of 2,5-dimethylfuran gave hex-3-en-2,5-dione. See Finlay, J.; McKervey, M.A.; Gunaratne, H.Q.N. *Tetrahedron Lett.* ***1998***, *39*, 5651.
[577]Fieser, L.F.; Fieser, M. *Reagents for Organic Synthesis* Vol. 1, Wiley, NY, ***1967***, p. 796.
[578]Fan, R.-H.; Hou, X.-L. *Org. Biomol. Chem.* ***2003***, *1*, 1565.
[579]Reddy, M.A.; Reddy, L.R.; Bhanumthi, N.; Rao, K.R. *Org. Prep. Proceed. Int.* ***2002***, *34*, 537.
[580]Berti, G.; Macchia, B.; Macchia, F. *Tetrahedron Lett.* ***1965***, 3421.
[581]Kotsuki, H.; Kataoka, M.; Nishizawa, H. *Tetrahedron Lett.* ***1993***, *34*, 4031.

opens epoxides with high enantioselectivity.[582] Cobalt salen [salen = bis(salicylidene)ethylenediamine] catalysts, in the presence of water, open epoxides with high stereoselectivity.[583] Photolysis of epoxy-ketones in the presence of 1,3-dimethylbenzimidazoline in AcOH/THF leads to β-hydroxy ketones.[584]

OS **V**, 414.

B. Attack by OR at an Alkyl Carbon

10-8 Alkylation With Alkyl Halides: The Williamson Reaction

Alkoxy-de-halogenation

$$RX + OR'^{-} \longrightarrow ROR'$$

The *Williamson reaction*, discovered in 1850, is still the best general method for the preparation of unsymmetrical or symmetrical ethers.[585] The reaction can also be carried out with aromatic R′, although *C*-alkylation is sometimes a side reaction (see p. 515).[586] The normal method involves treatment of the halide with alkoxide or aroxide ion prepared from an alcohol or phenol, although methylation using dimethyl carbonate has been reported.[587] It is also possible to mix the halide and alcohol or phenol directly with Cs_2CO_3 in acetonitrile,[588] or with solid KOH in Me_2SO.[589] The reaction can also be carried out in a dry medium,[590] on zeolite–HY[591] or neat[592] or in solvents[593] using microwave irradiation. Williamson ether synthesis in ionic liquids has also been reported.[594] The reaction is not successful for tertiary R (because of elimination), and low yields are often obtained with secondary R. Mono-ethers can be formed from diols and alkyl halides.[595] Many other

[582]Zhao, L.; Han, B.; Huang, Z.; Miller, M.; Huang, H.; Malashock, D.S.; Zhu, Z.; Milan, A.; Robertson, D.E.; Weiner, D.P.; Burk, M. J. *J. Am. Chem. Soc.* ***2004***, *126*, 11156; See also, Pedragosa-Moreau, S.; Archelas, A.; Furstoss, R. *Tetrahedron Lett.* ***1996***, *37*, 3319.

[583]Ready, J.M.; Jacobsen, E.N. *J. Am. Chem. Soc.* ***2001***, *123*, 2687.

[584]Hasegawa, E.; Chiba, N.; Nakajima, A.; Suzuki, K.; Yoneoka, A.; Iwaya, K. *Synthesis* ***2001***, 1248. For a related reaction with NO, see Liu, Z.; Li, R.; Yang, D.; Wu, L. *Tetrahedron Lett.* ***2004***, *45*, 1565.

[585]For a review, see Feuer, H.; Hooz, J., in Patai, S. *The Chemistry of the Ether Linkage*, Wiley, NY, ***1967***, pp. 446–450, 460–468.

[586]For a list of reagents used to convert alcohols and phenols to ethers, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 890–893.

[587]Ouk, S.; Thiebaud, S.; Borredon, E.; Legars, P.; Lecomte, L. *Tetrahedron Lett.* ***2002***, *43*, 2661.

[588]Lee, J.C.; Yuk, J.Y.; Cho, S.H. *Synth. Commun.* ***1995***, *25*, 1367.

[589]Benedict, D.A.; Bianchi, T.A.; Cate, L.A. *Synthesis* ***1979***, 428; Johnstone, R.A.W.; Rose, M.E. *Tetrahedron* ***1979***, *35*, 2169. See also, Loupy, A.; Sansoulet, J.; Vaziri-Zand, F. *Bull. Soc. Chim. Fr.* ***1987***, 1027.

[590]Bogdal, D.; Pielichowski, J.; Jaskot, K. *Org. Prep. Proceed. Int.* ***1998***, *30*, 427.

[591]Gadhwal, S.; Boruah, A.; Prajapati, D.; Sandhu, J.S. *Synth. Commun.* ***1999***, *29*, 1921.

[592]Yuncheng, Y.; Yulin, J.; Jun, P.; Xiaohui, Z.; Conggui, Y. *Gazz. Chim. Ital.*, ***1993***, *123*, 519.

[593]Paul, S.; Gupta, M. *Tetrahedron Lett.* ***2004***, *45*, 8825.

[594]In bmim PF_6, 1-butyl-3-methylimidazolium hexafluorophosphate: Xu, Z.Y.; Xu, D.Q.; Liu, B.Y. *Org. Prep. Proceed. Int.* ***2004***, *36*, 156.

[595]For an example, see Jha, S.C.; Joshi, N.N. *J. Org. Chem.* ***2002***, *67*, 3897.

functional groups can be present in the molecule without interference. Ethers with one tertiary group *can* be prepared by treatment of an alkyl halide or sulfate ester (**10-10**) with a tertiary alkoxide $R'O^-$. Di-*tert*-butylether was prepared in high yield by direct attack by *t*-BuOH on the *tert*-butylcation (at −80°C in SO_2ClF).[596] Di-*tert*-alkyl ethers in general have proved difficult to make, but they can be prepared in low-to-moderate yields by treatment of a tertiary halide with Ag_2CO_3 or Ag_2O.[597] Active halides, such as Ar_3CX, may react directly with the alcohol without the need for the more powerful nucleophile alkoxide ion.[598] Even tertiary halides have been converted to ethers in this way, with no elimination,[599] and hindered alcohols react as well.[600] Treatment of tertiary halides (R_3C—Cl) with zinc acetate and ultrasound leads to the corresponding acetate (R_3C—OAc) in a related reaction.[601] The mechanism is these cases is of course S_N1. *tert*-Butyl halides can be converted to aryl *tert*-butylethers by treatment with phenols and an amine, such as pyridine.[602] Aryl alkyl ethers can be prepared from alkyl halides by treatment with an aryl acetate (instead of a phenol) in the presence of K_2CO_3 and a crown ether.[603] It is possible to selectively alkylate the primary hydroxyl in a diol $HOCH_2CH(OH)R$ using a tin complex.[604] It is also possible to hydrogenate aldehydes and ketones (**19-36**) and trap the intermediate with an alcohol to form an ether.[605] The palladium-catalyzed displacement of allylic acetates with aliphatic alcohols has been shown to give the corresponding alkyl allyl ether.[606] The rhodium-catalyzed conversion of allylic carbonates to allylic benzyl ethers has also been reported.[607] Aryl ethers have been prepared using Mitsunobu conditions (see **10-17**).[608]

gem-Dihalides react with alkoxides to give acetals, and 1,1,1-trihalides give ortho esters.[609] Both aryl alkyl and dialkyl ethers can be efficiently prepared with

[596]Olah, G.A.; Halpern, Y.; Lin, H.C. *Synthesis* ***1975***, 315. For another synthesis of di-*tert*-butyl ether, see Masada, H.; Yonemitsu, T.; Hirota, K. *Tetrahedron Lett.* ***1979***, 1315.

[597]Masada, H.; Sakajiri, T. *Bull. Chem. Soc. Jpn.* ***1978***, *51*, 866.

[598]For a review of reactions in which alcohols serve as nucleophiles, see Salomaa, P.; Kankaanperä, A.; Pihlaja, K., in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 1, Wiley, NY, ***1971***, pp. 454–466.

[599]Biordi, J.; Moelwyn-Hughes, E.A. *J. Chem. Soc.* ***1962***, 4291.

[600]Aspinall, H.C.; Greeves, N.; Lee, W.-M.; McIver, E.G.; Smith, P.M. *Tetrahedron Lett.* ***1997***, *38*, 4679.

[601]Jayasree, J.; Rao, J.M. *Synth. Commun.* ***1996***, *26*, 1103.

[602]Masada, H.; Oishi, Y. *Chem. Lett.* ***1978***, 57. For another method, see Camps, F.; Coll, J.; Moretó, J.M. *Synthesis* ***1982***, 186.

[603]Banerjee, S.K.; Gupta, B.D.; Singh, K. *J. Chem. Soc., Chem. Commun.* ***1982***, 815.

[604]Boons, G.-J.; Castle, G.H.; Clase, J.A.; Grice, P.; Ley, S.V.; Pinel, C. *Synlett*, ***1993***, 913.

[605]Bethmont, V.; Fache, F.; LeMaire, M. *Tetrahedron Lett.* ***1995***, *36*, 4235.

[606]Nakagawa, H.; Hirabayashi, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* ***2004***, *69*, 3474; Haight, A.R.; Stoner, E.J.; Peterson, M.J.; Grover, V.K. *J. Org. Chem.* ***2003***, *68*, 8092.

[607]Evans, P.A.; Leahy, D.K. *J. Am. Chem. Soc.* ***2002***, *124*, 7882.

[608]Lepore, S.D.; He, Y. *J. Org. Chem.* ***2003***, *68*, 8261.

[609]For a review of the formation of ortho esters by this method, see DeWolfe, R.H. *Carboxylic Ortho Acid Derivatives*, Academic Press, NY, ***1970***, pp. 12–18.

the use of phase transfer catalysis (p. 511)[610] and with micellar catalysis.[611] Symmetrical benzylic ethers have been prepared by reaction of benzylic alcohols with Mg/I_2 followed by triflic anhydride.[612]

Hydroxy groups can be protected[613] by reaction of their salts with chloromethyl methyl ether.

$$RO^- + CH_3OCH_2Cl \longrightarrow ROCH_2OCH_3$$

This protecting group is known as MOM (methoxymethyl) and such compounds are called MOM ethers. The resulting acetals are stable to bases and are easily cleaved with mild acid treatment (**10-7**). Another protecting group, the 2-methoxyethoxymethyl group (the MEM group), is formed in a similar manner. Both MOM and MEM groups can be cleaved with dialkyl- and diarylboron halides, such as Me_2BBr.[614]

Aryl cyanates[615] can be prepared by reaction of phenols with cyanogen halides in the presence of a base: $ArO^- + ClCN \rightarrow ArOCN + Cl^-$.[616] This reaction has also been applied to certain alkyl cyanates.[617]

Most Williamson reactions proceed by the S_N2 mechanism, but there is evidence (see p. 446) that in some cases the SET mechanism can take place, especially with alkyl iodides.[618] Secondary alcohols have been converted to the corresponding methyl ether by reaction with methanol in the presence of ferric nitrate nonahydrate.[619] Vinyl ethers have been formed by coupling tetravinyl tin with phenols, in the presence of cupric acetate and oxygen.[620] The palladium-catalyzed coupling of vinyl triflates and phenols has also been reported.[621]

[610]For reviews, see Starks, C.M.; Liotta, C. *Phase Transfer Catalysis*, Springer, NY, ***1978***, pp. 128–138; Weber, W.P.; Gokel, G.W. *Phase Transfer Catalysis in Organic Synthesis*, Springer, NY, ***1977***, pp. 73–84. See also, Dueno, E.E.; Chu, F.; Kim, S.-I.; Jung, K.W. *Tetrahedron Lett.* ***1999***, *40*, 1843; Eynde, J.J.V.; Mailleux, I. *Synth. Commun.* ***2001***, *31*, 1. For the use of phase-transfer catalysis to convert one OH group of a diol or triol to a mono ether with selectivity, see de la Zerda, J.; Barak, G.; Sasson, Y. *Tetrahedron* ***1989***, *45*, 1533.

[611]Juršić, B. *Tetrahedron* ***1988***, *44*, 6677.

[612]Nishiyama, T.; Kameyama, H.; Maekawa, H.; Watanuki, K. *Can. J. Chem.* ***1999***, *77*, 258.

[613]For other protecting groups for OH, see Wuts, P.G.M.; Greene, T.W. *Protective Groups in Organic Synthesis Vol. II*, Wiley, NY, ***1991***, pp. 15–104; Wuts, P.G.M.; Greene, T.W. *Protective Groups in Organic Synthesis*, 3rd ed., Wiley, New York, ***1999***. pp. 23–127; Corey, E.J.; Gras, J.; Ulrich, P. *Tetrahedron Lett.* ***1976***, 809 and references cited therein.

[614]Guindon, Y.; Yoakim, C.; Morton, H.E. *J. Org. Chem.* ***1984***, *49*, 3912. For other methods, see Williams, D.R.; Sakdarat, S. *Tetrahedron Lett.* ***1983***, *24*, 3965; Hanessian, S.; Delorme, D.; Dufresne,Y. *Tetrahedron Lett.* ***1984***, *25*, 2515; Rigby, J.H.; Wilson, J.Z. *Tetrahedron Lett.* ***1984***, *25*, 1429.

[615]For reviews of alkyl and aryl cyanates, see Jensen, K.A.; Holm, A., in Patai, S. *The Chemistry of Cyanates and Their Thio Derivatives*, pt. 1, Wiley, NY, ***1977***, pp. 569–618; Grigat, E.; Pütter, R. *Angew. Chem. Int. Ed.* ***1967***, *6*, 206.

[616]Grigat, E.; Pütter, R. *Chem. Ber.* ***1964***, *97*, 3012; Martin, D.; Bauer, M. *Org. Synth.* ***VII***, 435.

[617]Kauer, J.C.; Henderson, W.W. *J. Am. Chem. Soc.* ***1964***, *86*, 4732.

[618]Ashby, E.C.; Bae, D.; Park, W.; Depriest, R.N.; Su, W. *Tetrahedron Lett.* ***1984***, *25*, 5107.

[619]Namboodiri, V.V.; Varma, R.S. *Tetrahedron Lett.* ***2002***, *43*, 4593.

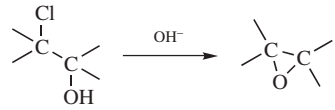
[620]Blouin, M.; Frenette, R. *J. Org. Chem.* ***2001***, *66*, 9043.

[621]Willis, M.C.; Taylor, D.; Gillmore, A.T. *Chem. Commun.* ***2003***, 2222.

OS **I**, 75, 205, 258, 296, 435; **II**, 260; **III**, 127, 140, 209, 418, 432, 544; **IV**, 427, 457, 558, 590, 836; **V**, 251, 258, 266, 403, 424, 684; **VI**, 301, 361, 395, 683; **VII**, 34, 386, 435; **VIII**, 26, 161, 155, 373; **80**, 227.

10-9 Epoxide Formation (Internal Williamson Ether Synthesis)

(3)*OC-cyclo*-Alkoxy-de-halogenation



This is a special case of **10-8**. The base removes the proton from the OH group and the resulting alkoxide subsequently attacks in an internal S_N2 reaction.[622] Many epoxides have been made in this way.[623] The course of the reaction can be influenced by neighboring group effects.[624] The method can also be used to prepare larger cyclic ethers: five- and six-membered rings.[625] Additional treatment with base yields the glycol (**10-7**). Thiiranes can be prepared by the reaction of α-chloro ketones with $(EtO)_2P(=O)-SH$ and $NaBH_4-Al_2O_3$ with microwave irradiation.[626]

OS **I**, 185, 233; **II**, 256; **III**, 835; **VI**, 560; **VII**, 164, 356; **VIII**, 434.

10-10 Alkylation With Inorganic Esters

Alkoxy-de-sulfonyloxy-substitution

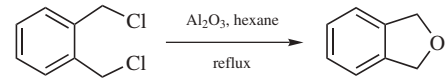
$$R-OSO_2OR'' + R'O^- \longrightarrow ROR$$

The reaction of alkyl sulfates with alkoxide ions is quite similar to **10-8** in mechanism and scope. Other inorganic esters can also be used. Methyl ethers of alcohols and phenols are commonly formd by treatment of alkoxides or aroxides with methyl sulfate. The alcohol or phenol can be methylated directly with dimethyl sulfate under various conditions.[627] Carboxylic esters sometimes give ethers when treated with alkoxides ($B_{AL}2$ mechanism, p. 1403) in a very similar process (see also, **16-64**). A related reaction heated **111** with alumina to give the corresponding benzofuran, **112**.[628]

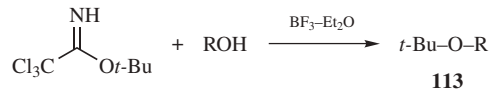
[622]See, for example, Swain, C.G.; Ketley, A.D.; Bader, R.F.W. *J. Am. Chem. Soc.* ***1959***, *81*, 2353; Knipe, A.C. *J. Chem. Soc. Perkin Trans. 2* ***1973***, 589.
[623]For a review, see Berti, G. *Top. Stereochem.* ***1973***, *7*, 93, pp. 187.
[624]Lang, F.; Kassab, D.J.; Ganem, B. *Tetrahedron Lett.* ***1998***, *39*, 5903.
[625]See Kim, K.M.; Jeon, D.J.; Ryu, E.K. *Synthesis* ***1998***, 835 for cyclization to an alkene in the presence of a catalytic amount of iodine. See Marek, I.; Lefrançois, J.-M.; Normant, J.-F. *Tetrahedron Lett.* ***1992***, *33*, 1747 for a related reaction.
[626]Yadav, L.D.S.; Kapoor, R. *Synthesis* ***2002***, 2344.
[627]Ogawa, H.; Ichimura, Y.; Chihara, T.; Teratani, S.; Taya, K. *Bull. Chem. Soc. Jpn.* ***1986***, *59*, 2481; Cao, Y.-Q.; Pei, B.-G. *Synth. Commun.* ***2000***, *30*, 1759.
[628]Mihara, M.; Ishino, Y.; Minakata, S.; Komatsu, M. *Synlett* ***2002***, 1526.

The reaction of aliphatic alcohols and potassium organotrifluoroborate salts also gives ethers.[629]

tert-Butyl ethers (**113**) can be prepared by treating the compound *tert*-butyl2,2,2-trichloroacetimidate with an alcohol or phenol in the presence of boron trifluoride etherate.[630] Trichloroimidates can be used to prepare other ethers as well.[631] *tert*-Butyl ethers can be cleaved by acid-catalyzed hydrolysis.[632]



111 **112**

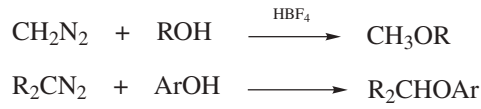


113

OS **I**, 58, 537; **II**, 387, 619; **III**, 127, 564, 800; **IV**, 588; **VI**, 737, 859, **VII**, 41. Also see, OS **V**, 431.

10-11 Alkylation With Diazo Compounds

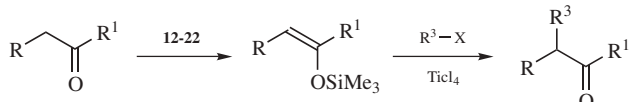
Hydro,alkoxy-de-diazo-bisubstitution



Alcohols react with diazo compounds to form ethers, but diazomethane and diazo ketones are most readily available, giving methyl ethers or α-keto ethers,[633] respectively. With diazomethane[634] the method is expensive and requires great caution, but the conditions are mild and high yields are obtained. Diazomethane is used chiefly to methylate alcohols and phenols that are expensive or available in small amounts. Hydroxy compounds react better as their acidity increases; ordinary alcohols do not react at all unless a catalyst, such as HBF_4[635] or silica gel,[636] is present. The more acidic phenols react very well in the absence of a catalyst. The reaction of oximes, and ketones that have substantial enolic contributions,

[629]Quach, T.D.; Batey, R.A. *Org. Lett.* ***2003***, *5*, 1381.
[630]Armstrong, A.; Brackenridge, I.; Jackson, R.F.W.; Kirk, J.M. *Tetrahedron Lett.* ***1988***, *29*, 2483.
[631]Rai, A.N.; Basu, A. *Tetrahedron Lett.* ***2003***, *44*, 2267.
[632]Lajunen, M.; Ianskanen-Lehti, K. *Acta Chem. Scand. B*, ***1994***, *48*, 861.
[633]Pansare, S.V.; Jain, R.P.; Bhattacharyya, A. *Tetrahedron Lett.* ***1999***, *40*, 5255.
[634]For a review of diazomethane, see Pizey, J.S. *Synthetic Reagents*, Vol. 2, Wiley, NY, ***1974***, pp. 65–142.
[635]Neeman, M.; Caserio, M.C.; Roberts, J.D.; Johnson, W.S. *Tetrahedron* ***1959***, *6*, 36.
[636]Ohno, K.; Nishiyama, H.; Nagase, H. *Tetrahedron Lett.* ***1979***, 4405; Ogawa, H.; Hagiwara, H.; Chihara, T.; Teratani, S.; Taya, K. *Bull. Chem. Soc. Jpn.* ***1987***, *60*, 627.

give *O*-alkylation to form, respectively, *O*-alkyl oximes and enol ethers. The mechanism[637] is as in **10-5**:



160

Diazoalkanes can also be converted to ethers by thermal or photochemical cleavage in the presence of an alcohol. These are carbene or carbenoid reactions.[638] Similar intermediates are involved when diazoalkanes react with alcohols in the presence of *t*-BuOCl to give acetals.[639]

$$R_2CN_2 \quad + \quad 2\,R'OH \xrightarrow{t\text{-BuOCl}} R_2C(OR')_2$$

OS **V**, 245. Also see, OS **V**, 1099.

10-12 Dehydration of Alcohols

Alkoxy-de-hydroxylation

$$2\ ROH \xrightarrow{H_2SO_4} ROR \quad + \quad H_2O$$

The dehydration of alcohols to form symmetrical ethers[640] is analogous to **10-8** and **10-10**, but the species from which the leaving group departs is ROH_2^+ or $ROSO_2OH$. The former is obtained directly on treatment of alcohols with sulfuric acid and may go, by an S_N1 or S_N2 pathway, directly to the ether if attacked by another molecule of alcohol. On the other hand, it may, again by either an S_N1 or S_N2 route, be attacked by the nucleophile HSO_4^-, in which case it is converted to $ROSO_2OH$, which in turn may be attacked by an alcohol molecule to give ROR. Elimination is always a side reaction and, in the case of tertiary alkyl substrates, completely predominates. Good yields of ethers were obtained by heating diarylcarbinols [$ArAr'CHOH \rightarrow (ArAr'CH)_2O$] with TsOH in the solid state.[641] Acids, such as Nafion-H with silyl ethers,[642] can be used in this transformation, and Lewis acids can be used with alcohols in some cases.[643]

[637]Kreevoy, M.M.; Thomas, S.J. *J. Org. Chem.* ***1977***, *42*, 3979. See also, McGarrity, J.F.; Smyth, T. *J. Am. Chem. Soc.* ***1980***, *102*, 7303.

[638]Bethell, D.; Newall, A.R.; Whittaker, D. *J. Chem. Soc. B* ***1971***, 23; Noels, A.F.; Demonceau, A.; Petiniot, N.; Hubert, A.J.; Teyssié, P. *Tetrahedron* ***1982***, *38*, 2733.

[639]Baganz, H.; May, H. *Angew. Chem. Int. Ed.* ***1966***, *5*, 420.

[640]For a review, see Feuer, H.; Hooz, J., in Patai, S. *The Chemistry of the Ether Linkage*, Wiley, NY, ***1967***, pp.457–460, 468–470.

[641]Toda, F.; Takumi, H.; Akehi, M. *J. Chem. Soc. Perkin Trans. 2* ***1990***, 1270.

[642]Zolfigol, M.A.; Mohammadpoor-Baltork, I.; Habibi, D.; Mirjalili, B.B.F.; Bamoniri, A. *Tetrahedron Lett.* ***2003***, *44*, 8165.

[643]For a reaction that used $MeAl(NTf)_2$, see Ooi, T.; Ichikawa, H.; Itagaki, Y.; Maruoka, K. *Heterocycles* ***2000***, *52*, 575.

Mixed (unsymmetrical) ethers can be prepared if one group is tertiary alkyl and the other primary or secondary, since the latter group is not likely to compete with the tertiary group in the formation of the carbocation, while a tertiary alcohol is a very poor nucleophile.[644] If one group is not tertiary, the reaction of a mixture of two alcohols leads to all three possible ethers. Unsymmetrical ethers have been formed by treatment of two different alcohols with $MeReO_3$[645] or with $BiBr_3$.[646] Unsymmetrical ethers have been prepared under Mitsunobu conditions (**10-17**) with a polymer-supported phosphine and diethyl azodicarboxylate (DEAD).[647] Diols can be converted to cyclic ethers,[648] although the reaction is most successful for five-membered rings, but five-, six-, and seven-membered rings have been prepared.[649] Thus, 1,6-hexanediol gives mostly 2-ethyltetrahydrofuran. This reaction is also important in preparing furfural derivatives from aldoses, with concurrent elimination:

Phenols and primary alcohols form ethers when heated with dicyclohexylcarbodiimide[650] (see **16-63**). 1,2-Diols can be converted to epoxides by treatment with DMF dimethyl acetal, $(MeO)_2CHNMe_2$,[651] with diethyl azodicarboxylate, EtOOCN=NCOOEt, and Ph_3P,[652] with a dialkoxytriphenylphosphorane,[653] or with $TsCl^-Na^-OHPhCH_2NEt_3^+ Cl^-$.[654]

OS **I**, 280; **II**, 126; **IV**, 25, 72, 266, 350, 393, 534; **V**, 539, 1024; **VI**, 887; **VIII**, 116. Also see, OS **V**, 721.

10-13 Transetherification

Hydroxy-de-alkoxylation and Alkoxy-de-hydroxylation

$$ROR' + R''OH \longrightarrow ROR'' + R'OH$$

The exchange of one alkoxy group for another is rare for *ethers* without a reactive R group, such as diphenylmethyl,[655] or by treatment of alkyl aryl ethers with

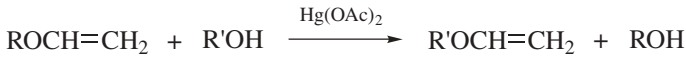
[644]See, for example, Jenner, G. *Tetrahedron Lett.* ***1988***, *29*, 2445.
[645]Zhu, Z.; Espenson, J.H. *J. Org. Chem.* ***1996***, *61*, 324.
[646]Boyer, B.; Keramane, E.-M.; Roque, J.-P.; Pavia, A.A. *Tetrahedron Lett.* ***2000***, *41*, 2891.
[647]Lizarzaburu, M.E.; Shuttleworth, S. *Tetrahedron Lett.* ***2002***, *43*, 2157.
[648]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 893–894.
[649]For an example, see Olah, G.A.; Fung, A.P.; Malhotra, R. *Synthesis* ***1981***, 474.
[650]Vowinkel, E. *Chem. Ber.* ***1962***, *95*, 2997; ***1963***, *96*, 1702; ***1966***, *99*, 42.
[651]Neumann, H. *Chimia*, ***1969***, *23*, 267.
[652]Guthrie, R.D.; Jenkins, I.D.; Yamasaki, R.; Skelton, B.W.; White, A.H. *J. Chem. Soc. Perkin Trans. 1* ***1981***, 2328 and references cited therein. For a review of diethyl azodicarboxylate-Ph_3P, see Mitsunobu, O. *Synthesis* ***1981***, 1.
[653]Kelly, J.W.; Evans, Jr., S.A. *J. Org. Chem.* ***1986***, *51*, 5490. See also, Hendrickson, J.B.; Hussoin, M.S. *Synlett*, ***1990***, 423.
[654]Szeja, W. *Synthesis* ***1985***, 983.
[655]Pratt, E.F.; Draper, J.D. *J. Am. Chem. Soc.* ***1949***, *71*, 2846. Transetherification using $Fe(ClO_4)_3$ was reported. See Salehi, P.; Irandoost, M.; Seddighi, B.; Behbahani, F.K.; Tahmasebi, D.P. *Synth. Commun.* ***2000***, *30*, 1743.

alkoxide ions: $ROAr + R'O^- \rightarrow ROR' + ArO^-$.[656] 3-(2-Benzyloxyethyl)-3-methyloxetane was transformed into 3-benzyloxymethyl-3-methyltetrahydrofuran by an internal transetherification catalyzed by BF_3•OEt_2.[657]

Acetals and ortho esters undergo transetherification readily,[658] as with the trasnfomraton of **114** to **115**.[659]

114 **115**

As seen in **10-6**, departure of the leaving group from an acetal gives a particularly stable carbocation. It is also possible to convert a dimethylketal directly to a dithiane by reaction with butane 1,4-dithiol on clay.[660] These are equilibrium reactions, and most often the equilibrium is shifted by removing the lower-boiling alcohol by distillation. Enol ethers can be prepared by treating an alcohol with an enol ester or a different enol ether, with mercuric acetate as a catalyst,[661] for example,

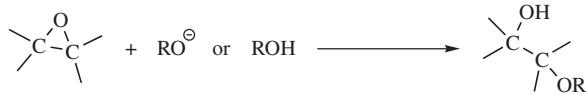


1,2-Diketones can be converted to α-keto enol ethers by treatment with an alkoxytrimethylsilane ($ROSiMe_3$).[662]

OS **VI**, 298, 491, 584, 606, 869; **VII**, 334; **VIII**, 155, 173. Also see, OS **V**, 1080, 1096.

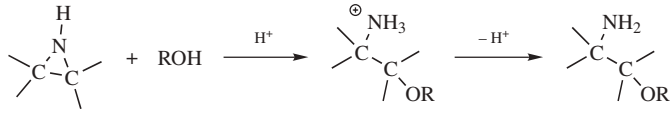
10-14 Alcoholysis of Epoxides

(3)*OC-seco*-alkoxy-de-alkoxylation



[656]Zoltewicz, J.A.; Sale, A.A. *J. Org. Chem.* ***1970***, *35*, 3462.
[657]Itoh, A.; Hirose, Y.; Kashiwagi, H.; Masaki, Y. *Heterocycles* ***1994***, *38*, 2165.
[658]For reviews, see Salomaa, P.; Kankaanperä, A.; Pihlaja, K., in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 1, Wiley, NY, ***1971***, pp. 458–463; DeWolfe, R.H. *Carboxylic Ortho Acid Derivatives*, Academic Press, NY, ***1970***, pp. 18–29, 146–148.
[659]McElvain, S.M.; Curry, M.J. *J. Am. Chem. Soc.* ***1948***, *70*, 3781.
[660]Jnaneshwara, G.K.; Barahate, N.B.; Sudalai, A.; Deshpande, V.H.; Wakharkar, R.D.; Gajare, A.S.; Shingare, M.S.; Sukumar, R. *J. Chem. Soc. Perkin Trans. 1* ***1998***, 965.
[661]Watanabe, W.H.; Conlon, L.E. *J. Am. Chem. Soc.* ***1957***, *79*, 2828; Büchi, G.; White, J.D. *J. Am. Chem. Soc.* ***1964***, *86*, 2884. For a review, see Shostakovskii, M.F.; Trofimov, B.A.; Atavin, A.S.; Lavrov, V.I. *Russ. Chem. Rev.* ***1968***, *37*, 907. For a discussion of the mechanism, see Gareev, G.A. *J. Org. Chem. USSR* ***1982***, *18*, 36.
[662]Ponaras, A.A.; Meah, M.Y. *Tetrahedron Lett.* ***1986***, *27*, 4953.

This reaction is analogous to **10-7**. It may be acid (including Lewis acids[663]), base, or alumina[664] catalyzed, occur with electrolysis,[665] and may occur by either an S_N1 or S_N2 mechanism. Catalysts, such as $[Rh(CO)_2Cl]_2$,[666] $TiCl_3$ (OTf),[667] $Fe(ClO_4)_3$,[668] $Cu(BF_4)_2 \bullet n\ H_2O$,[669] or $BiCl_3$,[670] have been used. β-Cyclodextrin has been used to promote the reaction with phenoxides in aqueous media.[671] Many of the β-hydroxy ethers produced in this way are valuable solvents, for example, diethylene glycol and Cellosolve. Reaction with thiols leads to hydroxy thioethers.[672] The reaction of alcohols with aziridines leads to β-amino ethers,[673] and reaction with thiols gives β-amino thioethers.[674] It has been shown that ring-opening of aziridines by phenols is promoted by tributylphosphine.[675]



Opening an epoxide by an alkoxide moiety can be done intramolecularly, and a new cyclic ether is generated. Ethers of various ring sizes can be produced depending on the length of the tether between the alkoxide unit and the epoxide. Specialized conditions are common, as in the conversion of **116** to **117**.[676] Another variant of this transformation used a cobalt–salen catalyst.[677] A specialized version has the alkoxide moiety on the carbon adjacent to the epoxide, leading to the *Payne rearrangement*, where a 2,3-epoxy alcohol is converted to an isomeric one, by treatment

[663]Iranpoor, N.; Tarrian, T.; Movahedi, Z. *Synthesis* ***1996***, 1473; Iranpoor, N.; Salehi, P. *Synthesis* ***1994***, 1152. See Moberg, C.; Rákos, L.; Tottie, L. *Tetrahedron Lett.* ***1992***, *33*, 2191 for an example that generates a hydroxy ether with high enantioselectivity. Also see, Chini, M.; Crotti, P.; Gardelli, C.; Macchia, F. *Synlett*, ***1992***, 673.

[664]See Posner, G.H.; Rogers, D.Z. *J. Am. Chem. Soc.* ***1977***, *99*, 8208, 8214.

[665]Safavi, A.; Iranpoor, N.; Fotuhi, L. *Bull. Chem. Soc. Jpn.* ***1995***, *68*, 2591.

[666]Fagnou, K.; Lautens, M. *Org. Lett.* ***2000***, *2*, 2319.

[667]Iranpoor, N.; Zeynizadeh, B. *Synth. Commun.* ***1999***, *29*, 1017.

[668]Salehi, P.; Seddighi, B.; Irandoost, M.; Behbahani, F.K. *Synth. Commun.* ***2000***, *30*, 2967.

[669]Barluenga, J.; Vázquez-Villa, H.; Ballesteros, A.; González, J.M. *Org. Lett.* ***2002***, *4*, 2817.

[670]Mohammadpoor-Baltork, I.; Tangestaninejad, S.; Aliyan, H.; Mirkhani, V. *Synth. Commun.*, ***2000***, *30*, 2365.

[671]Surendra, K.; Krishnaveni, N.; Nageswar, Y.V.D.; Rao, K.R. *J. Org. Chem.* ***2003***, *68*, 4994.

[672]Iida, T.; Yamamoto, N.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* ***1997***, *119*, 4783; Kesavan, V.; Bonnet-Delpon, D.; Bégué, J.-P. *Tetrahedron Lett.* ***2000***, *41*, 2895; Fringuelli, F.; Pizzo, F.; Toroioli, S.; Vaccaro, L. *J. Org. Chem.* ***2003***, *68*, 8248; Amantini, D.; Friguelli, F.; Pizzo, F.; Tortioli, S.; Vaccaro, L. *Synlett* ***2003***, 2292.

[673]For a review, see Dermer, O.C.; Ham, G.E. *Ethlenimine and Other Aziridines*, Academic Press, NY, ***1969***, pp. 224–227, 256–257.

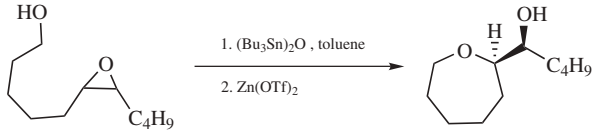
[674]Wu, J.; Hou, X.-L.; Dai, L.-X. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 1314.

[675]Hou, X.-L.; Fan, R.-H.; Dai, L.-X. *J. Org. Chem.* ***2002***, *67*, 5295.

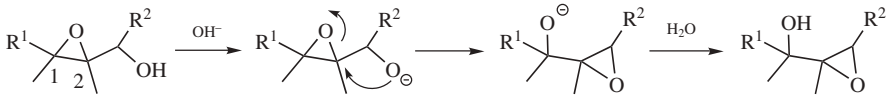
[676]Matsumura, R.; Suzuki, T.; Sato, K.; Oku, K.-i.; Hagiwara, H.; Hoshi, T.; Ando, M.; Kamat, V.P. *Tetrahedron Lett.* ***2000***, *41*, 7701. See also, Karikomi, M.; Watanabe, S.; Kimura, Y.; Uyehara, T. *Tetrahedron Lett.* ***2002***, *43*, 1495.

[677]Wu, M.H.; Hansen, K.B.; Jacobsen, E.N. *Angew. Chem. Int. Ed.* ***1999***, *38*, 2012.

with aqueous base:[678]



116 **117**



The reaction results in inverted configuration at C-2. Of course, the product can also revert to the starting material by the same pathway, so a mixture of epoxy alcohols is generally obtained.

Other nucleophilic oxygen or sulfur species have been shown to open epoxides. Examples include thiocyanate[679] and acetate via acetic anhydride and zeolite HY.[680] Epoxide react with sodium acetate and a cerium catalyst in detergent solutions to give hydroxy acetates.[681] In addition, *N*-tosylaziridines are opened by acetic acid in the presence of $In(OTf)_3$ to give *N*-tosylamino acetates.[682] The reaction of *N*-tosyl aziridines with 10% ceric ammonium nitrate in aqueous methanol leads to *N*-tosylamino alcohols,[683] and reaction with ethanol and 10% BF_3•OEt_2 gives *N*-tosyl ethers.[684] In the presence of Amberlyst 15, *N*-Boc (Boc = *tert*-butoxycarboxyl, $-CO_2t$-Bu) aziridines react with LiBr to give the corresponding bromo amide.[685]

10-15 Alkylation With Onium Salts

Alkoxy-de-hydroxylation

$$R_3O^+ + R'OH \longrightarrow ROR' + R_2O$$

Oxonium ions are excellent alkylating agents, and ethers can be conveniently prepared by treating them with alcohols or phenols.[686] Quaternary ammonium salts can sometimes also be used.[687]

OS **VIII**, 536.

[678]Payne, G.B. *J. Org. Chem.* ***1962***, *27*, 3819; Behrens, C.H.; Ko, S.Y.; Sharpless, K.B.; Walker, F.J. *J. Org. Chem.* ***1985***, *50*, 5687. See Yamazaki, T.; Ichige, T.; Kitazume, T. *Org. Lett.* ***2004***, *6*, 4073.
[679]Sharghi, H.; Nasserri, M.A.; Niknam, K. *J. Org. Chem.* ***2001***, *66*, 7287.
[680]Ramesh, P.; Reddy, V.L.N.; Venugopal, D.; Subrahmanya, M.; Venkateswarlu, Y. *Synth. Commun.* ***2001***, *31*, 2599.
[681]Iranpoor, N.; Firouzabadi, H.; Safavi, A.; Shekarriz, M. *Synth. Commun.* ***2002***, *32*, 2287.
[682]Yadav, J.S.; Reddy, B.V.S.; Sadashiv, K.; Harikishan, K. *Tetrahedron Lett.* ***2002***, *43*, 2099.
[683]Chandrasekhar, S.; Narshihmulu, Ch.; Sultana, S.S. *Tetrahedron Lett.* ***2002***, *43*, 7361.
[684]Prasad, B.A.B.; Sekar, G.; Singh, V.K. *Tetrahedron Lett.* ***2000***, *41*, 4677.
[685]Righi, G.; Potini, C.; Bovicelli, P. *Tetrahedron Lett.* ***2002***, *43*, 5867.
[686]Granik, V.G.; Pyatin, B.M.; Glushkov, R.G. *Russ. Chem. Rev.*, ***1971***, *40*, 747, see p. 749.
[687]For an example, see Vogel, D.E.; Büchi, G.H. *Org. Synth.*, ***66***, 29.

10-16 Hydroxylation of Silanes

Hydroxy-de-silylalkylation

$$R{-}SiR^1{}_2Ar \xrightarrow{F^-} R{-}SiR^1{}_2F \xrightarrow{\text{oxidation}} R{-}OH$$

$$R{-}SiR^1{}_2SiR^2{}_3 \xrightarrow{F^-} R{-}SiR^1{}_2F \xrightarrow{\text{oxidation}} R{-}OH$$

Alkylsilanes can be oxidized, with the silyl unit converted to a hydroxy unit. This usually requires either an aryl group[688] or another silyl group[689] attached to silicon. It has been shown that a strained four-membered ring silane (a siletane) also gives the corresponding alcohol upon oxidation.[690] Treatment with a fluorinating agent, such as tetrabutylammonium fluoride or CsF replaces Ar or SiR_3 with F, which is oxidized with hydrogen peroxide or a peroxy acid to give the alcohol. This sequence is often called the *Tamao–Fleming oxidation*.[688] There are several variation in substrate that allow versatility in the initial incorporation of the silyl unit.[691] Hydroperoxide oxidation of a cyclic silane leads to a diol.[692]

C. Attack by OCOR at an Alkyl Carbon

10-17 Alkylation of Carboxylic Acid Salts

Acyloxy-de-halogenation

$$RX + R'COO^- \xrightarrow{HMPA} R'COOR$$

Sodium salts of carboxylic acids, including hindered acids, such as mesitoic, rapidly react with primary and secondary bromides and iodides at room temperature in dipolar aprotic solvents, especially HMPA, to give high yields of carboxylic esters.[693] The mechanism is S_N2. Several bases or basic media have been used to generate the carboxylate salt.[694] Sodium salts are often used, but potassium, silver, cesium,[695] and substituted ammonium salts have also been used. An important

[688]Kumada, M.; Tamao, K.; Yoshida, J.I. *J. Organomet. Chem.* ***1982***, *239*, 115; Tamao, K.; Kakui, T.; Akita, M.; Iwahara, T.; Kanatani, R.; Yoshida, J.; Kumada, M. *Tetrahedron* ***1983***, *39*, 983; Fleming, I.; Henning, R.; Plaut, H. *J. Chem. Soc., Chem. Commun.* ***1984***, 29. For the protodesilylation step see Häbich, D.; Effenberger, F. *Synthesis* ***1979***, 841. For the peroxyacid reaction see Buncel, E.; Davies, A.G. *J. Chem. Soc.* ***1958***, 1550.

[689]Suginome, M.; Matsunaga, S.; Ito, Y. *Synlett*, ***1995***, 941.

[690]Sunderhaus, J.D.; Lam, H.; Dudley, G.B. *Org. Lett.* ***2003***, *5*, 4571.

[691]For examples see Matsumoto, Y.; Hayashi, T.; Ito, Y. *Tetrahedron* ***1994***, *50*, 335; Uozumi, Y.; Kitayama, K.; Hayashi, T.; Yanagi, K.; Fukuyo, E. *Bull. Chem. Soc. Jpn.* ***1995***, *68*, 713.

[692]Liu, D.; Kozmin, S.A. *Angew. Chem. Int. Ed.* ***2001***, *40*, 4757.

[693]Parker, A.J. *Adv. Org. Chem.* ***1965***, *5*, 1, 37; Alvarez, F.S.; Watt, A.N. *J. Org. Chem.* ***1968***, *33*, 2143; Mehta, G. *Synthesis* ***1972***, 262; Shaw, J.E.; Kunerth, D.C. *J. Org. Chem.* ***1974***, *39*, 1968; Larock, R.C. *J. Org. Chem.* ***1974***, *39*, 3721; Pfeffer, P.E.; Silbert, L.S. *J. Org. Chem.* ***1976***, *41*, 1373.

[694]Bases include DBU (p. $$$): See Mal, D. *Synth. Commun.* ***1986***, *16*, 331. Cs_2CO_3: Lee, J.C.; Oh, Y.S.; Cho, S.H.; Lee, J.I. *Org. Prep. Proceed. Int.* ***1996***, *28*, 480. CsF-Celite: Lee, J.C.; Choi, Y. *Synth. Commun.* ***1998***, *28*, 2021.

[695]See Dijkstra, G.; Kruizinga, W.H.; Kellogg, R.M. *J. Org. Chem.* ***1987***, *52*, 4230.

variation uses phase-transfer catalysis,[696] and good yields of esters have been obtained from primary, secondary, benzylic, allylic, and phenacyl halides.[697] Without phase-transfer catalysts and in protic solvents, the reaction is useful only for fairly active R, such as benzylic and allylic, (S_N1 mechanism), but not for tertiary alkyl, since elimination occurs instead.[698] Solid-state procedures are available. Addition of the dry carboxylate salt and the halide to alumina as a solid support, and microwave irradiation gives the ester in a procedure that is applicable to long-chain primary halides.[699] A similar reaction of hexanoic acid and benzyl bromide on solid benzyltributylammonium chloride gave the ester with microwave irradiation.[700] Ionic liquid solvents have been shown to facilitate this alkylation reaction.[701]

The reaction of an alcohol and a carboxylate anion with diethyl azodicarboxylate EtOOCN=NCOOEt and Ph_3P[702] is called the *Mitsunobu esterification reaction*.[703] This reaction can also be considered as an S_N2. Other Mitsunobu catalysts are available,[704] and a polymer-bound phosphine has been used.[705] A renewable phosphine ligand has been developed.[706] Note that other functional groups, including azides[707] and thiocyanates[708] can be generated from alcohols using Mitsunobu conditions.

Lactones can be prepared from halo acids by treatment with base (see **16-63**). This has most often been accomplished with γ and δ lactones, but macrocyclic

[696]For reviews of phase-transfer catalysis of this reaction, see Starks, C.M.; Liotta, C. *Phase Transfer Catalysis*, Acaemic Press, NY, ***1978***, pp. 140–155; Weber, W.P.; Gokel, G.W. *Phase Transfer Catalysis in Organic Synthesis Phase Transfer Catalysis in Organic Synthesis*, Springer, NY, ***1977***, pp. 85–95.

[697]For an alternative method for phenacyl halides, see Clark, J.H.; Miller, J.M. *Tetrahedron Lett.* ***1977***, 599.

[698]See, however, Moore, G.G.; Foglia, T.A.; McGahan, T.J. *J. Org. Chem.* ***1979***, *44*, 2425.

[699]Bram, G.; Loupy, A.; Majdoub, M.; Gutierrez, E.; Ruiz-Hitzky, E. *Tetrahedron* ***1990***, *46*, 5167. See Arrad, O.; Sasson, Y. *J. Am. Chem. Soc.* ***1988***, *110*, 185; Dakka, J.; Sasson, Y.; Khawaled, K.; Bram, G.; Loupy, A. *J. Chem. Soc., Chem. Commun.* ***1991***, 853.

[700]Yuncheng, Y.; Yulin, J.; Dabin, G. *Synth. Commun.* ***1992***, *22*, 3109.

[701]Brinchi, L.; Germani, R.; Savelli, G. *Tetraheron Lett.* ***2003***, *44*, 2027, 6583. In bmim BF_4, 1-butyl-3-methylimidazolium tetrafluoroborate: Liu, Z.; Chen, Z.-C.; Zheng, Q.-G. *Synthesis* ***2004***, 33.

[702]Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.* ***1967***, *40*, 2380; Camp, D.; Jenkins, I.D. *Aust. J. Chem.* ***1988***, *41*, 1835.

[703]For discussions of the mechanism, see Ahn, C.; Correia, R.; DeShong, P. *J. Org. Chem.* ***2002***, *67*, 1751 and references cited therein. See also, Hughes, D.L. *Org. Prep. Proceed. Int.* ***1996***, *28*, 127; Dembinski, R. *Eur. J. Org. Chem.* ***2004***, 2763; Dandapani, S.; Curran, D.P. *Chem. Eur. J.* ***2004***, *10*, 3131. For a discussion of microwave-promoted Mitsunobu reactions, see Steinreiber, A.; Stadler, A.; Mayer, S.F.; Faber, K.; Kappe, C.O. *Tetrahedron Lett.* ***2001***, *42*, 6283.

[704]See Tsunoda, T.; Yamamiya, Y.; Kawamura, Y.; Itô, S. *Tetrahedron Lett.* ***1995***, *36*, 2529; Tsunoda, T.; Nagaku, M.; Nagino, C.; Kawamura, Y.; Ozaki, F.; Hioki, H.; Itô, S. *Tetrahedron Lett.* ***1995***, *36*, 2531; Walker, M.A. *Tetrahedron Lett.* ***1994***, *35*, 665. For fluorous reactions and reagents, see Dandapani, S.; Curran, D.P. *Tetrahedron* ***2002***, *58*, 3855.

[705]Charette, A.B.; Janes, M.K.; Boezio, A.A. *J. Org. Chem.* ***2001***, *66*, 2178. See also, Elson, K.E.; Jenkins, I.D.; Loughlin, W.A. *Tetrahedron Lett.* ***2004***, *45*, 2491.

[706]Yoakim, C.; Guse, I.; O'Meara, J.A.; Thavonokham, B. *Synlett* ***2003***, 473.

[707]For an example, see Papeo, G.; Poster, H.; Vianello, P.; Varasi, M. *Synthesis* ***2004***, 2886.

[708]Iranpoor, N.; Firouzabadi, H.; Akhlaghinia, B.; Azadi, R. *Synthesis* ***2004***, 92.

lactones (e.g., 11–17 members) have also been prepared in this way.[709] An interesting variation treated 2-ethylbenzoic acid with hypervalent iodine and then $I_2/h\nu$ to give the five-membered ring lactone.[710]

Copper(I) carboxylates give esters with primary (including neopentyl without rearrangement), secondary, and tertiary alkyl, allylic, and vinylic halides.[711] A simple S_N mechanism is obviously precluded in this case. Vinylic halides can be converted to vinylic acetates by treatment with sodium acetate if palladium(II) chloride is present.[712]

A carboxylic acid (not the salt) can be the nucleophile if F^- is present.[713] Mesylates are readily displaced, for example, by benzoic acid/CsF.[714] Dihalides have been converted to diesters by this method.[713] A COOH group can be conveniently protected by reaction of its ion with a phenacyl bromide ($ArCOCH_2Br$).[715] The resulting ester is easily cleaved when desired with zinc and acetic acid. Dialkyl carbonates can be prepared without phosgene (see **16-61**) by phase-transfer catalyzed treatment of primary alkyl halides with dry $KHCO_3$ and K_2CO_3.[716]

Other leaving groups can also be replaced by OCOR. Alkyl chlorosulfites (ROSOCl) and other derivatives of sulfuric, sulfonic, and other inorganic acids can be treated with carboxylate ions to give the corresponding esters. Treatment with oxalyl chloride allows displacement by carboxylate salts.[717] The use of dimethyl sulfate[718] or trimethyl phosphate[719] allows sterically hindered COOH groups to be methylated. The reaction of benzoic acid with aqueous lithium hydroxide and then dimethyl sulfate gave methyl benzoate.[720] Dimethyl carbonate in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) has been used to prepare methyl esters.[721] With certain substrates, carboxylic acids are strong enough nucleophiles

[709]For example, see Galli, C.; Mandolini, L. *Org. Synth.* ***VI***, 698; Kruizinga, W.H.; Kellogg, R.M. *J. Am. Chem. Soc.* ***1981***, *103*, 5183; Kimura, Y.; Regen, S.L. *J. Org. Chem.* ***1983***, *48*, 1533.

[710]Togo, H.; Muraki, T.; Yokoyama, M. *Tetrahedron Lett.* ***1995***, *36*, 7089.

[711]Lewin, A.H.; Goldberg, N.L. *Tetrahedron Lett.* ***1972***, 491; Klumpp, G.W.; Bos, H.; Schakel, M.; Schmitz, R.F.; Vrielink, J.J. *Tetrahedron Lett.* ***1975***, 3429.

[712]Kohll, C.F.; van Helden, R. *Recl. Trav. Chim. Pays-Bas* ***1968***, *87*, 481; Volger, H.C. *Recl. Trav. Chim. Pays-Bas* ***1968***, *87*, 501; Yamaji, M.; Fujiwara, Y.; Asano, R.; Teranishi, S. *Bull. Chem. Soc. Jpn.* ***1973***, *46*, 90.

[713]Clark, J.H.; Emsley, J.; Hoyte, O.P.A. *J. Chem. Soc. Perkin Trans. 1* ***1977***, 1091; Ooi, T.; Sugimoto, H.; Doda, K.; Maruoka, K. *Tetrahedron Lett.* ***2001***, *42*, 9245.

[714]Sato, T.; Otera, J. *Synlett*, ***1995***, 336.

[715]Hendrickson, J.B.; Kandall, L.C. *Tetrahedron Lett.* ***1970***, 343.

[716]Lissel, M.; Dehmlow, E.V. *Chem. Ber.* ***1981***, *114*, 1210; Verdecchia, M.; Frochi, M.; Palombi, L.; Rossi, L. *J. Org. Chem.* ***2002***, *67*, 8287. See also, Kadokawa, J.-i.; Habu, H.; Fukamachi, S.; Karasu, M.; Tagaya, H.; Chiba, K. *J. Chem. Soc., Perkin Trans. 1* ***1999***, 2205.

[717]Barrett, A.G.M.; Braddock, D.C.; James, R.A.; Koike, N.; Procopiou, P.A. *J. Org. Chem.* ***1998***, *63*, 6273.

[718]Grundy, J.; James, B.G.; Pattenden, G. *Tetrahedron Lett.* ***1972***, 757.

[719]Harris, M.M.; Patel, P.K. *Chem. Ind. (London)* ***1973***, 1002.

[720]Chakraborti, A.K.; Basak, A.; Grover, V. *J. Org. Chem.* ***1999***, *64*, 8014. See also, Avila-Zárraga, J.G.; Martínez, R. *Synth. Commun.* ***2001***, *31*, 2177.

[721]Shieh, W.-C.; Dell, S.; Repič, O. *Tetrahedron Lett.* ***2002***, *43*, 5607.

for the reaction. Examples of such substrates are trialkyl phosphites $P(OR)_3$[722] and acetals of DMF.[723]

$$(RO)_2CHNMe_2 + R'COOH \longrightarrow R'COOR + ROH + HCONMe_2$$

This is an S_N2 process, since inversion is found at R. Another good leaving group is NTs_2 and ditosylamines react quite well with acetate ion in dipolar aprotic solvents:[724] $RNTs_2 + OAc^- \rightarrow ROAc$. Ordinary primary amines have been converted to acetates and benzoates by the Katritzky pyrylium–pyridinium method (p. 498).[725] Quaternary ammonium salts can be cleaved by heating with AcO^- in an aprotic solvent.[726] Oxonium ions can also be used as substrates:[727] $R_3O^+ + R'COO^- \rightarrow R'COOR + R_2O$. The reaction of potassium thioacetate with alkyl halides give dithiocarboxylic esters.[728]

In a variation of this reaction, alkyl halides can be converted to carbamates, by treatment with a secondary amine and K_2CO_3 under phase-transfer conditions.[729] The reaction of alcohols and alkyl halides can lead to carbonates.[730]

$$R{-}X + R'_2NH + K_2CO_3 \xrightarrow{Bu_4NH^+HSO_4^-} R{-}O{-}C(=O){-}NR'_2$$

OS **II**, 5; **III**, 650; **IV**, 582; **V**, 580; **VI**, 273, 576, 698.

10-18 Cleavage of Ethers With Acetic Anhydride or Acid Halides

Acyloxy-de-alkoxylation

$$R{-}O{-}R' + Ac_2O \xrightarrow{FeCl_3} ROAc + R'OAc$$

Dialkyl ethers can be cleaved by treatment with anhydrous ferric chloride in acetic anhydride,[731] or with Me_3SiOTf in acetic anhydride.[732] In this reaction both R groups are converted to acetates and yields are moderate to high. Ethers

[722]Szmuszkovicz, J. *Org. Prep. Proceed. Int.* ***1972***, *4*, 51.
[723]Vorbrüggen, H. *Angew. Chem. Int. Ed.* ***1963***, *2*, 211; Brechbühler, H.; Büchi, H.; Hatz, E.; Schreiber, J.; Eschenmoser, A. *Angew. Chem. Int. Ed.* ***1963***, *2*, 212.
[724]Andersen, N.H.; Uh, H. *Synth. Commun.* ***1972***, *2*, 297; Curtis, V.A.; Schwartz, H.S.; Hartman, A.F.; Pick, R.M.; Kolar, L.W.; Baumgarten, R.J. *Tetrahedron Lett.* ***1977***, 1969.
[725]See Katritzky, A.R.; Gruntz, U.; Kenny, D.H.; Rezende, M.C.; Sheikh, H. *J. Chem. Soc. Perkin Trans. 1* ***1979***, 430.
[726]Wilson, N.D.V.; Joule, J.A. *Tetrahedron* ***1968***, *24*, 5493.
[727]Raber, D.J.; Gariano Jr., P.; Brod, A.O.; Gariano, A.; Guida, W.C.; Guida, A.R.; Herbst, M.D. *J. Org. Chem.* ***1979***, *44*, 1149.
[728]Zheng, T.-C.; Burkart, M.; Richardson, D.E. *Tetrahedron Lett.* ***1999***, *40*, 603.
[729]Gómez-Parra, V.; Sánchez, F.; Torres, T. *Synthesis* ***1985***, 282; *J. Chem. Soc. Perkin Trans. 2* ***1987***, 695. For another method, with lower yields, see Yoshida, Y.; Ishii, S.; Yamashita, T. *Chem. Lett.* ***1984***, 1571.
[730]Dueno, E.E.; Chu, F.; Kim, S.-I.; Jung, K.W. *Tetrahedron Lett.* ***1999***, *40*, 1843. For the synthesis of cyclic carbonates see Yoshida, M.; Fujita, M.; Ishii, T.; Ihara, M. *J. Am. Chem. Soc.* ***2003***, *125*, 4874.
[731]Ganem, B.; Small, Jr., V.M. *J. Org. Chem.* ***1974***, *39*, 3728.
[732]Procopiou, P.A.; Baugh, S.P.D.; Flack, S.S.; Inglis, G.G.A. *Chem. Commun.* ***1996***, 2625.

can also be cleaved by the mixed anhydride acetyl tosylate:[733]

Epoxides give β-hydroxyalkyl carboxylates when treated with a carboxylic acid or a carboxylate ion and a suitable catalyst.[734] Tetrahydrofuran was opened to give *O*-acyl-4-iodo-1-butanol by treatment with acid chlorides and samarium halides[735] or BCl_3.[736] In a highly specialized transformation, the reaction of an epoxide with carbon dioxide and $ZnCl_2$ in an ionic liquid leads to a cyclic carbonate.[737] Epoxides react with CO and methanol in the presence of 10% of 3-hydroxypyridine and 5% of $Co_2(CO)_8$ to give a β-hydroxy methyl ester.[738]

OS **VIII**, 13.

10-19 Alkylation of Carboxylic Acids With Diazo Compounds

Hydro, acyloxy-de-diazo-bisubstitution

$$R_2CN_2 + R'COOH \longrightarrow R'COOCHR_2$$

Carboxylic acids can be converted to esters with diazo compounds in a reaction essentially the same as **10-11**. In contrast to alcohols, carboxylic acids undergo the reaction quite well at room temperature, since the reactivity of the reagent increases with acidity. The reaction is used where high yields are important or where the acid is sensitive to higher temperatures. Because of availability diazomethane (CH_2N_2)[634] is commonly used to prepare methyl esters, and diazo ketones are common. The mechanism is as shown in **10-11**.

OS **V**, 797.

D. Other Oxygen Nucleophiles

10-20 Formation of Oxonium Salts

$$RX + R_2O \longrightarrow R_3O^{\oplus}\ BF_4^{\ominus} + AgX \qquad \textbf{Dialkyloxonio-de-halogenation}$$

$$RX + R_2'CO \longrightarrow R_2'C{=}O^{\oplus}{-}R\ BF_4^{\ominus} + AgX$$

Alkyl halides can be alkylated by ethers or ketones to give oxonium salts, if a very weak, negatively charged nucleophile is present to serve as a counterion and a

[733]Karger, M.H.; Mazur, Y. *J. Am. Chem. Soc.* ***1968***, *90*, 3878. See also, Coffi-Nketsia, S.; Kergomard, A.; Tautou, H. *Bull. Soc. Chim. Fr.* ***1967***, 2788.
[734]See Otera, J.; Matsuzaki, S. *Synthesis* ***1986***, 1019; Deardorff, D.R.; Myles, D.C. *Org. Synth.*, ***67***, 114.
[735]Yu, Y.; Zhang, Y.; Ling, R. *Synth. Commun.* ***1993***, *23*, 1973; Kwon, D.W.; Kim, Y.H.; Lee, K. *J. Org. Chem.* ***2002***, *67*, 9488.
[736]Malladi, R.R.; Kabalka, G.W. *Synth. Commun.* ***2002***, *32*, 1997.
[737]Li, F.; Xiao, L.; Xia, C.; Hu, B. *Tetrahedron Lett.* ***2004***, *45*, 8307.
[738]Hinterding, K.; Jacobsen, E.N. *J. Org. Chem.* ***1999***, *64*, 2164.

Lewis acid is present to combine with X^-.[739] A typical procedure consists of treating the halide with the ether or the ketone in the presence of $AgBF_4$ or $AgSbF_6$. The Ag^+ serves to remove X^- and the BF_4^- or SbF_6^- acts as the counterion. Another method involves treatment of the halide with a complex formed between the oxygen compound and a Lewis acid, for example, $R_2O{\bullet}BF_3 + RX \rightarrow R_3O^+\ BF_4^-$, although this method is most satisfactory when the oxygen and halogen atoms are in the same molecule so that a cyclic oxonium ion is obtained. Ethers and oxonium ions also undergo exchange reactions:

$$2\ R_3O^+\ BF_4^- \quad + \quad 3\ R_2'O \quad \rightleftharpoons \quad 2\ R_3'O^+\ BF_4^- \quad + \quad 3\ R_2O$$

OS **V**, 1080, 1096, 1099; **VI**, 1019.

10-21 Preparation of Peroxides and Hydroperoxides

Hydroperoxy-de-halogenation

$$RX \quad + \quad {}^-OOH \longrightarrow \quad ROOH$$

Hydroperoxides can be prepared by treatment of alkyl halides, esters of sulfuric or sulfonic acids, or alcohols with hydrogen peroxide in basic solution, where it is actually HO_2^+.[740] Sodium peroxide is similarly used to prepare dialkyl peroxides ($2\,RX + Na_2O_2 \rightarrow ROOR$). Another method, which gives primary, secondary, or tertiary hydroperoxides and peroxides, involves treatment of the halide with H_2O_2 or a peroxide in the presence of silver trifluoroacetate.[741] Peroxides can also be prepared[742] by treatment of alkyl bromides or tosylates with potassium superoxide KO_2 in the presence of crown ethers (though alcohols may be side products[743]) and by the reaction between alkyl triflates and germanium or tin peroxide.[744] However, alkyl halides can be converted to symmetrical ethers by treatment with oxide ion generated *in situ* by a reaction between an organotin oxide and fluoride ion in the presence of a quaternary ammonium iodide or a crown ether.[745]

[739]Meerwein, H.; Hederich, V.; Wunderlich, K. *Arch. Pharm.* ***1958***, *291/63*, 541. For a review, see Perst, H.*Oxonium Ions in Organic Chemistry*, Verlag Chemie, Deerfield Beach, VA, ***1971***, pp. 22–39.

[740]For a review, see Hiatt, R., in Swern, D. *Organic Peroxides*, Vol. 2, Wiley, NY, ***1971***, pp. 1–151. For a review of hydrogen peroxide, see Pandiarajan, K., in Pizey, J.S. *Synthetic Reagents*, Vol. 6, Wiley, NY, ***1985***, pp. 60–155.

[741]Cookson, P.G.; Davies, A.G.; Roberts, B.P. *J. Chem. Soc., Chem. Commun.* ***1976***, 1022. For another preparation of unsymmetrical peroxides, see Bourgeois, M.; Montaudon, E.; Maillard, B. *Synthesis* ***1989***, 700.

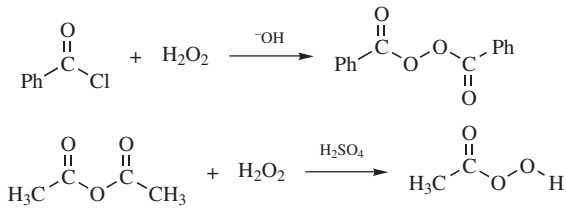
[742]Johnson, R.A.; Nidy, E.G.; Merritt, M.V. *J. Am. Chem. Soc.* ***1978***, *100*, 7960.

[743]Alcohols have also been reported to be the main products: San Filippo, Jr., J.; Chern, C.; Valentine, J.S. *J. Org. Chem.* ***1975***, *40*, 1678; Corey, E.J.; Nicolaou, K.C.; Shibasaki, M.; Machida, Y.; Shiner, C.S. *Tetrahedron Lett.* ***1975***, 3183.

[744]Salomon, M.F.; Salomon, R.G. *J. Am. Chem. Soc.* ***1979***, *101*, 4290.

[745]Harpp, D.N.; Gingras, M. *J. Am. Chem. Soc.* ***1988***, *110*, 7737.

Diacyl peroxides and acyl hydroperoxides can similarly be prepared[746] from acyl halides or anhydrides and from carboxylic acids.[747] Diacyl peroxides can

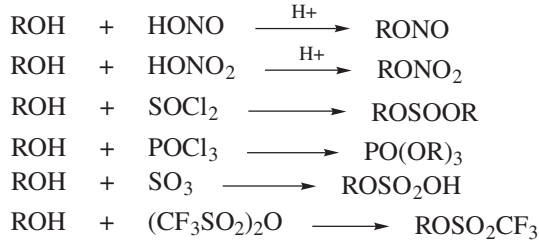


also be prepared by the treatment of carboxylic acids with hydrogen peroxide in the presence of dicyclohexylcarbodiimide,[748] H_2SO_4, methanesulfonic acid, or some other dehydrating agent. Mixed alkyl–acyl peroxides (peresters) can be made from acyl halides and hydroperoxides.

OS **III**, 619, 649; **V**, 805, 904; **VI**, 276.

10-22 Preparation of Inorganic Esters

Nitrosooxy-de-hydroxylation, and so on.



The above transformations show a few of the many inorganic esters that can be prepared by the reaction of an alcohol with an inorganic acid or, better, its acid halide or anhydride[749] These similar reactions are grouped together for convenience, but not all involve nucleophilic substitutions at R. The other possible pathway

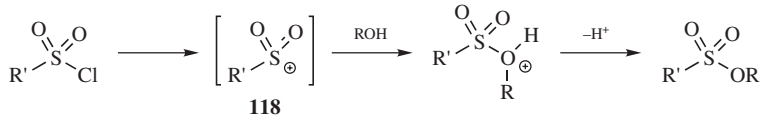
[746]For a review of the synthesis and reactions of acyl peroxides and peresters, see Bouillon, G.; Lick, C.; Schank, K., in Patai, S. *The Chemistry of Peroxides*, Wiley, NY, ***1983***, pp. 279–309. For a review of the synthesis of acyl peroxides, see Hiatt, R. Swern, D. *Organic Peroxides*, Vol. 2, Wiley, NY, ***1971***, pp. 799–929.

[747]See Silbert, L.S.; Siegel, E.; Swern, D. *J. Org. Chem.* ***1962***, *27*, 1336.

[748]Greene, F.D.; Kazan, J. *J. Org. Chem.* ***1963***, *28*, 2168.

[749]For a review, see Salomaa, P.; Kankaanperä, A.; Pihlaja, K., in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 1, Wiley, NY, ***1971***, pp. 481–497.

is nucleophilic substitution at the inorganic central atom, such as the attack of the alcohol oxygen at the electrophilic sulfur atom in **118**,[750] or a corresponding



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S_N2-type process (see p. 1470). In such cases, there is no alkyl-*O* cleavage. Mono esters of sulfuric acid (alkylsulfuric acids), which are important industrially because their salts are used as detergents, can be prepared by treating alcohols with SO_3, H_2SO_4, $ClSO_2OH$, or SO_3 complexes.[751] It is possible to prepare a primary sulfonate ester such as tosylate, in the presence of a secondary alcohol unit when tosic acid reacts with a 1,2-diol in the presence of Fe^{3+}-Montmorillonite.[752] Polymer-bound reagents have been used to prepared sulfonate esters.[753] Phenolic triflate have been prepared using *N,N*-ditrifylaniline and K_2CO_3 under microwave irradiation.[754] Alkyl nitrites[755] can be conveniently prepared by an exchange reaction $ROH + R'ONO \rightarrow RONO + R'OH$, where R = *t*-Bu.[756] Primary amines can be converted to alkyl nitrates ($RNH_2 \rightarrow RONO_2$) by treatment with N_2O_4 at −78°C in the presence of an excess of amidine base.[757] Mitsunobu conditions (**10-17**) can be used to prepare phosphate ester or phosphonate esters. The reaction can be done intramolecularly for prepare cyclic phosphonate esters.[758]

Alkyl halides are often used as substrates instead of alcohols. In such cases, the *salt* of the inorganic acid is usually used and the mechanism is nucleophilic substitution at the carbon atom. An important example is the treatment of alkyl halides with silver nitrate to form alkyl nitrates. This is used as a test for alkyl halides. In some cases, there is competition from the central atom. Thus nitrite ion is an ambident nucleophile that can give nitrites or nitro compounds (see **10-42**).[759] Dialkyl or aryl alkyl ethers can be cleaved with anhydrous sulfonic acids.[760]

$$ROR' + R''SO_2OH \longrightarrow ROSO_2R'' + R'OH$$

[750]For an example involving nitrite formation, see Aldred, S.E.; Williams, D.L.H.; Garley, M. *J. Chem. Soc. Perkin Trans. 2* ***1982***, 777.

[751]For a review, see Sandler, S.R.; Karo, W. *Organic Functional Group Preparations*, 2nd ed., Vol 3; Academic Press, NY, ***1989***, pp. 129–151.

[752]Choudary, B.M. Chowdari, N.S.; Kantam, M.L. *Tetraheron* ***2000***, *56*, 7291.

[753]Vignola, N.; Dahmen, S.; Enders, D.; Bräse, S. *Tetrahedron Lett.* ***2001***, *42*, 7833.

[754]Bengtson, A.; Hallberg, A.; Larhed, M. *Org. Lett.* ***2002***, *4*, 1231.

[755]For a review of alkyl nitrites, see Williams, D.L.H. *Nitrosation*, Cambridge University Press, Cambridge, ***1988***, pp. 150–172.

[756]Doyle, M.P.; Terpstra, J.W.; Pickering, R.A.; LePoire, D.M. *J. Org. Chem.* ***1983***, *48*, 3379. For a review of the nitrosation of alcohols, see Williams, D.L.H. *Nitrosation*, Cambridge University Press, Cambridge, ***1988***, pp. 150–156.

[757]Barton, D.H.R.; Narang, S.C. *J. Chem. Soc. Perkin Trans. 1* ***1977***, 1114.

[758]Pungente, M.D.; Weiler, L. *Org. Lett.* ***2001***, *3*, 643.

[759]For a review of formation of nitrates from alkyl halides, see Boguslavskaya, L.S.; Chuvatkin, N.N.; Kartashov, A.V. *Russ. Chem. Rev.* ***1988***, *57*, 760.

[760]Klamann, D.; Weyerstahl, P. *Chem. Ber.* ***1965***, *98*, 2070.

R″ may be alkyl or aryl. For dialkyl ethers, the reaction does not end as indicated above, since R′OH is rapidly converted to R′OR′ by the sulfonic acid (reaction **10-12**), which in turn is further cleaved to $R'OSO_2R''$ so that the product is a mixture of the two sulfonates. For aryl alkyl ethers, cleavage always takes place to give the phenol, which is not converted to the aryl ether under these conditions. Ethers can also be cleaved in a similar manner by mixed anhydrides of sulfonic and carboxylic acids[761] (prepared as in **16-68**). β-Hydroxyalkyl perchlorates[762] and sulfonates can be obtained from epoxides.[763] Epoxides and oxetanes give α,ω-dinitrates when treated with N_2O_5.[764] Aziridines and azetidines react similarly, giving nitramine nitrates; for example, *N*-butylazetidine gave $NO_2OCH_2CH_2CH_2$-N(Bu)NO_2.[764]

OS **II**, 106, 108, 109, 112, 204, 412; **III**, 148, 471; **IV**, 955; **V**, 839; **VIII**, 46, 50, 616. Also see, OS **II**, 111.

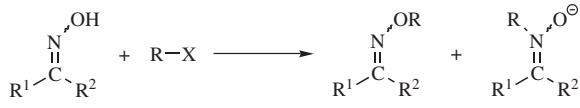
10-23 Alcohols from Amines

Hydroxy-de-amination

$$RNH_2 \longrightarrow ROH$$

This is a rare transformation. A rather direct method was reported whereby a primary amine reacted with KOH in diethylene glycol at 210°C.[765] The reaction of *S*-phenethylamine and the bis(sulfonyl chloride) of 1,2-benzenesulfonic acid, followed by KNO_2 and 18-crown-6 gave (*R*)-phenethyl alcohol in 70% yield and 40% enantiomeric excess (ee).[766]

10-24 Alkylation of Oximes[767]



A nitrone

Oximes can be alkylated by alkyl halides or sulfates. *N*-Alkylation is a side reaction, yielding a nitrone.[768] The relative yield of oxime ether and nitrone depends on the nature of the reagents, including the configuration of the oxime,

[761]Karger, M.H.; Mazur, Y. *J. Org. Chem.* ***1971***, *36*, 532, 540.

[762]For a review of the synthesis and reactions of organic perchlorates, see Zefirov, N.S.; Zhdankin, V.V.; Koz'min, A.S. *Russ. Chem. Rev.* ***1988***, *57*, 1041.

[763]Zefirov, N.S.; Kirin, V.N.; Yur'eva, N.M.; Zhdankin, V.V.; Kozmin, A.S. *J. Org. Chem. USSR* ***1987***, *23*, 1264.

[764]Golding, P.; Millar, R.W.; Paul, N.C.; Richards, D.H. *Tetrahedron Lett.* ***1988***, *29*, 2731, 2735.

[765]Rahman, S.M.A.; Ohno, H.; Tanaka, T. *Tetrahedron Lett.* ***2001***, *42*, 8007.

[766]Sørbye, K.; Tautermann, C.; Carlsen, P.; Fiksdahl, A. *Tetraheron Asymmetry*, ***1998***, *9*, 681.

[767]For a review of the chemistry of oximes see Ãbele, E.; Lukevics, E. *Org. Prep. Proceed. Int.* ***2000***, *32*, 235.

[768]For a review of nitrones, see Torssell, K.B.G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*, VCH, NY, ***1988***, pp. 75–93. For the synthesis of nitrones see Katritzky, A.R.; Cui, X.; Long, Q.; Yanga, B.; Wilcox, A.L.; Zhang, Y.-K. *Org. Prep. Proceed. Int.* ***2000***, *32*, 175.

and on the reaction conditions.[769] For example, *anti*-benzaldoximes give nitrones, while the syn isomers give oxime ethers.[770]

OS **III**, 172; **V**, 1031. Also see, OS **V**, 269; **VI**, 199.

SULFUR NUCLEOPHILES

Sulfur compounds[771] are better nucleophiles than their oxygen analogs (p. 491), so in most cases these reactions take place faster and more smoothly than the corresponding reactions with oxygen nucleophiles. There is evidence that some of these reactions take place by SET mechanisms.[772]

10-25 Attack by SH at an Alkyl Carbon: Formation of Thiols[773]

Mercapto-de-halogenation

$$RX + H_2S \longrightarrow RSH_2^+ \longrightarrow RSH + H^+$$

$$RX + HS^- \longrightarrow RSH$$

Sodium sulfhydride (NaSH) is a much better reagent for the formation of thiols (mercaptans) from alkyl halides than H_2S and is used much more often. It is easily prepared by bubbling H_2S into an alkaline solution, but hydrosulfide on a supported polymer resin has also been used.[774] The reaction is most useful for primary halides. Secondary substrates give much lower yields, and the reaction fails completely for tertiary halides because elimination predominates. Sulfuric and sulfonic esters can be used instead of halides. Thioethers (RSR) are often side products.[775] The conversion can also be accomplished under neutral conditions by treatment of a primary halide with F^- and a tin sulfide, such as $Ph_3SnSSnPh_3$.[776] An indirect method for the preparation of a thiol is the reaction of an alkyl halide with thiourea to give an isothiuronium salt (**119**), and subsequent treatment with alkali or a

[769]For a review, see Reutov, O.A.; Beletskaya, I.P.; Kurts, A.L. *Ambident Anions*, Plenum, NY, ***1983***, pp. 262–272.

[770]Buehler, E. *J. Org. Chem.* ***1967***, *32*, 261.

[771]For monographs on sulfur compounds, see Bernardi, F.; Csizmadia, I.G.; Mangini, A. *Organic Sulfur Chemistry*, Elsevier, NY, ***1985***; Oae, S. *Organic Chemistry of Sulfur*, Plenum, NY, ***1977***. For monographs on selenium compounds, see Krief, A.; Hevesi, L. *Organoselenium Chemistry I*, Springer, NY, ***1988***; Liotta, D. *Organoselenium Chemistry*, Wiley, NY, ***1987***.

[772]See Ashby, E.C.; Park, W.S.; Goel, A.B.; Su, W. *J. Org. Chem.* ***1985***, *50*, 5184.

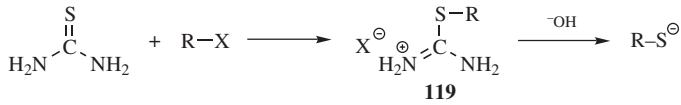
[773]For a review, see Wardell, J.L., in Patai, S. *The Chemistry of the Thiol Group*, pt. 1; Wiley, NY, ***1974***, pp. 179–211.

[774]Bandgar, B.P.; Sadavarte, V.S.; Uppalla, L.S. *Chem. Lett.* ***2000***, 1304.

[775]For a method of avoiding thioether formation, see Vasil'tsov, A.M.; Trofimov, B.A.; Amosova, S.V. *J. Org. Chem. USSR* ***1983***, *19*, 1197.

[776]Gingras, M.; Harpp, D.N. *Tetrahedron Lett.* ***1990***, *31*, 1397.

high-molecular-weight amine gives cleavage to the thiol.



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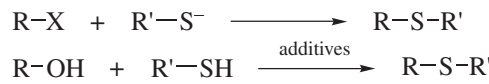
Other indirect methods are treatment of the halide with silyl-thiols and KH, followed by treatment with fluoride ion and water,[777] and hydrolysis of Bunte salts (see **10-28**) is another method.

Thiols have also been prepared from alcohols. One method involves treatment with H_2S and a catalyst, such as Al_2O_3,[778] but this is limited to primary alcohols. Another method involves treatment with Lawesson's reagent (see **16-10**).[779] When epoxides are substrates, the products are β-hydroxy thiols.[780] Tertiary nitro compounds give thiols ($RNO_2 \rightarrow RSH$) when treated with sulfur and sodium sulfide, followed by amalgamated aluminum.[781]

OS **III**, 363, 440; **IV**, 401, 491; **V**, 1046; **VIII**, 592. Also see, OS **II**, 345, 411, 573; **IV**, 232; **V**, 223; **VI**, 620.

10-26 Attack by S at an Alkyl Carbon: Formation of Thioethers

Alkylthio-de-halogenation; Alkylthio-de-hydroxylation



Thioethers (sulfides) can be prepared by treatment of alkyl halides with salts of thiols (thiolate ions).[782] The R′ groups may be alkyl or aryl, and organolithium bases can be used to deprotonate the thiol.[783] As in **10-25**, RX cannot be a tertiary halide, and sulfuric and sulfonic esters can be used instead of halides. As in the Williamson reaction (**10-8**), yields are improved by phase-transfer catalysis.[784] Thiols can be reacted directly with alkyl halides in the presence of bases such as

[777]Miranda, E.I.; Díaz, M.J.; Rosado, I.; Soderquist, J.A. *Tetrahedron Lett.* ***1994***, *35*, 3221; Rane, A.M.; Miranda, E.I.; Soderquist, J. *Tetrahedron Lett.* ***1994***, *35*, 3225.

[778]Lucien, J.; Barrault, J.; Guisnet, M.; Maurel, R. *Nouv. J. Chim.* ***1979***, *3*, 15.

[779]Nishio, T. *J. Chem. Soc., Chem. Commun.* ***1989***, 205; Nishio, T. *J. Chem. Soc. Perkin Trans. 1* ***1993***, 1113.

[780]For a review, see Wardell, J.L., in Patai, S. *The Chemistry of the Thiol Groups*, pt. 1, Wiley, NY, ***1974***, pp. 246–251.

[781]Kornblum, N.; Widmer, J. *J. Am. Chem. Soc.* ***1978***, *100*, 7086.

[782]For a review, see Peach, M.E., in Patai, S. *The Chemistry of the Thiol Groups*, pt. 2, Wiley, NY, ***1974***, pp. 721–735.

[783]Yin, J.; Pidgeon, C. *Tetrahedron Lett.* ***1997***, *38*, 5953.

[784]For a review of the use of phase transfer catalysis to prepare sulfur-containing compounds, see Weber, W.P.; Gokel, G.W. *Phase Transfer Catalysis in Organic Synthesis*, Springer, NY, ***1977***, pp. 221–233.

DBU (p. 1531)[785] or CsF.[786] Neopentyl bromide was converted to Me_3CCH_2SPh in good yield by treatment with PhS^- in liquid NH_3 at −33°C under the influence of light.[787] This probably takes place by an $S_{RN}1$ mechanism (see p. 862). Leaving groups other than chloride can be used, as in the ruthenium-catalyzed reaction of thiols with propargylic carbonates.[788] Vinylic sulfides can be prepared by treating vinylic bromides with PhS^- in the presence of a nickel complex,[789] with R_3SnSPh[790] or with PhSLi[791] in the presence of $Pd(PPh_3)_4$.

In some cases, alcohols can be converted to thioethers by reaction with thiols. Tertiary alcohols react with thiols in the presence of sulfuric acid to give thioethers, and the reaction works best with tertiary substrates.[792] This reaction is analogous to **10-12**. Thiophenol reacts with propargylic alcohols in the presence of a ruthenium catalysts to give propargylic thioethers.[793] Primary and secondary alcohols can be converted to alkyl aryl sulfides (ROH → RSAr) in high yields by treatment with Bu_3P and an *N*-(arylthio)succinimide in benzene.[794] Primary alcohols reacted with benzylic thiols in the presence of PMe_3, 1,1′(azodicarbonyl)dipyridine (ADDP) and imidazole to give the thioether.[795] Thioethers RSR′ can be prepared from an alcohol ROH and a halide R′Cl by treatment with tetramethylthiourea $Me_2NC(=S)NMe_2$ followed by NaH.[796]

Thiolate ions are also useful for the demethylation of certain ethers,[797] esters, amines, and quaternary ammonium salts. Aryl methyl ethers[798] can be cleaved by heating with EtS^- in the dipolar aprotic solvent DMF: $ROAr + EtS^- \rightarrow ArO^- + EtSR$.[799] Carboxylic esters and lactones are cleaved (the lactones give ω-alkylthio carboxylic acids) with a thiol and $AlCl_3$ or $AlBr_3$.[800] Esters and lactones

[785]Ono, N.; Miyake, H.; Saito, T.; Kaji, A. *Synthesis* ***1980***, 952. See also, Ferreira, J.T.B.; Comasseto, J.V.; Braga, A.L. *Synth. Commun.* ***1982***, *12*, 595; Ando, W.; Furuhata, T.; Tsumaki, H.; Sekiguchi, A. *Synth. Commun.* ***1982***, *12*, 627.; Feroci, M.; Inesi, A.; Rossi, L. *Synth. Commun.* ***1999***, *29*, 2611.

[786]Shah, S.T.A.; Khan, K.M.; Heinich, A.M.; Voelter, W. *Tetrahedron Lett.* ***2002***, *43*, 8281.

[787]Pierini, A.B.; Peñéñory, A.B.; Rossi, R.A. *J. Org. Chem.* ***1985***, *50*, 2739.

[788]Kondo, T.; Kanda, Y.; Baba, A.; Fukuda, K.; Nakamura, A.; Wada, K.; Morisaki, Y.; Mitsudo, T.-a. *J. Am. Chem. Soc.* ***2002***, *124*, 12960.

[789]Cristau, H.J.; Chabaud, B.; Labaudiniere, R.; Christol, H. *J. Org. Chem.* ***1986***, *51*, 875.

[790]Carpita, A.; Rossi, R.; Scamuzzi, B. *Tetrahedron Lett.* ***1989***, *30*, 2699. For another method, see Ogawa, T.; Hayami, K.; Suzuki, H. *Chem. Lett.* ***1989***, 769.

[791]Martínez, A.G.; Barcina, J.O.; Cerezo, A. de F.; Subramanian, L.R. *Synlett*, ***1994***, 561.

[792]See Cain, M.E.; Evans, M.B.; Lee, D.F. *J. Chem. Soc.* ***1962***, 1694.

[793]Inada, Y.; Nishibayashi, Y.; Hidai, M.; Uemura, S. *J. Am. Chem. Soc.* ***2002***, *124*, 15172.

[794]Walker, K.A.M. *Tetrahedron Lett.* ***1977***, 4475. See the references in this paper for other methods of converting alcohols to sulfides. See also, Cleary, D.G. *Synth. Commun.* ***1989***, *19*, 737.

[795]Falck, J.R.; Lai, J.-Y.; Cho, S.-D.; Yu, J. *Tetrahedron Lett.* ***1999***, *40*, 2903.

[796]Fujisaki, S.; Fujiwara, I.; Norisue, Y.; Kajigaeshi, S. *Bull. Chem. Soc. Jpn.* ***1985***, *58*, 2429.

[797]For a review, see Evers, M. *Chem. Scr.* ***1986***, *26*, 585.

[798]Certain other sulfur-containing reagents also cleave methyl and other ethers: see Hanessian, S.; Guindon, Y. *Tetrahedron Lett.* ***1980***, *21*, 2305; Williard, P.G.; Fryhle, C.B. *Tetrahedron Lett.* ***1980***, *21*, 3731; Node, M.; Nishide, K.; Fuji, K.; Fujita, E. *J. Org. Chem.* ***1980***, *45*, 4275. For cleavage with selenium-containing reagents, see Evers, M.; Christiaens, L. *Tetrahedron Lett.* ***1983***, *24*, 377. For a review of the cleavage of aryl alkyl ethers, see Tiecco, M. *Synthesis* ***1988***, 749.

[799]Feutrill, G.I.; Mirrington, R.N. *Tetrahedron Lett.* ***1970***, 1327, *Aust. J. Chem.* ***1972***, *25*, 1719, 1731.

[800]Node, M.; Nishide, K.; Ochiai, M.; Fuji, K.; Fujita, E. *J. Org. Chem.* ***1981***, *46*, 5163.

are similarly cleaved in high yield by phenyl selenide ion $PhSe^-$.[801] Allylic sulfides have been prepared by treating allylic carbonates ROCOOMe (R = an allylic group) with a thiol and a Pd(0) catalyst.[802] A good method for the demethylation of quaternary ammonium salts consists of refluxing them with PhS^- in butanone:[803]

$$R_3\overset{\oplus}{N}Me + Ph\overset{\ominus}{S} \xrightarrow{MeCOEt} R_3N + PhSMe$$

A methyl group is cleaved more readily than other simple alkyl groups (such as ethyl), although loss of these groups competes, but benzylic and allylic groups cleave even more easily, and this is a useful procedure for the cleavage of benzylic and allylic groups from quaternary ammonium salts, even if methyl groups are also present.[804]

Symmetrical thioethers can also be prepared by treatment of an alkyl halide with sodium sulfide.[805] Symmetrical thioethers have also been prepared by the reaction of $S(MgBr)_2$ with allylic halides.[806]

$$2\,RX + Na_2S \longrightarrow RSR$$

This reaction can be carried out internally, by treatment of sulfide ions with 1,4-, 1,5-, or 1,6-dihalides, to prepare five-, six-, and seven-membered[807] sulfur-containing heterocyclic rings. Certain larger rings have also been closed in this way.[808] A related variation converts epxoides to thiiranes with thiourea and $LiBF_4$ in acetonitrile.[809]

gem-Dihalides can be converted to dithioacetals $RCH(SR')_2$,[810] and acetals have been converted to monothioacetals $R_2C(OR')(SR^2)$,[811] and to dithioacetals.[812] The combination of carbon disulfide and $NaBH_4$ converted 1,3-dibromopropane to 1,3-dithiane.[813]

[801]Scarborough, Jr., R.M.; Smith III, A.B. *Tetrahedron Lett.* ***1977***, 4361; Liotta, D.; Sunay, U.; Santiesteban, H.; Markiewicz, W. *J. Org. Chem.* ***1981***, *46*, 2605; Kong, F.; Chen, J.; Zhou, X. *Synth. Commun.* ***1988***, *18*, 801.

[802]Trost, B.M.; Scanlan, T.S. *Tetrahedron Lett.* ***1986***, *27*, 4141; Goux, C.; Lhoste, P.; Sinou, D. *Tetrahedron Lett.* ***1992***, *33*, 8099; *Tetrahedron* ***1994***, *50*, 10321.

[803]Shamma, M.; Deno, N.C.; Remar, J.F. *Tetrahedron Lett.* ***1966***, 1375. For alternative procedures, see Hutchins, R.O.; Dux, F.J. *J. Org. Chem.* ***1973***, *38*, 1961; Posner, G.H.; Ting, J. *Synth. Commun.* ***1974***, *4*, 355.

[804]Kametani, T.; Kigasawa, T.; Hiiragi, M.; Wagatsuma, N.; Wakisaka, K. *Tetrahedron Lett.* ***1969***, 635.

[805]For another reagent, see Harpp, D.N.; Gingras, M.; Aida, T.; Chan, T.H. *Synthesis* ***1987***, 1122.

[806]Nedugov, A.N.; Pavlova, N.N. *Zhur. Org. Khim.*, ***1992***, *28*, 1401 (Engl. 1103).

[807]Tan, L.C.; Pagni, R.M.; Kabalka, G.W.; Hillmyer, M.; Woosley, J. *Tetrahedron Lett.* ***1992***, *33*, 7709.

[808]See Hammerschmidt, E.; Bieber, W.; Vögtle, F. *Chem. Ber.* ***1978***, *111*, 2445; Singh, A.; Mehrotra, A.; Regen, S.L. *Synth. Commun.* ***1981***, *11*, 409.

[809]Kazemi, F.; Kiasat, A.R.; Ebrahimi, S. *Synth. Commun.* ***2003***, *33*, 595.

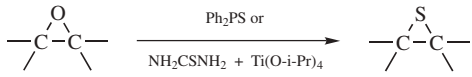
[810]See, for example, Wähälä, K.; Ojanperä, I.; Häyri, L.; Hase, T.A. *Synth. Commun.* ***1987***, *17*, 137.

[811]Masaki, Y.; Serizawa, Y.; Kaji, K. *Chem. Lett.* ***1985***, 1933; Sato, T.; Kobayashi, T.; Gojo, T.; Yoshida, E.; Otera, J.; Nozaki, H. *Chem. Lett.* ***1987***, 1661.

[812]Firouzabadi, H.; Iranpoor, N.; Hazarkhami, H. *J. Org. Chem.* ***2001***, *66*, 7527, and references cited therein; Ranu, B.C.; Das, A.; Samanta, S. *Synlett.* ***2002***, 727.

[813]Wan,Y.; Kurchan, A.N.; Barnhurst, L.A.; Kutateladze, A.G. *Org. Lett.* ***2000***, *2* , 1133.

When epoxides are substrates,[814] reaction with $PhSeSnBu_3/BF_3{\bullet}OEt_2$[815] gives the corresponding β-hydroxy selenide in a manner analogous to that mentioned in **10-25**. Reaction of an epoxide with Ph_3SiSH followed by treatment with Bu_4NF gives hydroxy-thiols.[816] Epoxides can also be directly converted to episulfides[817] by treatment with a phosphine sulfide, such as Ph_3PS,[818] with thiourea and titanium tetraisopropoxide,[819] with NH_4SCN and $TiO(tfa)_2$,[820] with $(EtO)_2P(=O)H/S/Al_2O_3$,[821] with KSCN and $InBr_3$,[822] and with KSCN in ionic liquids.[823]

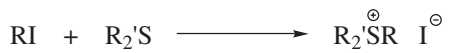


Alkyl halides, treated with thioethers, give sulfonium salts.[824] Other leaving groups have also been used for this purpose.[825]

Selenides (selenoethers)and tellurides can be prepared via RSe^- and RTe^- species,[826] and selenium and borohydride exchange resin followed by the halide give the selenoether.[827] The La/I_2-catalyzed reaction of diphenyl diselenide with primary alkyl iodides gave arylalkyl selenides,[828] and InI has been used with benzyl halides.[829] Diaryl selenides (Ar—Se—Ar′) have been prepared by coupling aryl iodides with tin reagents ($ArSeSnR_3$) with a palladium(0) catalyst.[830]

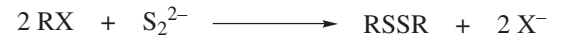
[814]Chini, M.; Crotti, P.; Giovani, E.; Macchia, F.; Pineschi, M. *Synlett*, ***1992***, 303.
[815]Nishiyama, Y.; Ohashi, H.; Itoh, K.; Sonoda, N. *Chem. Lett.* ***1998***, 159.
[816]Brittain, J.; Gareau, Y. *Tetrahedron Lett.* ***1993***, *34*, 3363.
[817]For a review of episulfides, see Fokin, A.V.; Kolomiets, A.F. *Russ. Chem. Rev.* ***1975***, *44*, 138.
[818]Chan, T.H.; Finkenbine, J.R. *J. Am. Chem. Soc.* ***1972***, *94*, 2880.
[819]Gao, Y.; Sharpless, K.B. *J. Org. Chem.* ***1988***, *53*, 4114. For other methods, see Calō, V.; Lopez, L.; Marchese, L.; Pesce, G. *J. Chem. Soc., Chem. Commun.* ***1975***, 621; Takido, T.; Kobayashi, Y.; Itabashi, K. *Synthesis* ***1986***, 779; Bouda, H.; Borredon, M.E.; Delmas, M.; Gaset, A. *Synth. Commun.* ***1987***, *17*; 943, ***1989***, *19*, 491.
[820]Iranpoor, N.; Zeynizadeh, B. *Synth. Commun.* ***1998***, *28*, 3913. See also, Tamami, B.; Kolahdoozan, M. *Tetrahedron Lett.* ***2004***, *45*, 1535.
[821]Kaboudin, B.; Norouzi, H. *Tetrahedron Lett.* ***2004***, *45*, 1283.
[822]Yadav, J.S.; Reddy, B.V.S.; Baishya, G. *Synlett.* ***2003***, 396.
[823]Yadav, J.S.; Reddy, B.V.S.; Reddy, Ch.S.; Rajasekhar, K. *J. Org. Chem.* ***2003***, *68*, 2525.
[824]For a review of the synthesis of sulfonium salts, see Lowe, P.A., in Stirling, C.J.M. *The Chemistry of the Sulphonium Group*, pt. 1, Wiley, NY, ***1981***, pp. 267–312.
[825]See Badet, B.; Jacob, L.; Julia, M. *Tetrahedron* ***1981***, *37*, 887; Badet, B.; Julia, M. *Tetrahedron Lett.* ***1979***, 1101, and references cited in the latter paper.
[826]Brandsma, L.; Wijers, H.E. *Recl. Trav. Chim. Pays-Bas* ***1963***, *82*, 68; Clarembeau, M.; Krief, A. *Tetrahedron Lett.* ***1984***, *25*, 3625; Cohen, R.J.; Fox, D.L.; Salvatore, R.N. *J. Og. Chem.* ***2004***, *69*, 4265. For a review of nucleophilic selenium, see Monahan, R.; Brown, D.; Waykole, L.; Liotta, D., in Liotta, D.C. *Organoselenium Chemistry*, Wiley, NY, ***1987***, pp. 207–241.
[827]Yanada, K.; Fujita, T.; Yanada, R. *Synlett*, ***1998***, 971.
[828]Nishino, T.; Okada, M.; Kuroki, T.; Watanabe, T.; Nishiyama, Y.; Sonoda, N. *J. Org. Chem.* ***2002***, *67*, 8696. Zinc in aqueous media has also been used: see Bieber, L.W.; de Sá, A.C.P.F.; Menezes, P.H. Gonçalves, S.M.C. *Tetrahedron Lett.* ***2001***, *42*, 4597.
[829]Ranu, B.C.; Mandal, T.; Samanta, S. *Org. Lett.* ***2003***, *5*, 1439.; Ranu, B.C.; Mandal, T. *J. Org. Chem.* ***2004***, *69*, 5793.
[830]Nishiyama, Y.; Tokunaga, K.; Sonoda, N. *Org. Lett.* ***1999***, *1*, 1725.

OS **II**, 31, 345, 547, 576; **III**, 332, 751, 763; **IV**, 396, 667, 892, 967; **V**, 562, 780, 1046; **VI**, 5, 31, 268, 364, 403, 482, 556, 601, 683, 704, 737, 833, 859; **VII**, 453; **VIII**, 592. See also, OS **VI**, 776.



10-27 Formation of Disulfides[831]

Dithio-de-dihalo-*aggre*-substitution

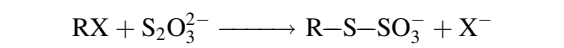


Disulfides can be prepared by treatment of alkyl halides with disulfide ions and also indirectly by the reaction of Bunte salts (see **10-28**) with acid solutions of iodide, thiocyanate ion, or thiourea,[832] or by pyrolysis or treatment with hydrogen peroxide. Alkyl halides also give disulfides when refluxed with sulfur and NaOH,[833] and with piperidinium tetrathiotungstate or piperidinium tetrathiomolybdate.[834] Other molybdenum compounds convert alkyl halides to disulfides, including $(BnNEt_3)_6Mo_7S_{24}$.[835]

There are no OS references, but a similar preparation of a polysulfide may be found in OS **IV**, 295.

10-28 Formation of Bunte Salts

Sulfonatothio-de-halogenation



Primary and secondary, but not tertiary, alkyl halides are easily converted to Bunte salts ($RSSO_3^-$) by treatment with thiosulfate ion.[836] Bunte salts can be hydrolyzed with acids to give the corresponding thiols[837] or converted to disulfides, tetrasulfides, or pentasulfides.[838]

OS **VI**, 235.

[831]For a discussion of disulfide exchange reactions, see Arisawa, M.; Yamaguchi, M. *J. Am. Chem. Soc.* ***2004***, *125*, 6624.
[832]Milligan, B.; Swan, J.M. *J. Chem. Soc.* ***1962***, 2712.
[833]Chorbadjiev, S.; Roumian, C.; Markov, P. *J. Prakt. Chem.* ***1977***, *319*, 1036. For an example using microwave irradiation, see Wang, J.-X.; Gao, L.; Huang, D. *Synth. Commun.* ***2002***, *32*, 963.
[834]Dhar, P.; Chandrasekaran, S. *J. Org. Chem.* ***1989***, *54*, 2998.
[835]Polshettiwar, V.; Nivsarkar, M.; Acharya, J.; Kaushik, M.P. *Tetrahedron Lett.* ***2003***, *44*, 887.
[836]For a review of Bunte salts, see Distler, H. *Angew. Chem. Int. Ed.* ***1967***, *6*, 544–553.
[837]Kice, J.L. *J. Org. Chem.* ***1963***, *28*, 957.
[838]Milligan, B.; Saville, B.; Swan, J.M. *J. Chem. Soc.* ***1963***, 3608.

10-29 Alkylation of Sulfinic Acid Salts

Alkylsulfonyl-de-halogenation

$$RX + R'SO_2^- \longrightarrow R{-}SO_2{-}R' + X^-$$

Alkyl halides or alkyl sulfates, treated with the salts of sulfinic acids, give sulfones.[839] A palladium catalyzed reaction with a chiral complexing agent led to sulfones with modest asymmetric induction.[840] Alkyl sulfinates R′SO–OR may be side products.[841] Sulfonic acids themselves can be used, if DBU (p. 1530) is present.[842] Sulfonyl halides react with allylic halides in the presence of $AlCl_3^-Fe$[843] and wit benzyl hlaides in the presence of $Sm/HgCl_2$.[844] Sulfones have also been prepared by treatment of alkyl halides with tosylhydrazide.[845]

Vinyl sulfones were prepared from $PhSO_2Na$ and vinyl iodinium salts $C{=}C{-}I^+Ph\ BF_4^-$.[846] Sulfinate esters (RS(=O)OR′ were prepared from alcohols and sulfinyl chlorides, in the presence of Proton Sponge®.[847]

OS **IV**, 674; **IX**, 497. See also, OS **VI**, 1016.

10-30 Formation of Alkyl Thiocyanates

Thiocyanato-de-halogenation

$$RX + SCN^- \longrightarrow RSCN + X^-$$

Alkyl halides[848] or sulfuric or sulfonic esters can be heated with sodium or potassium thiocyanate to give alkyl thiocyanates,[849] although the attack by the analogous cyanate ion (**10-44**) gives exclusive *N*-alkylation. Primary amines can be converted to thiocyanates by the Katritzky pyrylium–pyridinium method (p. 498).[850] Tertiary

[839]For a review, see Schank, K., in Patai, S.; Rappoport, Z.; Stirling, C. *The Chemistry of Sulphones and Sulphoxides*, Wiley, NY, ***1988***, pp. 165–231, 177–188.

[840]Eichelmann, H.; Gais, H.-J. *Tetrahedron Asymmetry*, ***1995***, *6*, 643.

[841]See, for example Meek, J.S.; Fowler, J.S. *J. Org. Chem.* ***1968***, *33*, 3422; Kiełbasiński, P.; Żurawiński, R.; Drabowicz, J.; Mikołajczyk, M. *Tetrahedron* ***1988***, *44*, 6687.

[842]Biswas, G.; Mal, D. *J. Chem. Res. (S)* ***1988***, 308.

[843]Saikia, P.; Laskar, D.D.; Prajapati, D.; Sandhu, J.S. *Chem. Lett.* ***2001***, 512.

[844]Zhang, J.; Zhang, Y. *J. Chem. Res. (S)* ***2001***, 516.

[845]Ballini, R.; Marcantoni, E.; Petrini, M. *Tetrahedron* ***1989***, *45*, 6791.

[846]Ochiai, M.; Oshima, K.; Masaki, Y.; Kunishima, M.; Tani, S. *Tetrahedron Lett.* ***1993***, *34*, 4829.

[847]Evans, J.W.; Fierman, M.B.; Miller, S.J.; Ellman, J.A. *J. Am. Chem. Soc.* ***2004***, *126*, 8134.

[848]Renard, P.-Y.; Schwebel, H.; Vayron, P.; Leclerc, E.; Dias, S.; Mioskowski, C. *Tetrahedron Lett.* ***2001***, *42*, 8479. For a variation involving *in situ* halogenation of active methylene compounds with formation of the thiocyanate, see Prakash, O.; Kaur, H.; Batra, H.; Rani, N.; Singh, S.P.; Moriarty, R.M. *J. Org. Chem.* ***2001***, *66*, 2019. The reagent $Ph_3P(SCN)_2$ has also been used: see Iranpoor, N.; Firouzabadi, H.; Shaterian, H.R. *Tetrahedron Lett.* ***2002***, *43*, 3439.

[849]For a review of thiocyanates, see Guy, R.G., in Patai, S. *The Chemistry of Cyanates and Their Thio Derivatives*, pt. 2; pp. 819–886, Wiley, NY, ***1977***, pp. 819–886.

[850]Katritzky, A.R.; Gruntz, U.; Mongelli, N.; Rezende, M.C. *J. Chem. Soc. Perkin Trans. 1* ***1979***, 1953. For the conversion of primary alcohols to thiocyanates, see Tamura, Y.; Kawasaki, T.; Adachi, M.; Tanio, M.; Kita, Y. *Tetrahedron Lett.* ***1977***, 4417.

chlorides are converted to tertiary thiocyanates with $Zn(SCN)_2$ in pyridine and ultrasound.[851]

OS **II**, 366.

NITROGEN NUCLEOPHILES

A. Attack by NH_2, NHR, or NR_2 at an Alkyl Carbon

10-31 Alkylation of Amines

Amino-de-halogenation (alkyl)

$$3\,RX + NH_3 \longrightarrow R_3N + RX \longrightarrow R_4N^+\ X^-$$
$$2\,RX + R'NH_2 \longrightarrow R_2R'N + RX \longrightarrow R_3R'N^+\ X^-$$
$$RX + R''R'NH_2 \longrightarrow RR'R''N + RX \longrightarrow R_2R'R''N^+\ X^-$$
$$RX + RR'R''N \longrightarrow RR'R''R''N^+\ X^-$$

The reaction between alkyl halides and ammonia or primary amines is not usually a feasible method for the preparation of primary or secondary amines, since they are stronger bases than ammonia and preferentially attack the substrate. However, the reaction is very useful for the preparation of tertiary amines[852] and quaternary ammonium salts. If ammonia is the nucleophile,[853] the three or four alkyl groups on the nitrogen of the product must be identical. If a primary, secondary, or tertiary amine is used, then different alkyl groups can be placed on the same nitrogen atom. The conversion of tertiary amines to quaternary salts is called the *Menshutkin reaction*.[854] It is sometimes possible to use this method for the preparation of a primary amine by the use of a large excess of ammonia or a secondary amine by the use of a large excess of primary amine. The use of ammonia in methanol with microwave irradiation has also been effective.[855] Microwave irradiation has also been used in reactions of aniline with allyl iodides.[856] A base other than the amine

[851]Bettadaiah, B.K.; Gurudutt, K.N.; Srinivas, P. *Synth. Commun.* ***2003***, *33*, 2293.

[852]For reviews of this reaction, see Gibson, M.S., in Patai, S. *The Chemistry of the Amino Group*, Wiley, NY, ***1968***, pp. 45–55; Spialter, L.; Pappalardo, J.A. *The Acyclic Aliphatic Tertiary Amines*, Macmillan, NY, ***1965***, pp. 14–29.

[853]For a review of ammonia as a synthetic reagent, see Jeyaraman, R., in Pizey, J.S. *Synthetic Reagents*, Vol. 5, Wiley, NY, ***1983***, pp. 9–83.

[854]For a discussion of solvent effects see Deleuze, M.S.; Leigh, D.A.; Zerbetto, F. *J. Am. Chem. Soc.* ***1999***, *121*, 2364. For a review of stereoselectivity in this reaction see Bottini, A.T. *Sel. Org. Transform.* ***1970***, *1*, 89. For a discussion of steric effects, see Persson, J.; Berg, U.; Matsson, O. *J. Org. Chem.* ***1995***, *60*, 5037. For a review of quaternization of heteroaromatic rings, see Zoltewicz, J.A.; Deady, L.W. *Adv. Heterocycl. Chem.* ***1978***, *22*, 71. See Shaik, S.; Ioffe, A.; Reddy, A.C.; Pross, A. *J. Am. Chem. Soc.* ***1994***, *116*, 262 for a discussion of the transition state for this reaction.

[855]Saulnier, M.G.; Zimmermann, K.; Struzynski, C.P.; Sang, X.; Velaparthi, U.; Wittman, M.; Frennesson, D.B. *Tetrahedron Lett.* ***2004***, *45*, 397.

[856]Romera, J.L.; Cid, J.M.; Trabanco, A.A. *Tetrahedron Lett.* ***2004***, *45*, 8797.

can be added to facilitate the reaction. Sodium carbonate has been used,[857] as has lithium hydroxide.[858] Cesium hydroxide was successfully used as a base in the presence of molecular sieve 4 Å,[859] and cesium fluoride has been used with benzylic halides.[860] Potassium carbonate in DMSO has been used for the alkylation of aniline.[861] Bromides react faster than chlorides, and secondary amines reaction with 3-chloro-1-bromopropane via the bromide, in the presence of Zn and THF.[862]

The limitations of this approach can be seen in the reaction of a saturated solution of ammonia in 90% ethanol with ethyl bromide in a 16:1 molar ratio, under which conditions the yield of primary amine was 34.2% (at a 1:1 ratio the yield was 11.3%).[863] Alkyl amines can be one type of substrate that does give reasonable yields of primary amine (provided a large excess of NH_3 is used) are α-halo acids, which are converted to amino acids. *N*-Chloromethyl lactams also react with amines to give good yields to the *N*-aminomethyl lactam.[864] Primary amines can be prepared from alkyl halides by **10-43**, followed by reduction of the azide (**19-32**),[865] or by the Gabriel synthesis (**10-41**).

The immediate product in any particular step is the protonated amine, but it rapidly loses a proton to another molecule of ammonia or amine in an equilibrium process, for example,

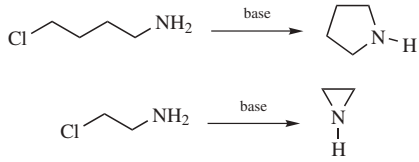
$$RX + R_2NH \longrightarrow R_3\overset{\oplus}{N}H + R_2NH \rightleftharpoons R_3N + R_2\overset{\oplus}{N}H_2$$

When it is desired to convert a primary or secondary amine directly to the quaternary salt (*exhaustive alkylation*), the rate can be increased by the addition of a nonnucleophilic strong base that serves to remove the proton from $RR'NH_2^+$ or $RR'R^2NH^+$ and thus liberates the amine to attack another molecule of RX.[866]

The conjugate bases of ammonia and of primary and secondary amines (NH_2^-, RNH^- R_2N^-) are sometimes used as nucleophiles,[867] including amide bases generated from organolithium reagents and amines (R_2NLi).[868] This is in contrast to the

[857]Faul, M.M.; Kobierski, M.E.; Kopach, M.E. *J. Org. Chem.* ***2003***, *68*, 5739.
[858]Cho, J.H.; Kim, B.M. *Tetrahedron Lett.* ***2002***, *43*, 1273.
[859]Salvatore, R.N.; Nagle, A.S.; Schmidt, S.E.; Jung, K.W. *Org. Lett.* ***1999***, *1*, 1893; Salvatore, R.N.; Schmidt, S.E.; Shin, S.I.; Nagle, A.S.; Worrell, J.H.; Jung, K.W. *Tetrahedron Lett.* ***2000***, *41*, 9705.
[860]Hayat, S.; Rahman, A.-U.; Choudhary, M.I.; Khan, K.M.; Schumann, W.; Bayer, E. *Tetrahedron* ***2001***, *57*, 9951.
[861]Srivastava, S.K.; Chauhan, P.M.S.; Bhaduri, A.P. *Synth. Commun.* ***1999***, *29*, 2085; Jaisinghani, H.G.; Khadilkar, B.M. *Synth. Commun.* ***1999***, *29*, 3693; Salvatore, R.N.; Nagle, A.S.; Jung, K.W. *J. Org. Chem.* ***2002***, *67*, 674.
[862]Murty, M.S.R.; Jyothirmai, B.; Krishna, P.R.; Yadav, J.S. *Synth. Commun.* ***2003***, *33*, 2483.
[863]Werner, E.A. *J. Chem. Soc.* ***1918***, *113*, 899.
[864]Chen, P.; Suh, D.J.; Smith, M.B. *J. Chem. Soc. Perkin Trans. 1* ***1995***, 1317; Deskus, J.; Fan, D.-p.; Smith. M.B. *Synth. Commun.* ***1998***, *28*, 1649.
[865]See Kumar, H.M.S.; Anjaneyulu, S.; Reddy, B.V.S.; Yadav, J.S. *Synlett.* ***1999***, 551.
[866]Sommer, H.Z.; Jackson, L.L. *J. Org. Chem.* ***1970***, *35*, 1558; Sommer, H.Z.; Lipp, H.I.; Jackson, L.L. *J. Org. Chem.* ***1971***, *36*, 824. See also, Chuang, T.-H.; Sharpless, K.B. *Org. Lett.* ***2000***, *2*, 3555.
[867]For a discussion of the mechanism of the reaction between a primary halide and Ph_2NLi, see DePue, J.S.; Collum, D.B. *J. Am. Chem. Soc.* ***1988***, *110*, 5524.
[868]Vitale, A.A.; Chiocconi, A.A. *J. Chem. Res. (S)* ***1996***, 336.

analogous methods **10-1**, **10-8**, **10-25**, and **10-26**. Pyrrole is converted to *N*-methylpyrrole with KOH, iodomethane in ionic liquids.[869] Primary alkyl, allylic, and benzylic bromides, iodides, and tosylates react with sodium bis(trimethylsilyl) amide to give derivatives that are easily hydrolyzed to produce amine salts in high overall yields.[870] Primary arylamines are easily alkylated, but diaryl- and triarylamines are very poor nucleophiles. However, the reaction has been carried out with diarylamines.[871] Sulfates or sulfonates can be used instead of halides. The reaction can be carried out intramolecularly to give cyclic amines, with three-, five-, and six-membered (but not four-membered) rings being easily prepared. Thus, 4-chloro-1-aminobutane treated with base gives pyrrolidine, and 2-chloroethylamine gives aziridine[872] (analogous to **10-9**):



Reduction of *N*-(3-bromopropyl) imines gives a bromo-amine *in situ*, which cyclizes to the aziridine.[873] Five-membered ring amines (pyrrolidines) can be prepared from alkenyl amines via treatment with *N*-chlorosuccinimide and then Bu_3SnH.[874] Internal addition of amine to allylic acetates, catalyzed by $Pd(PPh_3)_4$, leads to cyclic products via a S_N2' reaction.[875] Three-membered cyclic amines (aziridines) can be prepared from chiral conjugated amides via bromination and reaction with an amine.[876] Four-membered cyclic amines (azetidines) have been prepared in a different way:[877]

This reaction was also used to close five-, six-, and seven-membered rings.

As usual, tertiary substrates do not give the reaction at all but undergo preferential elimination. However, tertiary (but not primary or secondary) halides R_3CCl can be converted to primary amines R_3CNH_2 by treatment with NCl_3 and $AlCl_3$[878] in a reaction related to **10-39**.

[869]In bmim PF_6, 1-butyl-3-methylimidazolium hexafluorophosphate: Le, Z.-G.; Chen, Z.-C.; Hu, Y.; Zheng, Q.-G. *Synthesis* ***2004***, 1951.
[870]Bestmann, H.J.; Wölfel, G. *Chem. Ber.* ***1984***, *117*, 1250.
[871]Patai, S.; Weiss, S. *J. Chem. Soc.* ***1959***, 1035.
[872]For a review of aziridine formation by this method, see Dermer, O.C.; Ham, G.E. *Ethylenimine and Other Aziridines*, Academc Press, NY, ***1969***, pp. 1–59.
[873]DeKimpe, N.; DeSmaele, D. *Tetrahedron Lett.*, ***1994***, *35*, 8023. Also see, De Kimpe, N.; Boelens, M.; Piqueur, J.; Baele, J. *Tetrahedron Lett.* ***1994***, *35*, 1925.
[874]Tokuda, M.; Fujita, H.; Suginome, H. *J. Chem. Soc. Perkin Trans. 1* ***1994***, 777.
[875]Grellier, M.; Pfeffer, M.; van Koten, G. *Tetrahedron Lett.* ***1994***, *35*, 2877.
[876]Garner, P.; Dogan, O.; Pillai, S. *Tetrahedron Lett.*,**1994**, 35, 1653.
[877]Juaristi, E.; Madrigal, D. *Tetrahedron* ***1989***, *45*, 629.
[878]Strand, J.W.; Kovacic, M.K. *J. Am. Chem. Soc.* ***1973***, *95*, 2977.

Amines can be *N*-alkylated by reaction with alcohols, in a sealed tube with microwave irradiation,[879] by ruthenium-catalyzed,[880] palladium-[881] or iridium-catalyzed[882] reactions. Heating indoles with benzylic alcohols in the presence of $Me_3P{=}CH(CN)$ give the *N*-benzylindole.[883] Heating an alcohol on γ-Al_2O_3 leads to an amine,[884] as does treatment with the amine, $SnCl_2$ and $Pd(PPh_3)_4$.[885] The palladium-catalyzed displacement of allylic acetates leads to allylic amines.[886] Chlorodiethylaluminum (Et_2AlCl), with a Cu(II) catalysts can be used to prepare *N*-ethylaniline derivatives.[887] *tert*-Butylamines can be prepared from isobutylene, HBr and the amine by heating a sealed tube.[888]

Phosphines behave similarly, and compounds of the type R_3P and $R_4P^+ X^-$ can be so prepared.[889] The reaction between triphenylphosphine and quaternary salts of nitrogen heterocycles in an aprotic solvent is probably the best way of dealkylating the heterocycles, for example,[890]

Primary amines can be prepared from alkyl halides by the use of hexamethylenetetramine[891] followed by cleavage of the resulting salt with ethanolic HCl. The method, called the *Delépine reaction*, is most successful for active halides such as allylic and benzylic halides and α-halo ketones, and for primary

A convenient way of obtaining secondary amines without contamination by primary or tertiary amines involves treatment of alkyl halides with the sodium or

[879]Jiang, Y.-L.; Hu, Y.-Q.; Feng, S.-Q.; Wu, J.-S.; Wu, Z.-W.; Yuan, Y.-C.; Liu, J.-M.; Hao, Q.-S.; Li, D.-P. *Synth. Commun.* ***1996***, *26*, 161.

[880]Watanabe, Y.; Morisaki, Y.; Kondo, T.; Mitsudo, T. *J. Org. Chem.* ***1996***, *61*, 4214.

[881]Yang, S.-C.; Yu, C.-L.; Tsai, Y.-C. *Tetrahedron Lett.* ***2000***, *41*, 7097; Shue, Y.-J.; Yang, S.-C.; Lai, H.-C. *Tetrahedron Lett.* ***2003***, *44*, 1481; Kimura, M.; Futamata, M.; Shibata, K.; Tamaru, Y. *Chem. Commun.* ***2003***, 234.

[882]Takeuchi, R.; Ue, N.; Tanabe, K.; Yamashita, K.; Shiga, N. *J. Am. Chem. Soc.* ***2001***, *123*, 9525; Fujita, K.-i.; Li, Z.; Ozeki, N.; Yamaguchi, R. *Tetrahedron Lett.* ***2003***, *44*, 2687.

[883]Bombrun, A.; Casi, G. *Tetrahedron Lett.* ***2002***, *43*, 2187.

[884]Valot, F.; Fache, F.; Jacquot, R.; Spagnol, M.; Lemaire, M. *Tetrahedron Lett.* ***1999***, *40*, 3689. For a zeolite mediated reaction that uses methyl acetate, see Selva, M.; Tundo, P.; Perosa, A. *J. Org. Chem.* ***2003***, *68*, 7374.

[885]Masuyama, Y.; Kagawa, M.; Kurusu, Y. *Chem. Lett.* ***1995***, 1121.

[886]Kodama, H.; Taiji, T.; Ohta, T.; Furukawa, I. *Synlett* ***2001***, 385; Feuerstein, M.; Laurenti, D.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* ***2001***, *42*, 2313; Watson, I.D.G.; Styler, S.A.; Yudin, A.K. *J. Am. Chem. Soc.* ***2004***, *126*, 5086; Ohta, T.; Sasayama, H.; Nakajima, O.; Kurahashi, N.; Fujii, J.; Furukawa, I. *Tetrahedron Asymmetry* ***2003***, *14*, 537. See also, Evans, P.A.; Robinson, J.E.; Moffett, K.K. *Org. Lett.* ***2001***, *3*, 3269. For a titanium-catalyzed variation see Mahrwald, R.; Quint, S. *Tetrahedron Lett.* ***2001***, *42*, 1655.

[887]Barton, D.H.R.; Doris, E. *Tetrahedron Lett.* ***1996***, *37*, 3295.

[888]Gage, J.R.; Wagner, J.M. *J. Org. Chem.* ***1995***, *60*, 2613.

[889]See Honaker, M.T.; Sandefur, B.J.; Hargett, J.L.; McDaniel, A.L.; Salvatore, R.N. *Tetrahedron Lett.* ***2003***, *44*, 8373.

[890]For example, see Deady, L.W.; Finlayson, W.L.; Korytsky, O.L. *Aust. J. Chem.* ***1979***, *32*, 1735.

[891]For a review of the reactions of this reagent, see Blažević, N.; Kolbah, D.; Belin, B.; Šunjić, V.; Kajfež, F. *Synthesis* ***1979***, 161.

calcium salt of cyanamide NH_2—CN to give disubstituted cyanamides, which are then hydrolyzed and decarboxylated to secondary amines. Good yields are obtained when the reaction is carried out under phase-transfer conditions.[892] The R group may be primary, secondary, allylic, or benzylic. 1,ω-Dihalides give cyclic secondary amines. Aminoboranes react with sulfonate esters to give a derivative that can be hydrolyzed to a tertiary amine.[893] An aminyl-radical cyclization process was used to prepare cyclic amines.[894]

N-Silylalkyl amines are formed from amines by reaction with halotrialkylsilanes and a suitable base.[895] Amines react directly with triarylsilanes in the presence of Yb catalysts.[896]

OS **I**, 23, 48, 102, 300, 488; **II**, 85, 183, 290, 328, 374, 397, 419, 563; **III**, 50, 148, 254, 256, 495, 504, 523, 705, 753, 774, 813, 848; **IV**, 84, 98, 383, 433, 466, 582, 585, 980; **V**, 88, 124, 306, 361, 434, 499, 541, 555, 608, 736, 751, 758, 769, 825, 883, 985, 989, 1018, 1085, 1145; **VI**, 56, 75, 104, 106, 175, 552, 652, 704, 818, 967; **VIII**, 9, 152, 231, 358. Also see, OS **II**, 395; **IV**, 950; OS **V**, 121; OS **I**, 203.

For *N*-arylation of amines see **13-5**.

10-32 Replacement of a Hydroxy or Alkoxy by an Amino Group

Amino-de-hydroxylation and Amino-de-alkoxylation

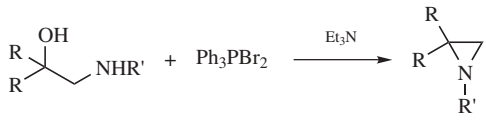
$$\mathrm{R{-}OH \longrightarrow R{-}NH_2}$$
$$\mathrm{Ar{-}OR' \longrightarrow R'{-}NH_2 + ArOH}$$

Alcohols can be converted to alkyl halides, which then react with amines (**10-43**). Alcohols react with various amine reagents that give products convertible to the amine.[897] The conversion ROH → RNH_2 can be accomplished for primary and secondary alcohols by treatment with hydrazoic acid (HN_3), diisopropyl azodicarboxylate (*i*Pr—OOCN=NCOO—*i*Pr), and excess Ph_3P in THF, followed by water or aqueous acid.[898] This is a type of Mitsunobu reaction (see **10-17**). Other

[892]Jończyk, A.; Ochal, Z.; Makosza, M. *Synthesis* ***1978***, 882.
[893]Thomas, S.; Huynh, T.; Enriquez-Rios, V.; Singaram, B. *Org. Lett.* ***2001***, *3*, 3915.
[894]Crich, D.; Shirai, M.; Rumthao, S. *Org. Lett.* ***2003***, *5*, 3767.
[895]Greene, T.W. *Protective Groups in Organic Synthesis* Wiley, NY, ***1980***, p. 283; Wuts, P.G.M.; Greene, T.W. *Protective Groups in Organic Synthesis 2nd ed.*, Wiley, NY, ***1991***, pp. 69–71; Wuts, P.G.M.; Greene, T.W. *Protective Groups in Organic Synthesis 3rd ed.*, Wiley, NY, ***1999***; Pratt, J.R.; Massey, W.D.; Pinkerton, F.H.; Thames, S.F. *J. Org. Chem.* ***1975***, *40*, 1090.
[896]Takaki, K.; Kamata, T.; Miura, Y.; Shishido, T.; Takehira, K. *J. Org. Chem.* ***1999***, *64*, 3891.
[897]See Laurent, M.; Marchand-Brynaert, J. *Synthesis* ***2000***, 667; Jirgensons, A.; Kauss, V.; Kalvinsh, I.; Gold, M.R. *Synthesis* ***2000***, 1709; Katritzky, A.R.; Huang, T.-B.; Voronkov, M.V. *J. Org. Chem.* ***2001***, *66*, 1043; Cami-Kobeci, G.; Williams, J.M.J. *Chem. Commun.* ***2004***, 1072. See also, Salehi, P.; Motlagh, A.R. *Synth. Commun.* ***2000***, *30*, 671; Lakouraj. M.M.; Movassagh, B.; Fasihi, J. *Synth. Commun.* ***2000***, *30*, 821.
[898]Fabiano, E.; Golding, B.T.; Sadeghi, M.M. *Synthesis* ***1987***, 190. See also, Klepacz, A.; Zwierzak, A. *Synth. Commun.* ***2001***, *31*, 1683.

alcohol-to-amine Mitsunobu reactions have also been reported.[899] Primary and secondary alcohols ROH (but not methanol) can be converted to tertiary amines,[900] R'_2NR, by treatment with the secondary amine R'_2NH and $(t\text{-BuO})_3Al$ in the presence of Raney nickel.[901] The use of aniline gives secondary amines PhNHR. Allylic alcohols ROH react with primary ($R'NH_2$) or secondary (R'_2NH) amines in the presence of platinum or palladium complexes, to give secondary ($RNHR'$) or tertiary (RNR'_2) allylic amines.[902] Conversion of an allyic alcohol to the corresp-sodning allylic crbonate, foolwed by reacatin with an *N*-tosylamine and lihtium hexamethyldisilazide, followedby by $Rh(PPh_3)_3Cl$ and $P(OMe)_3$, gives the *N*-tosylallylic amine.[903] α-Hydroxy phosphonates react with aniline on alumina with microwave irradiation.[904] The ruthenium-catalyzed reaction of amines and diols leads to cyclic amines.[905]

β-Amino alcohols give aziridines (**120**) when treated with triphenylphosphine dibromide in the presence of triethylamine.[906] The fact that inversion takes place at the OH carbon indicates that an S_N2 mechanism is involved, with $OPPh_3$ as the leaving group.



120

Alcohols can be converted to amines in an indirect manner.[907] The alcohols are converted to alkyloxyphosphonium perchlorates which in DMF successfully

[899]See, for example, Henry, J.R.; Marcin, L.R.; McIntosh, M.C.; Scola, P.M.; Harris Jr., G.D.; Weinreb, S.M. *Tetrahedron Lett.* ***1989***, *30*, 5709; Edwards, M.L.; Stemerick, D.M.; McCarthy, J.R. *Tetrahedron Lett.* ***1990***, *31*, 3417.

[900]For other methods of converting certain alcohols to secondary and tertiary amines, see Murahashi, S.; Kondo, K.; Hakata, T. *Tetrahedron Lett.* ***1982***, *23*, 229; Baiker, A.; Richarz, W. *Tetrahedron Lett.* ***1977***, 1937; *Helv. Chim. Acta* ***1978***, *61*, 1169; *Synth. Commun.* ***1978***, *8*, 27; Grigg, R.; Mitchell, T.R.B.; Sutthivaiyakit, S.; Tongpenyai, N. *J. Chem. Soc., Chem. Commun.* ***1981***, 611; Arcelli, A.; Bui-The-Khai; Porzi, G. *J. Organomet. Chem.* ***1982***, *235*, 93; Kelly, J.W.; Eskew, N.L.; Evans, Jr., S.A. *J. Org. Chem.* ***1986***, *51*, 95; Huh, K.; Tsuji, Y.; Kobayashi, M.; Okuda, F.; Watanabe, Y. *Chem. Lett.* ***1988***, 449.

[901]Botta, M.; De Angelis, F.; Nicoletti, R. *Synthesis* ***1977***, 722.

[902]Atkins, K.E.; Walker, W.E.; Manyik, R.M. *Tetrahedron Lett.* ***1970***, 3821; Tsuji, Y.; Takeuchi, R.; Ogawa, H.; Watanabe, Y. *Chem. Lett.* ***1986***, 293.

[903]Evans, P.A.; Robinson, J.E.; Nelson, J.D. *J. Am. Chem. Soc.* ***1999***, *121*, 6761.

[904]Kaboudin, B. *Tetrahedron Lett.* ***2003***, *44*, 1051.

[905]Fujita, K.-i.; Fujii, T.; Yamaguchi, R. *Org. Lett.* ***2004***, *6*, 3525.

[906]Okada, I.; Ichimura, K.; Sudo, R. *Bull. Chem. Soc. Jpn.* ***1970***, *43*, 1185. See also, Pfister, J.R. *Synthesis* ***1984***, 969; Suzuki, H.; Tani, H. *Chem. Lett.* ***1984***, 2129; Marsella, J.A. *J. Org. Chem.* ***1987***, *52*, 467.

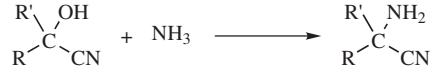
[907]For some other indirect methods, see White, E.H.; Ellinger, C.A. *J. Am. Chem. Soc.* ***1965***, *87*, 5261; Burgess, E.M.; Penton Jr., H.R.; Taylor, E.A. *J. Am. Chem. Soc.* ***1970***, *92*, 5224; Hendrickson, J.B.; Joffee, I. *J. Am. Chem. Soc.* ***1973***, *95*, 4083; Trost, B.M.; Keinan, E. *J. Org. Chem.* ***1979***, *44*, 3451; Koziara, A.; Osowska-Pacewicka, K.; Zawadzki, S.; Zwierzak, A. *Synthesis* ***1985***, 202; ***1987***, 487.

monoalkylate not only secondary but also primary amines.[908]

$$\mathrm{ROH} \xrightarrow[2.\ \mathrm{NH_4ClO_4}]{1.\ \mathrm{CCl_4{-}P(NMe_2)_3}} \mathrm{RO^{\oplus}P(NMe_2)_3\ ^{\ominus}ClO_4} \xrightarrow[\mathrm{R'R''NH}]{\mathrm{DMF}} \mathrm{RR'R''N + OP(NMe_2)_3}$$

Thus by this means secondary as well as tertiary amines can be prepared in good yields. Benzylic alcohols can be converted to an azide and then treated with triphenylphosphine to give the amine (**19-50**).[909]

Cyanohydrins can be converted to amines by treatment with ammonia. The use of primary or secondary amines instead of ammonia leads to secondary and tertiary cyanoamines, respectively. It is more common to perform the conversion of an aldehyde or ketone directly to the cyanoamine without isolation of the cyanohydrin (see **16-52**). α-Hydroxy ketones (acyloins and benzoins) behave similarly.[910]



A solution of the sodium salt of *N*-methylaniline in HMPA can be used to cleave the methyl group from aryl methyl ethers:[911] $\mathrm{ArOMe + PhNMe^- \rightarrow ArO^- + PhNMe_2}$. This reagent also cleaves benzylic groups. In a similar reaction, methyl groups of aryl methyl ethers can be cleaved with lithium diphenylphosphide, $\mathrm{Ph_2PLi}$.[912] This reaction is specific for methyl ethers and can be carried out in the presence of ethyl ethers with high selectivity. Phenyl allyl ethers react with secondary amines in the presence of a palladium catalyst to give phenol and the tertiary allyl amine.[913]

OS **II**, 29, 231; **IV**, 91, 283; **VI**, 567, 788; **VII**, 501. Also see, OS **I**, 473; **III**, 272, 471.

10-33 Transamination

Alkylamino-de-amination

$$\mathrm{RNH_2 + R'NH^- \longrightarrow RR'NH + NH_2^-}$$

Where the nucleophile is the conjugate base of a primary amine, $\mathrm{NH_2}$ can be a leaving group. The method has been used to prepare secondary amines.[914] In another process, primary amines are converted to secondary amines in which

[908]Castro, B.; Selve, C. *Bull. Soc. Chim. Fr.* ***1971***, 4368. For a similar method, see Tanigawa, Y.; Murahashi, S.; Moritani, I. *Tetrahedron Lett.* ***1975***, 471.
[909]Reddy, G.V.S.; Rao, G.V.; Subrmanyam, R.V.K.; Iyengar, D.S. *Synth. Commun.* ***2000***, *30*, 2233.
[910]For example, see Klemmensen, P.; Schroll, G.; Lawesson, S. *Ark. Kemi*, ***1968***, *28*, 405.
[911]Loubinoux, B.; Coudert, G.; Guillaumet, G. *Synthesis* ***1980***, 638.
[912]Ireland, R.E.; Walba, D.M. *Org. Synth.* ***VI***, 567.
[913]Widehem, R.; Lacroix, T.; Bricout, H.; Monflier, E. *Synlett* ***2000***, 722.
[914]Baltzly, R.; Blackman, S.W. *J. Org. Chem.* ***1963***, *28*, 1158.

both R groups are the same ($2\ RNH_2 \rightarrow R_2NH + NH_3$)[915] by refluxing in xylene in the presence of Raney nickel.[916] Quaternary salts can be dealkylated with ethanolamine.[917]

$$R_4N^+ + NH_2CH_2CH_2OH \longrightarrow R_3N + \overset{\oplus}{R}NH_2CH_2CH_2OH$$

In this reaction, methyl groups are cleaved in preference to other saturated alkyl groups. A similar reaction takes place between a Mannich base (see **16-19**) and a secondary amine, where the mechanism is elimination–addition (see p. 477). See also, **19-5**.

OS **V**, 1018.

10-34 Alkylation of Amines With Diazo Compounds

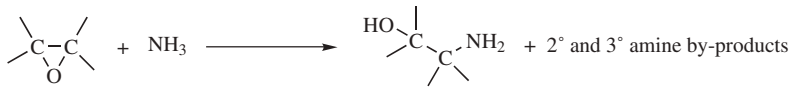
Hydro,dialkylamino-de-diazo-bisubstitution

$$CR_2N_2 + R'_2NH \xrightarrow{BF_3} CHR_2NR'_2$$

The reaction of diazo compounds with amines is similar to **10-11**.[918] The acidity of amines is not great enough for the reaction to proceed without a catalyst, but BF_3, which converts the amine to the $F_3B{-}NHR'_2$ complex, enables the reaction to take place. Cuprous cyanide can also be used as a catalyst.[919] The most common substrate is diazomethane,[630] in which case this is a method for the methylation of amines. Ammonia has been used as the amine but, as in the case of **10-31**, mixtures of primary, secondary, and tertiary amines are obtained. Primary aliphatic amines give mixtures of secondary and tertiary amines. Secondary amines give successful alkylation. Primary aromatic amines also give the reaction, but diaryl or arylalkylamines react very poorly.

10-35 Reaction of Epoxides With Nitrogen Reagents

(3)*OC-seco*-Amino-de-alkoxylation



[915]In a similar manner, a mixture of primary amines can be converted to a mixed secondary amine. For a review of the mechanism, see Geller, B.A. *Russ. Chem. Rev.* ***1978***, *47*, 297.

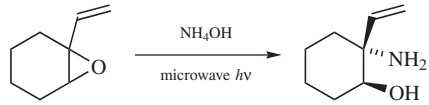
[916]De Angelis, F.; Grgurina, I.; Nicoletti, R. *Synthesis* ***1979***, 70; See also, Ballantine, J.A.; Purnell, H.; Rayanakorn, M.; Thomas, J.M.; Williams, K.J. *J. Chem. Soc., Chem. Commun.* ***1981***, 9; Arcelli, A.; Bui-The-Khai; Porzi, G. *J. Organomet. Chem.* ***1982***, *231*, C31; Jung, C.W.; Fellmann, J.D.; Garrou, P.E. *Organometallics* ***1983***, *2*, 1042; Tsuji, Y.; Shida, J.; Takeuchi, R.; Watanabe, Y. *Chem. Lett.* ***1984***, 889; Bank, S.; Jewett, R. *Tetrahedron Lett.* ***1991***, *32*, 303.

[917]Hünig, S.; Baron W. *Chem. Ber.* ***1957***, *90*, 395, 403.

[918]Müller, E.; Huber-Emden, H.; Rundel, W. *Liebigs Ann. Chem.* ***1959***, *623*, 34.

[919]Saegusa, T.; Ito, Y.; Kobayashi, S.; Hirota, K.; Shimizu, T. *Tetrahedron Lett.* ***1966***, 6131.

The reaction between epoxides and ammonia[920] (or ammonium hydroxide)[921] is a general and useful method for the preparation of β-hydroxyamines. With epoxide derived from terminal alkenes, the reaction with ammonia gives largely the primary amine, but secondary and tertiary amine products are possible from the appropriate epoxide. The reaction of **121** with ammonium hydroxide with microwave irradiation, for example, gave **122**.[922] Ethanolamines, which are useful solvents



121 **122**

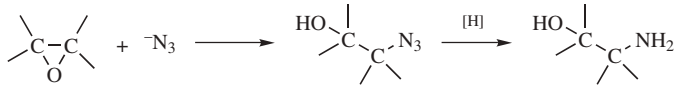
as well as synthetic precursors, are prepared by this reaction. Similar ring opening occurs with alkyl and aromatic amines.[923] For another way of accomplishing this conversion, see **10-40**. The reaction can be catalyzed with $Yb(OTf)_3$ and in the presence of (*R*)-BINOL (BINOL = 1,1′-bi-2-naphthol) gives amino alcohols with high asymmetric induction.[924] Many other metal-catalyzed ring-opening reactions have been reported.[925] Ring opening has been accomplished with aniline on silica gel.[926]

Primary and secondary amines give, respectively, secondary and tertiary amines (**121**). Aniline reacts with epoxides in the presence of aqueous β-cyclodextrin[927] in 5 *M* $LiClO_4$ in ether,[928] or in fluoro-alcohol solvents.[929] Aniline reacts with epoxides in the presence of a VCl_3 catalyst.[930] *N*-Boc-amine ($H_2N—CO_2t$-Bu) reacted

[920]For an example, see McManus, S.P.; Larson, C.A.; Hearn, R.A. *Synth. Commun.* ***1973***, *3*, 177; Charrada, B.; Hedhli, A.; Baklouti, A. *Tetrahedron Lett.* ***2000***, *41*, 7347.
[921]Pastó, M.; Rodríguez, B.; Riera, A.; Pericàs, M.A. *Tetrahedron Lett.* ***2003***, *44*, 8369.
[922]Lindström, U.M.; Olofsson, B.; Somfai, P. *Tetrahedron Lett.* ***1999***, *40*, 9273.
[923]See Harrack, Y.; Pujol, M.D. *Tetrahedron Lett.* ***2002***, *43*, 819; Steiner, D.; Sethofer, S.G.; Goralski, C.T.; Singaram, B. *Tetrahedron Asymmetry* ***2002***, *13*, 1477. For a reaction catalyzed by LiBr, see Chakraborti, A.K.; Rudrawar, S.; Kondaskar, A. *Eur. J. Org. Chem.* ***2004***, 3597.
[924]Hou, X.-L.; Wu, J.; Dai, L.-X.; Xia, L.-J.; Tang, M.-H. *Tetrahedron Asymmetry* ***1998***, *9*, 1747.
[925]Examples include, **$Sn(OTf)_2$**: Sekar, G.; Singh, V.K. *J. Org. Chem.* ***1999***, *64*, 287; **$CeCl_3$-NaI**: Reddy, L.R.; Reddy, M.A.; Bhanumathi, N.; Rao, K.R. *Synthesis* ***2001***, 831; **Zr catalysts**: Curini, M.; Epifano, F.; Marcotullio, M.C.; Rosati, O. *Eur. J. Org. Chem.* ***2001***, 4149 and Charkraborti, A.K.; Kondaskar, A. *Tetrahedron Lett.* ***2003***, *44*, 8315; **$LiNTf_2$**: Cossy, J.; Bellosta, V.; Hamoir, C.; Desmurs, J.-R. *Tetrahedron Lett.* ***2002***, *43*, 7083; **Bi compounds**: Ollevier, T.; Lavie-Compin, G. *Tetrahedron Lett.* ***2002***, *43*, 7891 and ***2004***, *45*, 49; **$ZnCl_2$:** Pachón, L.D.; Gamez, P.; van Brussel, J.J.M.; Reedijk, J. *Tetrahedron Lett.* ***2003***, *44*, 6025; **$InBr_3$:** Rodríguez, J.R.; Navarro, A. *Tetrahedron Lett.* ***2004***, *45*, 7495; **$SmI_2(thf)_2$:** Carrée, F.; Gil, R.; Collin, J. *Tetrahedron Lett.* ***2004***, *45*, 7749; **$CoCl_2$**: Sundararajan, G.; Viyayakrishna, K.; Varghese, B. *Tetrahedron Lett.* ***2004***, *45*, 8253.
[926]Chakraborti, A.K.; Rudrawar, S.; Kondaskar, A. *Org. Biomol. Chem.* ***2004***, *2*, 1277.
[927]Reddy, L.R.; Reddy, M.A.; Chanumathi, N.; Rao, K.R. *Synlett* ***2000***, 339.
[928]Heydar, A.; Mehrdad, M.; Malecki, A.; Ahmadi, N. *Synthesis* ***2004***, 1563.
[929]Das, U.; Crousse, B.; Kesavan, V.; Bonnet-Delpon, D.; Bégue, J.P. *J. Org. Chem.* ***2000***, *65*, 6749.
[930]Sabitha, G.; Reddy, G.S.K.K.; Reddy, K.B.; Yadav, J.S. *Synthesis* ***2003***, 2298.

with epoxides in the presence of a cobalt–salen catalyst to give the amido alcohol.[931] Solvent free reactions using a catalytic amount of $SnCl_4$ are known.[932] Tetrahydropyrimidones can be used to mediate the addition of indole to epoxides.[933] Amide bases react differently with epoxides. Lithium tetramethylpiperidide (LTMP), for example, reacted with epoxides, but the product was the corresponding enamine.[934] This latter reaction follows a very different mechanism. Initial formation of the lithio-epoxide is followed by rearrangement to give the aldehyde,[935] and subsequent reaction with the amine by-product of the lithiation leads to the enamine.

An indirect method for generating an amino alcohol (**124**) is to open an epoxide with azide to give the azido-alcohol **123**,[936] and subsequent reduction (**19-50**) gives the amine group.[937] Sodium azide and Oxone® react with epoxides to give an azido-alcohol.[938] Under Mitsunobu conditions (**10-17**), epoxides are converted to 1,2-diazides with HN_3.[939] The reaction of trimethylsilyl azide and an epoxide was reported using an ionic solvent.[940] The cerium ammonium nitrate catalyzed reaction of epoxides and sodium azide, for example, gave the azido alcohol with selectivity for the azide group on the more substituted position.[941] Cerium chloride has also been used, giving the azide on the less substituted carbon.[942] Manganese–salen complexes, immobilized on mesoporous material has also been used to mediate the ring opening of epoxides by azide.[943] In the presence of $AlCl_3$ in water at pH 4, sodium azide reacts with epxoy acids to give the β-azido-α-hydroxycarboxylic acid.[944] Silylazides can be used as well.[945]



123 **124**

[931]Bartoli, G.; Bosco, M.; Carlone, A.; Locatelli, M.; Mechiorre, P.; Sambri, L. *Org. Lett.* ***2004***, *6*, 3973.
[932]Zhao, P.-Q.; Xu, L.-W.; Xia, C.-G. *Synlett* ***2004***, 846.
[933]Fink, D.M. *Synlett* ***2004***, 2394.
[934]Hodgson, D.M.; Bray, C.D.; Kindon, N.D. *J. Am. Chem. Soc.* ***2004***, *126*, 6870.
[935]Yanagisawa, A.; Yasue, K.; Yamamoto, H. *J. Chem. Soc., Chem. Commun.* ***1994***, 2103.
[936]Kazemi, F.; Kiasat, A.R.; Ebrahimi, S. *Synth. Commun.* ***2003***, *33*, 999. For a reaction done under phase-transfer conditions, see Tamami, B.; Mahdavi, H. *Tetrahedron Lett.* ***2001***, *42*, 8721.
[937]Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley–VCH, NY, ***1999***, p. 815.
[938]Sabitha, G.; Babu, R.S.; Reddy, M.S.K.; Yadav, J.S. *Synthesis* ***2002***, 2254.
[939]Göksu, S.; Soçen, H.; Sütbeyaz, Y. *Synthesis* ***2002***, 2373.
[940]In emim, 1-ethyl-3-methylimidazolium: Song, C.E.; Oh, C.R.; Roh, E.J.; Choo, D.J. *Chem. Commun.* ***2000***, 1743.
[941]Iranpoor, N.; Kazemi, F. *Synth. Commun.* ***1999***, *29*, 561.
[942]Sabitha, G.; Babu, R.S.; Rajkumar, M.; Yadav, J.S. *Org. Lett.* ***2002***, *4*, 343.
[943]Kantam, M.L.; Choudary, B.M.; Bharathi, B. *Synth. Commun.* ***1999***, *29*, 1121.
[944]Fringuelli, F.; Pizzo, F.; Vaccaro, L. *Tetrahedron Lett.* ***2001***, *42*, 1131.
[945]Schneider, C. *Synlett* ***2000***, 1840.

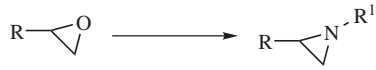
Sodium nitrate ($NaNO_2$) reacts with epoxides in the presence of $MgSO_4$ to give the nitro alcohol.[946] The nitro group can also be reduced to give the amine (**19-45**).[947]

Episulfides, which can be generated *in situ* in various ways, react similarly to give β-amino thiols,[948] and aziridines react with amines to give 1,2-diamines (**10-38**). Triphenylphosphine similarly reacts with epoxides to give an intermediate that undergoes elimination to give alkenes (see the Wittig reaction, **16-44**).

OS **X**, 29. See OS **VI**, 652 for a related reaction.

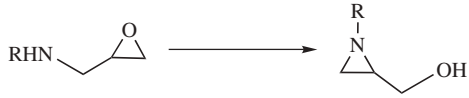
10-36 Formation of Aziridines from Epoxides

Amino-de-alkoxylation



It is possible to prepare aziridines, which are synthetically important molecules, directly from the corresponding epoxide. Reaction of $Ph_3P{=}NPh$ with an epoxide in the presence of $ZnCl_2$ gives the *N*-phenyl aziridine.[949] Guanidines have also been used to prepare aziridnes from epoxides.[950] Tosylamines react with epoxides to give the *N*-tosylaziridine.[951]

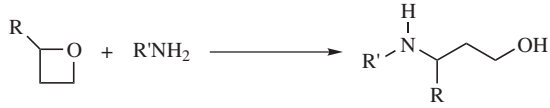
Various methods are available to convert an aminomethyl epoxide to a hydroxymethyl aziridine, **125**[952]



125

10-37 Amination of Oxetanes

(4)*OC-homoseco*-Amino-de-alkoxylation



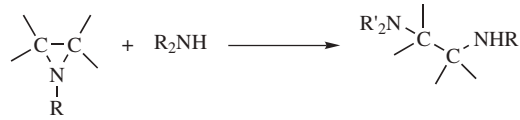
Oxetanes are significantly less reactive with nucleophiles due to diminished ring strain. Under certain conditions, however, amines can open oxetanes to give amino

[946]Kalita, B.; Barua, N.C.; Bezbarua, M.; Bez, G. *Synlett* ***2001***, 1411.
[947]Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, p. 821.
[948]Dong, Q.; Fang, X.; Schroeder, J.D.; Garvey, D.S. *Synthesis* ***1999***, 1106.
[949]Kühnau, D.; Thomsen, I.; Jørgensen, K.A. *J. Chem. Soc. Perkin Trans. 1*, ***1996***, 1167.
[950]Tsuchiya, Y.; Kumamoto, T.; Ishikawa, T. *J. Org. Chem.* ***2004***, *69*, 8504.
[951]Albanese, D.; Landini, D.; Penso, M.; Petricci, S. *Tetrahedron* ***1999***, *55*, 6387.
[952]Najime, R.; Pilard, S.; Vaultier, M. *Tetrahedron Lett.* ***1992***, *33*, 5351; Moulines, J.; Bats, J.-P.; Hautefaye, P.; Nuhrich, A.; Lamidey, A.-M. *Tetrahedron Lett.* ***1993***, *34*, 2315; Moulines, J.; Charpentier, P.; Bats, J.-P.; Nuhrich, A.; Lamidey, A.-M. *Tetrahedron Lett.* ***1992***, *33*, 487.

alcohols. *tert*-Butylamine reacts with oxetanes in the presence of $Yb(OTf)_3$, for example, to give 3-hydroxy amines.[953] Lithium tetrafluoroborate has also been used for this purpose.[954]

10-38 Reaction of Aziridines With Nitrogen

(3)*NC-seco*-Amino-de-aminoalkylation



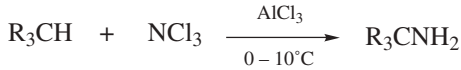
Just as epoxides can be opened by amines to give hydroxy amines, aziridines can be opened to give diamines.[955] With bicyclic aziridines, the major product is usually the trans diamine. *N*-Aryl or *N*-alkyl aziridines react with amines in the presence of $Sn(OTf)_2$[956] or $B(C_6F_5)_3$[957] to give the diamine. Amines react with *N*-tosylaziridines, in the presence of various catalysts or additives to give the corresponding diamine.[958] This reaction also takes place on activated silica.[959] The reaction of $LiNTf_2$ and an amine, in the presence of an *N*-alkyl aziridine gives the diamine.[960]

As with epoxides, tosyl-aziridines react with azide to generate azido tosylamines.[961] Reduction of the azide (**19-50**) gives the diamine. Silylazides, such as Me_3SiN_3, also react with aziridine derivatives to give the azidoamine.[962] This latter reaction can be catalyzed by $InCl_3$.[963]

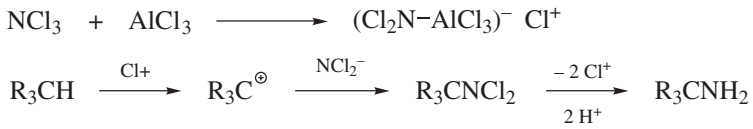
[953]Crotti, P.; Favero, L.; Macchia, F.; Pineschi, M. *Tetrahedron Lett.* ***1994***, *35*, 7089.
[954]Chini, M.; Crotti, P.; Favero, L.; Macchia, F. *Tetrahedron Lett.* ***1994***, *35*, 761.
[955]For a review, see Dermer, O.C.; Ham, G.E. *Ethylenimine and Other Aziridines*, Academic Press, NY, ***1969***, pp. 262–268. See also, Scheuermann, J.E.W.; Ilyashenko, G.; Griffiths, D.V.; Watkinson, M. *Tetrahedron Asymmetry* ***2002***, *13*, 269.
[956]Sekar, G.; Singh, V.K. *J. Org. Chem.* ***1999***, *64*, 2537.
[957]Watson, I.D.G.; Yudin, A.K. *J. Org. Chem.* ***2003***, *68*, 5160.
[958]Examples include **$Yb(OTf)_3$**: Meguro, M.; Yamamoto, Y. *Heterocycles* ***1996***, *43*, 2473. **PBu_3**: Fan, R.-H.; Hou, X-L. *J. Org. Chem.* ***2003***, *68*, 726. **Aqueous media with β-cyclodextrin:** Reddy, M.A.; Reddy, L.R.; Bhanamathi, N.; Rao, K.R. *Chem. Lett.* ***2001***, 246. **$TaCl_5/SiO_2$:** Chandrasekhar, S.; Prakash, S.J.; Shyamsunder, T.; Ramachandar, T. *Synth. Commun.* ***2004***, *34*, 3865. **$InCl_3$**: Yadav, J.S.; Reddy, B.V.S.; Abraham, S.; Sabitha, G. *Tetrahedron Lett.* ***2002***, *43*, 1565; **$InBr_3$:** Yadav, J.S.; Reddy, B.V.S.; Rao, K.; Raj, K.S.; Prasad, A.R. *Synthesis* ***2002***, 1061. **$BiCl_3$:** Swamy, N.R.; Venkateswarlu, Y. *Synth. Commun.* ***2003***, *33*, 547. **$LiClO_4$**: Yadav, J.S.; Reddy, B.V.S.; Jyothivmai, B.; Murty, M.S.R. *Synlett* ***2002***, 53; Yadav, J.S.; Reddy, B.V.S.; Parimala, G.; Reddy, P.V. *Synthesis* ***2002***, 2383.
[959]Anand, R.V.; Pandey, G.; Singh, V.K. *Tetrahedron Lett.* ***2002***, *43*, 3975; Kumar, G.D.K.; Baskaran, S. *Synlett* ***2004***, 1719.
[960]Cossy, J.; Bellosta, V.; Alauze, V.; Desmurs, J.-R. *Synthesis* ***2002***, 2211.
[961]Bisai, A.; Pandey, G.; Pandey, M.K.; Singh, V.K. *Tetrahedron Lett.* ***2003***, *44*, 5839.
[962]Chandrasekhar, M.; Sekar, G.; Singh, V.K. *Tetrahedron Lett.* ***2000***, *41*, 10079.
[963]Yadav, J.S.; Reddy, B.V.S.; Kumar, G.M.; Murthy, Ch.V.S.R. *Synth. Commun.* ***2002***, *32*, 1797.

10-39 Amination of Alkanes

Amino-de-hydrogenation or Amination



Alkanes, arylalkanes, and cycloalkanes can be aminated, at tertiary positions only, by treatment with trichloroamine and aluminum chloride at 0–10°C.[964] For example, *p*-$MeC_6H_4CHMe_2$ gives *p*-$MeC_6H_4CMe_2NH_2$, methylcyclopentane gives 1-amino-1-methylcyclopentane, and adamantane gives 1-aminoadamantane, all in good yields. This is a useful reaction, since there are not many other methods for the preparation of *tert*-alkyl amines. The mechanism has been rationalized as an S_N1 process with H^- as the leaving group:[964]

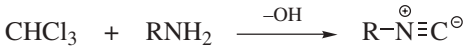


It is noted than under photochemical conditions, ammonia opens cyclopropane derivatives to give the corresponding alkyl amine.[965] See also, **12-12**.

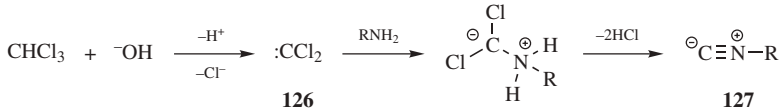
OS **V**, 35.

10-40 Formation of Isocyanides (Isonitriles)

Haloform-isocyanide transformation



Reaction with chloroform under basic conditions is a common test for primary amines, both aliphatic and aromatic, since isocyanides (**126**) have very strong bad odors. The reaction probably proceeds by an S_N1cB mechanism with dichlorocarbene (**127**) as an intermediate.

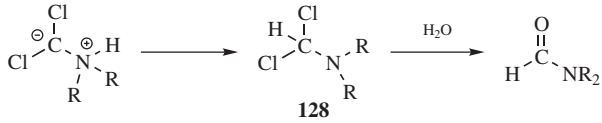


126 **127**

The reaction can also be used synthetically for the preparation of isocyanides, although yields are generally not high.[966] An improved procedure has been reported.[967] When

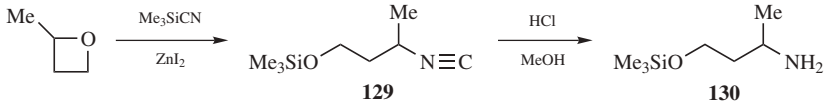
[964]Wnuk, T.A.; Chaudhary, S.S.; Kovacic, P. *J. Am. Chem. Soc.* ***1976***, *98*, 5678, and references cited therein.
[965]Yasuda, M.; Kojima, R.; Tsutsui, H.; Utsunomiya, D.; Ishii, K.; Jinnouchi, K.; Shiragami, T.; Yamashita, T. *J. Org. Chem.* ***2003***, *68*, 7618.
[966]For a review of isocyanides, see Periasamy, M.P.; Walborsky, H.M. *Org. Prep. Proced. Int.* ***1979***, *11*, 293.
[967]Weber, W.P.; Gokel, G.W. *Tetrahedron Lett.* ***1972***, 1637; Weber, W.P.; Gokel, G.W.; Ugi, I. *Angew. Chem. Int. Ed.* ***1972***, *11*, 530.

secondary amines are involved, the adduct **128** cannot lose 2 mol of HCl. Instead it is hydrolyzed to an *N,N*-disubstituted formamide.[968]



128

A completely different way of preparing isocyanides involves the reaction of epoxides or oxetanes with trimethylsilyl cyanide and zinc iodide to give the isocyanide **129**.[969]



129 **130**

The products can be hydrolyzed to protected hydroxy-amines, such as **130**.

OS **VI**, 232.

B. Attack by NHCOR

10-41 *N*-Alkylation or *N*-Arylation of Amides and Imides

Acylamino-de-halogenation

$$RX + {}^{\ominus}NHCOR' \longrightarrow RNHCOR'$$
$$ArX + {}^{\ominus}NHCOR' \longrightarrow ArNHCOR'$$

Amides are very weak nucleophiles,[970] far too weak to attack alkyl halides, so they must first be converted to their conjugate bases. By this method, unsubstituted amides can be converted to *N*-substituted, or *N*-substituted to *N,N*-disubstituted, amides.[971] Esters of sulfuric or sulfonic acids can also be substrates. Tertiary substrates give elimination. *O*-Alkylation is at times a side reaction.[972] Both amides and sulfonamides have been alkylated under phase-transfer conditions.[973] Lactams can be alkylated using similar procedures. Ethyl pyroglutamate (5-carboethoxy

[968]Saunders, M.; Murray, R.W. *Tetrahedron* ***1959***, *6*, 88; Frankel, M.B.; Feuer, H.; Bank, J. *Tetrahedron Lett.* ***1959***, no. 7, 5.

[969]Gassman, P.G.; Haberman, L.M. *Tetrahedron Lett.* ***1985***, *26*, 4971, and references cited therein.

[970]Brace, N.O. *J. Org. Chem.* ***1993***, *58*, 1804.

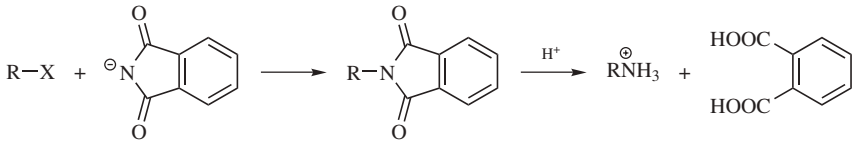
[971]For procedures, see Zawadzki, S.; Zwierzak, A. *Synthesis* ***1979***, 549; Yamawaki, J.; Ando, T.; Hanafusa, T. *Chem. Lett.* ***1981***, 1143; Sukata, K. *Bull. Chem. Soc. Jpn.* ***1985***, *58*, 838.

[972]For a review of alkylation of amides, see Challis, B.C.; Challis, J.A., in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 734–754.

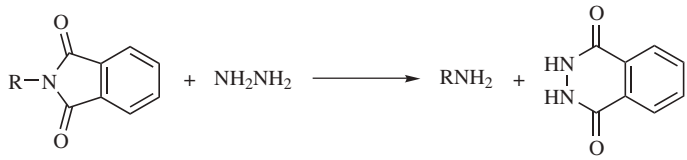
[973]Loupy, A.; Sansoulet, J.; Díez-Barra, E.; Carrillo, J.R. *Synth. Commun.* ***1992***, *22*, 1661; Salvatore, R.N.; Shin, S.I.; Flanders, V.L.; Jung, K.w. *Tetrahedron Lett.* ***2001***, *42*, 1799.

2-pyrrolidinone) and related lactams were converted to *N*-alkyl derivatives via treatment with NaH (short contact time) followed by addition of the halide.[974] 2-Pyrrolidinone derivatives can be alkylated using a similar procedure.[975] Lactams can be reductively alkylated using aldehydes under catalytic hydrogenation conditions (reductive alkylation).[976] *N*-Aryl lactams can be prepared using Ph_3Bi and $Cu(OAc)_2$.[977] *N*-Arylation of sulfonamides has been reported using a palladium catalysis.[978] *N*-Alkenyl amides have been prepared from vinyl iodides and primary amides, using 10% CuI and two equivalents of cesium carbonate.[979] A related palladium-catalyzed vinylation of lactams was repeated using vinyl ethers as a substrate.[980] Oxazolidin-2-ones (a cyclic carbamate) can be *N*-alkylated using an alkyl halide with KF/Al_2O_3.[981]

The *Gabriel synthesis*[982] for converting halides to primary amines is based on this reaction. The halide is treated with potassium phthalimide and the product hydrolyzed (**16-60**):



It is obvious that the primary amines formed in this reaction will be uncontaminated by secondary or tertiary amines (unlike **10-31**). The reaction is usually rather slow, but can be conveniently speeded by the use of a dipolar aprotic solvent, such as DMF[983] or with a crown ether.[984] Hydrolysis of the phthalimide, whether acid or base catalyzed (acid catalysis is used far more frequently), is also usually very slow, and better procedures are generally used. A common one is the *Ing–Manske procedure*,[985] in which the phthalimide is heated with hydrazine in an exchange



[974]Simandan, T.; Smith, M.B. *Synth. Commun.* ***1996***, *26*, 1827; Keusenkothen, P.F.; Smith, M.B. *Synth. Commun.* ***1992***, *22*, 2935.
[975]Liu, H.; Ko, S.-B.; Josien, H.; Curran, D.P. *Tetrahedron Lett.* ***1995***, *36*, 8917.
[976]Fache, F.; Jacquot, L.; Lemaire, M. *Tetrahedron Lett.* ***1994***, *35*, 3313.
[977]Chan, D.M.T. *Tetrahedron Lett.* ***1996***, *37*, 9013.
[978]Burton, G.; Cao, P.; Li, G.; Rivero, R. *Org. Lett.* ***2003***, *5*, 4373.
[979]Pan, X.; Cai, Q.; Ma, D. *Org. Lett.* ***2004***, *6*, 1809.
[980]Brice, J.L.; Meerdink, J.E.; Stahl, S.S. *Org. Lett.* ***2004***, *6*, 1845.
[981]Blass, B.E.; Drowns, M.; Harris, C.L.; Liu, S.; Portlock, D.E. *Tetrahedron Lett.* ***1999***, *40*, 6545.
[982]For a review, see Gibson, M.S.; Bradshaw, R.W. *Angew. Chem. Int. Ed.* ***1968***, *7*, 919.
[983]For example, see Sheehan, J.C.; Bolhofer, W.A. *J. Am. Chem. Soc.* ***1950***, *72*, 2786. See also, Landini, D.; Rolla, F. *Synthesis* ***1976***, 389.
[984]Soai, K.; Ookawa, A.; Kato, K. *Bull. Chem. Soc. Jpn.* ***1982***, *55*, 1671.
[985]Ing, H.R.; Manske, R.H.F. *J. Chem. Soc.* ***1926***, 2348.

reaction,[986] but other methods have been introduced, using Na_2S in aqueous THF or acetone,[987] $NaBH_4$-2-propanol followed by acetic acid;[988] and 40% aqueous methylamine.[989] *N*-aryl imides can be prepared from $ArPb(OAc)_3$ and NaH.[990]

An alternative to the Gabriel synthesis, in which alkyl halides can be converted to primary amines in good yields, involves treatment of the halide with the strong base guanidine followed by alkaline hydrolysis.[991] There are several alternative procedures.[992]

N-Alkyl amides or imides can also be prepared starting from alcohols by treatment of the latter with equimolar amounts of the amide or imide, Ph_3P, and diethyl azodicarboxylate (EtOOCN=NCOOEt) at room temperature (the Mitsunobu reaction, **10-17**).[993] A related reaction treats the alcohol with $ClCH{=}NMe_2^+Cl^-$, followed by potassium phthalimide and treatment with hydrazine give the amine.[994]

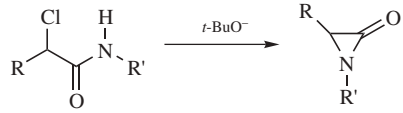
Amides can also be alkylated with diazo compounds, as in **10-34**. Salts of sulfonamides ($ArSO_2NH^-$) can be used to attack alkyl halides to prepare *N*-alkyl sulfonamides ($ArSO_2NHR$) that can be further alkylated to $ArSO_2NRR'$. Hydrolysis of the latter is a good method for the preparation of secondary amines. Secondary amines can also be made by crown ether assisted alkylation of $F_3CCONHR$ (R = alkyl or aryl) and hydrolysis of the resulting $F_3CCONRR'$.[995]

The reaction of a primary amide and benzaldehyde, in the presence of a silane and trifluoroacetic acid, leads to the corresponding *N*-benzylamide.[996] This transformation is a reductive alkylation. *N*-Alkynyl amides have been prepared by the copper-catalyzed reaction of 1-bromoalkynes and secondary amides.[997] 1-Haloalkynes

[986]See Khan, M.N. *J. Org. Chem.* ***1995***, *60*, 4536 for the kinetics of hydrazinolysis of phthalimides.
[987]Kukolja, S.; Lammert, S.R. *J. Am. Chem. Soc.* ***1975***, *97*, 5582.
[988]Osby, J.O.; Martin, M.G.; Ganem, B. *Tetrahedron Lett.* ***1984***, *25*, 2093.
[989]Wolfe, S.; Hasan, S.K. *Can. J. Chem.* ***1970***, *48*, 3572.
[990]López-Alvarado, P.; Avendaño, C.; Menéndez, J.C. *Tetrahedron Lett.* ***1992***, *33*, 6875.
[991]Hebrard, P.; Olomucki, M. *Bull. Soc. Chim. Fr.* ***1970***, 1938.
[992]For other methods, see Mukaiyama, T.; Taguchi, T.; Nishi, M. *Bull. Chem. Soc. Jpn.* ***1971***, *44*, 2797; Hendrickson, J.B.; Bergeron R.; Sternbach, D.D. *Tetrahedron* ***1975***, *31*, 2517; Clarke, C.T.; Elliott, J.D.; Jones, J.H. *J. Chem. Soc. Perkin Trans 1*, ***1978***, 1088; Mukaiyama, T.; Tsuji, T.; Watanabe, Y. *Chem. Lett.* ***1978***, 1057; Zwierzak, A.; Pilichowska, S. *Synthesis* ***1982***, 922; Calverley, M.J. *Synth. Commun.* ***1983***, *13*, 601; Harland, P.A.; Hodge, P.; Maughan, W.; Wildsmith, E. *Synthesis* ***1984***, 941; Grehn, L.; Ragnarsson, U. *Synthesis* ***1987***, 275; Dalla Croce, P.; La Rosa, C.; Ritieni, A. *J. Chem. Res. (S)* ***1988***, 346; Yinglin, H.; Hongwen, H. *Synthesis* ***1990***, 122.
[993]Mitsunobu, O.; Wada, M.; Sano, T. *J. Am. Chem. Soc.* ***1972***, *94*, 679; Grunewald, G.L.; Paradkar, V.M.; Pazhenchevsky, B.; Pleiss, M.A.; Sall, D.J.; Seibel, W.L.; Reitz, T.J. *J. Org. Chem.* ***1983***, *48*, 2321; Ślusarska, E.; Zwierzak, A. *Liebigs Ann. Chem.* ***1986***, 402; Kolasa, T.; Miller, M.J. *J. Org. Chem.* ***1987***, *52*, 4978; Sammes, P.G.; Thetford, D. *J. Chem. Soc. Perkin Trans. 1* ***1989***, 655.
[994]Barrett, A.G.M.; Braddock, D.C.; James, R.A.; Procopiou, P.A. *Chem. Commun.* ***1997***, 433.
[995]Nordlander, J.E.; Catalane, D.B.; Eberlein, T.H.; Farkas, L.V.; Howe, R.S.; Stevens, R.M.; Tripoulas, N.A. *Tetrahedron Lett.* ***1978***, 4987. For other methods, see Zwierzak, A.; Brylikowska-Piotrowicz, J. *Angew. Chem. Int. Ed.* ***1977***, *16*, 107; Briggs, E.M.; Brown, G.W.; Jiricny, J.; Meidine, M.F. *Synthesis* ***1980***, 295; Zwierzak, A.; Brylikowska-Piotrowicz, J. *Synthesis* ***1982***, 922
[996]Dubé, D.; Scholte, A.A. *Tetrahedron Lett.* ***1999***, *40*, 2295.
[997]Zhang, Y.; Hsung, R.P.; Tracey, M.R.; Kurtz, K.C.M.; Vera, E.L. *Org. Lett.* ***2004***, *6*, 1151; Frederick, M.O.; Mulder, J.A.; Tracey, M.R.; Hsung, R.P.; Huang, J.; Kurtz, K.C.M.; Shen, L.; Douglas, C.J. *J. Am. Chem. Soc.* ***2003***, *125*, 2368.

are typically prepared by base-induced elimination of 1,1-dihaloalkenes[998] or by direct halogenation of an alkyne with sodium or potassium hypohalite, prepared by reaction of the appropriate base with the halogen.[999]

Internal *N*-alkylation has been used to prepare the highly strained compounds α-lactams.[1000]



OS **I**, 119, 203, 271; **II**, 25, 83, 208; **III**, 151; **IV**, 810; **V**, 1064; **VI**, 951; **VII**, 501.

C. Other Nitrogen Nucleophiles

10-42 Formation of Nitro Compounds[1001]

Nitro-de-halogenation

$$RX + NO_2^- \longrightarrow RNO_2$$

Sodium nitrite can be used to prepare nitro compounds from primary or secondary alkyl bromides or iodides, but the method is of limited scope. Silver nitrite gives nitro compounds only when RX is a primary bromide or iodide.[1002] Nitrite esters are an important side product in all these cases (**10-22**) and become the major product (by an S_N1 mechanism) when secondary or tertiary halides are treated with silver nitrite. Alkyl nitro compounds can be prepared from the alkyl halide via the corresponding azide, by treatment with HOF in acetonitrile.[1003]

Nitro compounds can be prepared from alcohols using $NaNO_2$/AcOH/HCl.[1004]

OS **I**, 410; **IV**, 368, 454, 724.

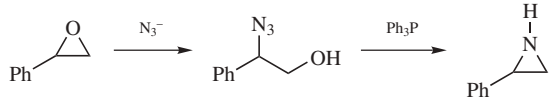
10-43 Formation of Azides

Azido-de-halogenation

$$RX + N_3^- \longrightarrow RN_3$$
$$RCOX + N_3^- \longrightarrow RCON_3$$

[998]For an example involving bromine see Bestmann, H.-J.; Frey, H. *Liebigs Ann. Chem.* ***1980***, *12*, 2061.
[999]For examples with hypobromite, see Mozūraitis, R.; Būda, V.; Liblikas, I.; Unelius, C.R.; Borg-Karlson, A.-K. *J. Chem. Ecol.* ***2002***, *28*, 1191; Barbu, E.; Tsibouklis, J. *Tetrahedron Lett.* ***1996***, *37*, 5023; Brandsma, L.; Verkruijsse, H.D *Synthesis* ***1990***, 984.
[1000]See Quast, H.; Leybach, H. *Chem. Ber.* ***1991***, *124*, 849. For a review of α-lactams, see Lengyel, I.; Sheehan, J.C. *Angew. Chem. Int. Ed.* ***1968***, *7*, 25.
[1001]For reviews, see Larson, H.O. in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, pt. 1, Wiley, NY, ***1969***, pp. 325–339; Kornblum, N. *Org. React.* ***1962***, *12*, 101.
[1002]See Ballini, R.; Barboni, L.; Giarlo, G. *J. Org. Chem.* ***2004***, *69*, 6907.
[1003]Rozen, S.; Carmeli, M. *J. Am. Chem. Soc.* ***2003***, *125*, 8118.
[1004]Baruah, A.; Kalita, B.; Barua, N.C. *Synlett* ***2000***, 1064.

Alkyl azides can be prepared by treatment of the appropriate halide with azide ion.[1005] Phase-transfer catalysis,[1006] ultrasound,[1007] and the use of reactive clays[1008] are important variations. Substrates other than alkyl halides have been used,[1009] including OH,[1010] OMs, OTs,[1011] and OAc.[1012] Epoxides react with NaN_3 (**10-35**), $SnCl_2$/Mg with NaN_3,[1013] $TMSN_3$ and Ph_4SbOH[1014] or SmI_2,[1015] or $(i\text{-Bu})_2AlHN_3Li$[1016] to give β-azido alcohols; these are easily converted to aziridines, **131**.[1017]



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This conversion has been used as a key step in the preparation of optically active aziridines from optically active 1,2-diols (prepared by **15-48**).[1018] Even hydrogen can be the leaving group. Benzylic hydrogens have been replaced by N_3 by treatment with HN_3 in $CHCl_3$ in the presence of DDQ (p. 1710).[1019]

Tertiary alkyl azides can be prepared by stirring tertiary alkyl chlorides with NaN_3 and $ZnCl_2$ in CS_2[1020] or by treating tertiary alcohols with NaN_3 and CF_3COOH[1021] or with HN_3 and $TiCl_4$[1022] or BF_3.[1023] Aryl azides can be prepared from aniline and aniline derivatives.[1024] Acyl azides, which can be used in the Curtius reaction (**18-14**),

[1005]For reviews, see Scriven, E.F.V.; Turnbull, K. *Chem. Rev.* ***1988***, *88*, 297; Biffin, M.E.C.; Miller, J.; Paul, D.B., in Patai, S. *The Chemistry of the Azido Group*, Wiley, NY, ***1971***, pp. 57–119; Alvarez, S.G.; Alvarez, M.T. *Synthesis* ***1997***, 413.

[1006]See Reeves, W.P.; Bahr, M.L. *Synthesis* ***1979***, 823; Marti, M.J.; Rico, I.; Ader, J.C.; de Savignac, A.; Lattes, A. *Tetrahedron Lett.* ***1989***, *30*, 1245.

[1007]Priebe, H. *Acta Chem. Scand. Ser. B*, ***1984***, *38*, 895.

[1008]See, for example, Varma, R.S.; Naicker, K.P.; Aschberger, J. *Synth. Commun.* ***1999***, *29*, 2823.

[1009]See, for example, Hojo, K.; Kobayashi, S.; Soai, K.; Ikeda, S.; Mukaiyama, T. *Chem. Lett.* ***1977***, 635; Murahashi, T.; Tanigawa, Y.; Imada, Y.; Taniguchi, Y. *Tetrahedron Lett.* ***1986***, *27*, 227.

[1010]See, for example, Yu, C.; Liu, B.; Hu, L. *Org. Lett.* ***2000***, *2*, 1959.

[1011]Scriven, E.F.V.; Turnbull, K. *Chem. Rev.* ***1988***, *88*, 297, see p. 306.

[1012]Murahashi, S.; Taniguchi, Y.; Imada, Y.; Tanigawa, Y. *J. Org. Chem.* ***1989***, *54*, 3292.

[1013]Sarangi, C.; Das, N.B.; Nanda, B.; Nayak, A.; Sharma, R.P. *J. Chem. Res. (S)* ***1997***, 378.

[1014]Fujiwara, M.; Tanaka, M.; Baba, A.; Ando, H.; Souma, Y. *Tetrahedron Lett.* ***1995***, *36*, 4849.

[1015]Van de Weghe, P.; Collin, J. *Tetrahedron Lett.* ***1995***, *36*, 1649.

[1016]Youn, Y.S.; Cho, I.S.; Chung, B.Y. *Tetrahedron Lett.* ***1998***, *39*, 4337.

[1017]See, for example, Ittah, Y.; Sasson, Y.; Shahak, I.; Tsaroom, S.; Blum, J. *J. Org. Chem.* ***1978***, *43*, 4271. For the mechanism of the conversion to aziridines, see Pöchlauer, P.; Müller, E.P.; Peringer, P. *Helv. Chim. Acta* ***1984***, *67*, 1238.

[1018]Lohray, B.B.; Gao, Y.; Sharpless, K.B. *Tetrahedron Lett.* ***1989***, *30*, 2623.

[1019]Guy, A.; Lemor, A.; Doussot, J.; Lemaire, M. *Synthesis* ***1988***, 900.

[1020]Miller, J.A. *Tetrahedron Lett.* ***1975***, 2959. See also, Koziara, A.; Zwierzak, A. *Tetrahedron Lett.* ***1987***, *28*, 6513.

[1021]Balderman, D.; Kalir, A. *Synthesis* ***1978***, 24.

[1022]Hassner, A.; Fibiger, R.; Andisik, D. *J. Org. Chem.* ***1984***, *49*, 4237.

[1023]See, for example, Adam, G.; Andrieux, J.; Plat, M. *Tetrahedron* ***1985***, *41*, 399.

[1024]Liu, Q.; Tor, Y. *Org. Lett.* ***2003***, *5*, 2571.

can be similarly prepared from acyl halides, anhydrides,[1025] esters,[1026] or other acyl derivatives.[1027] Acyl azides can also be prepared form aldehydes using $SiCl_4$/NaN_3—MnO_2,[1028] $TMSN_3/CrO_3$[1029] or the Dess–Martiin periodinane (see p. 1723) with NaN_3.[1030]

α-Azido ketones have been prepared from ketones via reaction with [hydroxy (*p*-nitrobenzenesulfonyloxy)iodo]benzene followed by reaction with sodium azide.[1031]

OS **III**, 846; **IV**, 715; **V**, 273, 586; **VI**, 95, 207, 210, 910; **VII**, 433; **VIII**, 116; **IX**, 220; **X**, 378. See also, OS **VII**, 206.

10-44 Formation of Isocyanates and Isothiocyanates

Isocyanato-de-halogenation

Isothiocyanato-de-halogenation

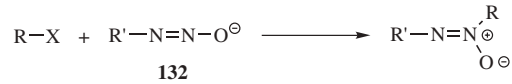
$$RX + NCO^- \longrightarrow RNCO$$
$$RX + NCS^- \longrightarrow RNCS$$

When the reagent is the thiocyanate ion, *S*-alkylation is an important side reaction (**10-30**), but the cyanate ion practically always gives exclusive *N*-alkylation.[478] Primary alkyl halides have been converted to isocyanates by treatment with sodium nitrocyanamide ($NaNCNNO_2$) and *m*-chloroperoxybenzoic acid, followed by heating of the initially produced $RN(NO_2)CN$.[1032] When alkyl halides are treated with NCO^- in the presence of ethanol, carbamates can be prepared directly (see **16-8**).[1033] Acyl halides give the corresponding acyl isocyanates and isothiocyanates.[1034] For the formation of isocyanides, see **10-75**.

OS **III**, 735.

10-45 Formation of Azoxy Compounds

Alkyl-*NNO*-azoxy-de-halogenation



132

[1025]For a review of acyl azides, see Lwowski, W., in Patai, S. *The Chemistry of the Azido Group*, Wiley, NY, ***1971***, pp. 503–554.
[1026]Rawal, V.H.; Zhong, H.M. *Tetrahedron Lett.* ***1994***, *35*, 4947.
[1027]Affandi, H.; Bayquen, A.V.; Read, R.W. *Tetrahedron Lett.* ***1994***, *35*, 2729. For a preparation using triphosgene, see Gumaste, V.K.; Bhawal, B.M.; Deshmukh, A.R.A.S. *Tetrahedron Lett.* ***2002***, *43*, 1345.
[1028]Elmorsy, S.S. *Tetrahedron Lett.* ***1995***, *36*, 1341.
[1029]Lee, J.G.; Kwak, K.H. *Tetrahedron Lett.* ***1992***, *33*, 3165.
[1030]Bose, D.S.; Reddy, A.V.N. *Tetrahedron Lett.* ***2003***, *44*, 3543.
[1031]Lee, J.C.; Kim, S.; Shin, W.C. *Synth. Commun.* ***2000***, *30*, 4271.
[1032]Manimaran, T.; Wolford, L.T.; Boyer, J.H. *J. Chem. Res. (S)* ***1989***, 331.
[1033]Argabright, P.A.; Rider, H.D.; Sieck, R. *J. Org. Chem.* ***1965***, *30*, 3317; Effenberger, F.; Drauz, K.; Förster, S.; Müller, W. *Chem. Ber.* ***1981***, *114*, 173.
[1034]For reviews of acyl isocyanates, see Tsuge, O., in Patai, S. *The Chemistry of Cyanates and Their Thio Derivatives*, pt. 1, Wiley, NY, ***1977***, pp. 445–506; Nuridzhanyan, K.A. *Russ. Chem. Rev.* ***1970***, *39*, 130; Lozinskii, M.O.; Pel'kis, P.S. *Russ. Chem. Rev.* ***1968***, *37*, 363.

The reaction between alkyl halides and alkanediazotates (**132**) gives azoxyalkanes.[1035] The R and R′ groups may be the same or different, but neither may be aryl or tertiary alkyl. The reaction is regioselective; only the isomer shown is obtained.

HALOGEN NUCLEOPHILES[1036]

10-46 Halide Exchange.

Halo-de-halogenation

$$RX + X'^{-} \rightleftharpoons RX' + X^{-}$$

Halide exchange, sometimes call the *Finkelstein reaction*, is an equilibrium process, but it is often possible to shift the equilibrium.[1037] The reaction is most often applied to the preparation of iodides and fluorides. Iodides can be prepared from chlorides or bromides by taking advantage of the fact that sodium iodide, but not the bromide or chloride, is soluble in acetone. When an alkyl chloride or bromide is treated with a solution of sodium iodide in acetone, the equilibrium is shifted by the precipitation of sodium chloride or bromide. Since the mechanism is S_N2, the reaction is much more successful for primary halides than for secondary or tertiary halides; sodium iodide in acetone can be used as a test for primary bromides or chlorides. Tertiary chlorides can be converted to iodides by treatment with excess NaI in CS_2, with $ZnCl_2$ as catalyst.[1038] Vinylic bromides give vinylic iodides with retention of configuration when treated with KI and a nickel bromide-zinc catalyst,[1039] or with KI and CuI in hot HMPA.[1040]

Fluorides[1041] are prepared by treatment of other alkyl halides with any of a number of fluorinating agents,[1042] among them anhydrous HF (which is useful only for

[1035]For reviews, see Yandovskii, V.N.; Gidaspov, B.V.; Tselinskii, I.V. *Russ. Chem. Rev.* ***1980***, *49*, 237; Moss, R.A. *Acc. Chem. Res.* ***1974***, *7*, 421.

[1036]For a review of the formation of carbon-halogen bonds, see Hudlický, M.; Hudlicky, T., in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement D*, pt. 2, Wiley, NY, ***1983***, pp. 1021–1172.

[1037]For a list of reagents for alkyl halide interconversion, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 667–671.

[1038]Miller, J.A.; Nunn, M.J. *J. Chem. Soc. Perkin Trans. 1* ***1976***, 416.

[1039]Takagi, K.; Hayama, N.; Inokawa, S. *Chem. Lett.* ***1978***, 1435.

[1040]Suzuki, H.; Aihara, M.; Yamamoto, H.; Takamoto, Y.; Ogawa, T. *Synthesis* ***1988***, 236.

[1041]For reviews of the introduction of fluorine into organic compounds, see Mann, J. *Chem. Soc. Rev.* ***1987***, *16*, 381; Rozen, S.; Filler, R. *Tetrahedron* ***1985***, *41*, 1111; Hudlický, M. *Chemistry of Organic Fluorine Compounds*, pt. 2, Ellis Horwood, Chichester, ***1976***, pp. 24–169; Sheppard, W.A.; Sharts, C.M., *Organic Fluorine Chemistry*, W.A. Benjamin, NY, ***1969***, pp. 52–184, 409–430.

[1042]For reviews of the use of halogen exchange to prepare alkyl fluorides, see Sharts, C.M.; Sheppard, W.A. *Org. React.* ***1974***, *21*, 125; Hudlický, M. *Chemistry of Organic Fluorine Compunds*, pt. 2, Ellis Horwood, Chichester, ***1976***, pp. 91–136.

reactive substrates, e.g., benzylic or allylic), AgF, KF,[1043] HgF_2, $Et_3N{\bullet}2HF$,[1044] 4-Me-$C_6H_4IF_2$,[1045] and $Me_2SiF_2Ph^+ \ ^-NBu_4$.[1046] The equilibria in these cases are shifted because the alkyl fluoride once formed has little tendency to react, owing to the extremely poor leaving-group ability of fluorine. Phase-transfer catalysis of the exchange reaction is a particularly effective way of preparing both fluorides and iodides.[1047]

Primary alkyl chlorides can be converted to bromides with ethyl bromide, *N*-methyl-2-pyrrolidinone and a catalytic amount of NaBr,[1048] with LiBr under phase-transfer conditions,[1049] and with $Bu_4N^+ \ Br^-$.[1050] Primary bromides were converted to chlorides with TMSCl/imidazole in hot DMF.[1051] For secondary and tertiary alkyl chlorides, treatment in CH_2Cl_2 with excess gaseous HBr and an anhydrous $FeBr_3$ catalyst has given high yields[1052] (this procedure is also successful for chloride-to-iodide conversions). Alkyl chlorides or bromides can be prepared from iodides by treatment with HCl or HBr in the presence of HNO_3, making use of the fact that the leaving I^- is oxidized to I_2 by the HNO_3.[1053] Primary iodides give the chlorides when treated with PCl_5 in $POCl_3$.[1054] Alkyl fluorides and chlorides are converted to the bromides and iodides (and alkyl fluorides to the chlorides) by heating with the corresponding HX in excess amounts.[1055]

OS **II**, 476; **IV**, 84, 525; **VIII**, 486; **IX**, 502.

10-47 Formation of Alkyl Halides from Esters of Sulfuric and Sulfonic Acids

Halo-de-sulfonyloxy-substitution, and so on

$$ROSO_2R' + X^- \longrightarrow RX$$

[1043]See Mąkosza, M.; Bujok, R. *Tetrahedron Lett.* ***2002***, *43*, 2761.
[1044]Giudicelli, M.B.; Picq, D.; Veyron B. *Tetrahedron Lett.* ***1990***, *31*, 6527. For an electrolytic procedure using $Et_3{\bullet}n$ HF see Sawaguchi, M.; Ayuba, S.; Nakamura, Y.; Fukuhara, J.; Hara, S.; Yoneda, N. *Synlett* ***2000***, 999.
[1045]Sawaguchi, M.; Hara, S.; Nakamura, Y.; Ayuba, S.; Kukuhara, T.; Yoneda, N. *Tetrahedron* ***2001***, 57, 3315.
[1046]Kvíala, J.; Mysík, P.; Paleta, O. *Synlett* ***2001***, 547.
[1047]For reviews, see Starks, C.M.; Liotta, C. *Phase Transfer Catalysis*, Academic Press, NY, ***1978***, pp. 112–125; Weber, W.P.; Gokel, G.W. *Phase Transfer Catalysis in Organic Synthesis*, Springer, NY, ***1977***, pp. 117–124. See also, Clark, J.H.; Macquarrie, D.J. *Tetrahedron Lett.* ***1987***, *28*, 111; Bram, G.; Loupy, A.; Pigeon, P. *Synth. Commun.* ***1988***, *18*, 1661.
[1048]Willy, W.E.; McKean, D.R.; Garcia, B.A. *Bull. Chem. Soc. Jpn.* ***1976***, *49*, 1989. See also, Babler, J.H.; Spina, K.P. *Synth. Commun.* ***1984***, *14*, 1313.
[1049]Loupy, A.; Pardo, C. *Synth. Commun.* ***1988***, *18*, 1275.
[1050]Bidd, I.; Whiting, M.C. *Tetrahedron Lett.* ***1984***, *25*, 5949.
[1051]Peyrat, J.-F.; Figadère, B.; Cavé, A. *Synth. Commun.* ***1996***, *26*, 4563.
[1052]Yoon, K.B.; Kochi, J.K. *J. Org. Chem.* ***1989***, *54*, 3028.
[1053]Svetlakov, N.V.; Moisak, I.E.; Averko-Antonovich, I.G. *J. Org. Chem. USSR* ***1969***, *5*, 971.
[1054]Bartley, J.P.; Carman, R.M.; Russell-Maynard, J.K.L. *Aust. J. Chem.* ***1985***, *38*, 1879.
[1055]Namavari, M.; Satyamurthy, N.; Phelps, M.E.; Barrio, J.R. *Tetrahedron Lett.* ***1990***, *31*, 4973.

Alkyl sulfates, tosylates, and other esters of sulfuric and sulfonic acids can be converted to alkyl halides with any of the four halide ions.[1056] Neopentyl tosylate reacts with Cl^-, Br^-, or I^- without rearrangement in HMPA.[1057] Similarly, allylic tosylates can be converted to chlorides without allylic rearrangement by reaction with LiCl in the same solvent.[1058] Inorganic esters are intermediates in the conversion of alcohols to alkyl halides with $SOCl_2$, PCl_5, PCl_3, and so on (**10-48**), but are seldom isolated.

OS **I**, 25; **II**, 111, 404; **IV**, 597, 753; **V**, 545.

10-48 Formation of Alkyl Halides from Alcohols

Halo-de-hydroxylation

$$ROH + HX \longrightarrow RX$$
$$ROH + SOCl_2 \longrightarrow RCl$$

Alcohols can be converted to alkyl halides with several reagents,[1059] the most common of which are halogen acids HX and inorganic acid halides, such as $SOCl_2$,[1060] PCl_5, PCl_3, and $POCl_3$.[1061] The reagent HBr is usually used for alkyl bromides[1062] and HI for alkyl iodides. These reagents are often generated *in situ* from the halide ion and an acid such as phosphoric or sulfuric. The use of HI sometimes results in reduction of the alkyl iodide to the alkane (**19–53**) and, if the substrate is unsaturated, can also reduce the double bond.[1063] The reaction can be used to prepare primary, secondary, or tertiary halides, but alcohols of the isobutyl or neopentyl type often give large amounts of rearrangement products.[1064] Tertiary chlorides are easily made with concentrated HCl, but primary and secondary alcohols react with HCl so slowly that a catalyst, usually zinc chloride, is required.[1065] Primary alcohols give good yields of chlorides upon treatment with HCl in

[1056]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 697–700.

[1057]Stephenson, B.; Solladié, G.; Mosher, H.S. *J. Am. Chem. Soc.* ***1974***, *96*, 3171.

[1058]Stork, G.; Grieco, P.A.; Gregson, M. *Tetrahedron Lett.* ***1969***, 1393.

[1059]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 689–697.

[1060]For a review of thionyl chloride ($SOCl_2$), see Pizey, J.S. *Synthetic Reagents*, Vol. 1, Wiley, NY, ***1974***, pp. 321–357. See Mohanazadeh, F.; Momeni, A.R. *Org. Prep. Proceed. Int.* ***1996***, *28*, 492 for the use of $SOCl_2$ on silica gel.

[1061]For a review, see Salomaa, P.; Kankaanperä, A.; Pihlaja, K., in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 1, Wiley, NY, ***1971***, pt. 1, pp. 595–622.

[1062]Mas, J.-M.; Metivier, P. *Synth. Commun.* ***1992***, *22*, 2187; Chong, J.M.; Heuft, M.A.; Rabbat, P. *J. Org. Chem.* ***2000***, *65*, 5837.

[1063]Jones, R.; Pattison, J.B. *J. Chem. Soc. C* ***1969***, 1046.

[1064]For a reaction using $CeCl_3 \bullet 7\ H_2O$ and NaI with neopentyl alcohol to give 2-iodo-2-methylbutane see Di Deo, M.; Marcantoni, E.; Torregiani, E.; Bartoli, G.; Bellucci, M. C.; Bosco, M.; Sambri, L. *J. Org. Chem.* ***2000***, *65*, 2830.

[1065]Phase-transfer catalysts have been used instead of $ZnCl_2$; Landini, D.; Montanari, F.; Rolla, F. *Synthesis* ***1974***, 37.

HMPA.[1066] The inorganic acid chlorides $SOCl_2$,[1067] PCl_3, and so on, give primary, secondary, or tertiary alkyl chlorides with much less rearrangement than is observed with HCl. Iodides have been prepared by simply heating the alcohol with iodine.[1068] Trichloroisocyanuric acid (1,3,5-trichlorohexahydrotriazin-2,4,6-trione) and triphenylphosphine converts primary alcohols to the corresponding chloride.[1069]

Analogous bromides and iodides, especially PBr_3, have also been used, but they are more expensive and used less often than HBr or HI, although some of them may also be generated *in situ* (e.g., PBr_3 from phosphorous and bromine). Bromides have also been prepared with NaBr on doped Montmorillonite K10 clay[1070] and iodides were prepared by using NaI on KSF-clay,[1071] both using with microwave irradiation. Secondary alcohols always gives *some* rearranged bromides if another secondary position is available, even with PBr_3, PBr_5, or $SOBr_2$; thus 3-pentanol gives both 2- and 3-bromopentane. Such rearrangement can be avoided by converting the alcohol to a sulfonate and then using **10-47**,[1072] or by the use of phase transfer catalysis.[1073] Tertiary alcohols can be converted to the bromide with BBr_3 at 0°C.[1074] HF does not generally convert alcohols to alkyl fluorides.[1075] The most important reagent for this purpose is the commercially available diethylaminosulfur trifluoride Et_2NSF_3 (DAST),[1076] which converts primary, secondary, tertiary, allylic, and benzylic alcohols to fluorides in high yields under mild conditions.[1077] Fluorides have also been prepared from alcohols by treatment with SF_4,[1078] SeF_4,[1079] TsF,[1080] CsI/BF_3,[1081] and indirectly, by conversion to a sulfate or tosylate, and so on (**10-47**). Sodium iodide and Amberlyst-15[1082] or tosic acid and KI with microwave irradiation[1083] converts primary alcohols to the iodide. A mixture of IF_5, NEt_3

[1066]Fuchs, R.; Cole, L.L. *Can. J. Chem.* ***1975***, *53*, 3620.
[1067]For a transformation involving a primary benzylic alcohol, thionyl chloride and benzotriazole, see Chaudhari, S.S.; Akamanchi, K.G. *Synlett* ***1999***, 1763.
[1068]Joseph, R.; Pallan, P.S.; Sudalai, A.; Ravindranathan, T. *Tetrahedron Lett.* ***1995***, *36*, 609.
[1069]Hiegel, G.A.; Rubino, M. *Synth. Commmun.* ***2002***, *32*, 2691.
[1070]Kad, G.L.; Singh, V.; Kaur, K.P.; Singh. J. *Tetrahedron Lett.* ***1997***, *38*, 1079.
[1071]Kad, G.L.; Kaur, J.; Bansal, P.; Singh, J. *J. Chem. Res. (S)* ***1996***, 188.
[1072]Cason, J.; Correia, J.S. *J. Org. Chem.* ***1961***, *26*, 3645.
[1073]Dakka, G.; Sasson, Y. *Tetrahedron Lett.* ***1987***, *28*, 1223.
[1074]Pelletier, J.D.; Poirier, D. *Tetrahedron Lett.* ***1994***, *35*, 1051.
[1075]For an exception, see Hanack, M.; Eggensperger, H.; Hähnle, R. *Liebigs Ann. Chem.* ***1962***, *652*, 96; See also, Politanskii, S.F.; Ivanyk, G.D.; Sarancha, V.N.; Shevchuk, V.U. *J. Org. Chem. USSR* ***1974***, *10*, 697.
[1076]For a review of this reagent, see Hudlický, M. *Org. React.* ***1988***, *35*, 513.
[1077]Middleton, W.J. *J. Org. Chem.* ***1975***, *40*, 574.
[1078]For reviews, see Wang, C.J. *Org. React.* ***1985***, *34*, 319; Kollonitsch, J. *Isr. J. Chem.* ***1978***, *17*, 53; Boswell, Jr., G.A.; Ripka, W.C.; Scribner, R.M.; Tullock, C.W. *Org. React.* ***1974***, *21*, 1.
[1079]Olah, G.A.; Nojima, M.; Kerekes, I. *J. Am. Chem. Soc.* ***1974***, *96*, 925.
[1080]Shimizu, M.; Nakahara, Y.; Yoshioka, H. *Tetrahedron Lett.* ***1985***, *26*, 4207. For another method, see Olah, G.A.; Li, X. *Synlett*, ***1990***, 267.
[1081]Hayat, S.; Atta-ur-Rahman, Khan, K.M.; Choudhary, M.I.; Maharvi, G.M.; Zia-Ullah; Bayer, E. *Synth. Commun.* ***2003***, *33*, 2531.
[1082]Tajbakhsh, M.; Hosseinzadeh, R.; Lasemi, Z. *Synlett* ***2004***, 635.
[1083]Lee, J.C.; Park, J.Y.; Yoo, E.S. *Synth. Commun.* ***2004***, *34*, 2095.

and excess KF[1084] or $(Cl_3CO)_2C{=}O$, bis(trichloromethyl)carbonate, and KF (which gives COF_2 *in situ*)with 18-crown-6[1085] also converts primary alcohols to primary fluorides.

Primary, secondary, and tertiary alcohols can be converted to any of the four halides by treatment with the appropriate NaX, KX, or NH_4X in polyhydrogen fluoride–pyridine solution.[1086] This method is even successful for neopentyl halides. Another reagent that converts neopentyl alcohol to neopentyl chloride, in 95% yield, is $PPh_3{-}CCl_3CN$.[1087] Ionic liquids can be used for halogenation, and bmim-Cl (1-*n*-butyl-3-methylimidazolium chloride) generates the chloride directly from the alcohol without any additional reagent.[1088]

Other reagents[1089] have also been used, including $ZrCl_4$/NaI,[1090] 2,4,6-trichloro [1,3,5]triazine (cyanuric acid) and DMF,[1091] Me_3SiCl and $BiCl_3$[1092] or Me_3SiCl and 5% $InCl_3$[1093] or simply Me_3SiCl in DMSO.[1094] Other specialized reagents include $(RO)_3PRX$[1095] and R_3PX_2[1096] (made from R_3P and X_2), which give good yields for primary (including neopentyl), secondary, and tertiary halides without rearrange-

[1084]Yoneda, N. Fukuhara, T. *Chem. Lett.* ***2001***, 222.
[1085]Flosser, D.A.; Olofson, R.A. *Tetrahedron Lett.* ***2002***, *43*, 4275.
[1086]Olah, G.A.; Welch, J.; Vankar, Y.D.; Nojima, M.; Kerekes, I.; Olah, J.A. *J. Org. Chem.* ***1979***, *44*, 3872. See also, Yin, J.; Zarkowsky, D.S.; Thomas, D.W.; Zhao, M.W.; Huffman, M.A. *Org. Lett.* ***2004***, *6*, 1465.
[1087]Matveeva, E.D.; Yalovskaya, A.I.; Cherepanov, I.A.; Kurts, A.L.; Bundel', Yu.G. *J. Org. Chem. USSR* ***1989***, *25*, 587.
[1088]Ren, R. X.; Wu, J. X. *Org. Lett.* ***2001***, *3*, 3727.
[1089]For some other reagents, not listed here, see Echigo, Y.; Mukaiyama, T. *Chem. Lett.* ***1978***, 465; Barton, D.H.R.; Stick, R.V.; Subramanian, R. *J. Chem. Soc. Perkin Trans. 1* ***1976***, 2112; Savel'yanov, V.P.; Nazarov, V.N.; Savel'yanova, R.T.; Suchkov, V.V. *J. Org. Chem. USSR* ***1977***, *13*, 604; Jung, M.E.; Hatfield, G.L. *Tetrahedron Lett.* ***1978***, 4483; Sevrin, M.; Krief, A. *J. Chem. Soc., Chem. Commun.* ***1980***, 656; Hanessian, S.; Leblanc, Y.; Lavallée, P. *Tetrahedron Lett.* ***1982***, *23*, 4411; Cristol, S.J.; Seapy, D.G. *J. Org. Chem.* ***1982***, *47*, 132; Richter, R.; Tucker, B. *J. Org. Chem.* ***1983***, *48*, 2625; Imamoto, T.; Matsumoto, T.; Kusumoto, T.; Yokoyama, M. *Synthesis* ***1983***, 460; Olah, G.A.; Husain, A.; Singh, B.P.; Mehrotra, A.K. *J. Org. Chem.* ***1983***, *48*, 3667; Toto, S.D.; Doi, J.T. *J. Org. Chem.* ***1987***, *52*, 4999; Camps, F.; Gasol, V.; Guerrero, A. *Synthesis* ***1987***, 511; Schmidt, S.P.; Brooks, D.W. *Tetrahedron Lett.* ***1987***, *28*, 767; Collingwood, S.P.; Davies, A.P.; Golding, B.T. *Tetrahedron Lett.* ***1987***, *28*, 4445; Kozikowski, A.P.; Lee, J. *Tetrahedron Lett.* ***1988***, *29*, 3053; Classon, B.; Liu, Z.; Samuelsson, B. *J. Org. Chem.* ***1988***, *53*, 6126; Munyemana, F.; Frisque-Hesbain, A.; Devos, A.; Ghosez, L. *Tetrahedron Lett.* ***1989***, *30*, 3077; Ernst, B.; Winkler, T. *Tetrahedron Lett.* ***1989***, *30*, 3081.
[1090]Firouzabadi, H.; Iranpoor, N.; Jafarpour, M. *Tetrahedron Lett.* ***2004***, *45*, 7451.
[1091]De Luca, L.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* ***2002***, *4*, 553.
[1092]Labrouillère, M.; LeRoux, C.; Oussaid, A.; Gaspard-Iloughmane, H.; Dubac, J. *Bull. Soc. Chim. Fr.* ***1995*** *132*, 522.
[1093]Yasuda, M.; Yamasaki, S.; Onishi, Y.; Baba, A. *J. Am. Chem. Soc.* ***2004***, *126*, 7186.
[1094]Snyder, D.C. *J. Org. Chem.* ***1995***, *60*, 2638.
[1095]Rydon, H.N. *Org. Synth.* ***VI***, 830.
[1096]Wiley, G.A.; Hershkowitz, R.L.; Rein, B.M.; Chung, B.C. *J. Am. Chem. Soc.* ***1964***, *86*, 964; Wiley, G.A.; Rein, B.M.; Hershkowitz, R.L. *Tetrahedron Lett.* ***1964***, 2509; Schaefer, J.P.; Weinberg, D.S. *J. Org. Chem.* ***1965***, *30*, 2635; Kaplan, L. *J. Org. Chem.* ***1966***, *31*, 3454; Weiss, R.G.; Snyder, E.I. *J. Org. Chem.* ***1971***, *36*, 403; Garegg, P.J.; Johansson, R.; Samuelsson, B. *Synthesis* ***1984***, 168; Sandri, J.; Viala, J. *Synth. Commun.* ***1992***, *22*, 2945.

ments.[1097] Similarly, Me_2SBr_2[1098] (prepared from Me_2S and Br_2), and a mixture of PPh_3 and CCl_4[1099] (or CBr_4[1100]).

$$ROH + Ph_3P + CCl_4 \longrightarrow RCl + Ph_3PO + HCCl_3$$

The last method converts allylic alcohols[1101] to the corresponding halides without allylic rearrangements[1102] and also cyclopropylcarbinyl alcohols to the halides without ring opening.[1103] A simple method that is specific for benzylic and allylic alcohols (and does not give allylic rearrangement) involves reaction with *N*-chloro- or *N*-bromosuccinimide and methyl sulfide.[1104] The specificity of this method is illustrated by the conversion, in 87% yield, of (*Z*)-$HOCH_2CH_2CMe{=}CHCH_2OH$ to (*Z*)-$HOCH_2CH_2Me{=}CHCH_2Cl$. Only the allylic OH group was affected. A mixture of NBS, $Cu(OTf)_2$ and diisopropylcarbodiimide converted primary alcohols to the corresponding bromide.[1105] The use of NCS gave the chloride and NIS gave the iodide under identical conditions. Thiols are converted to alkyl bromides by a similar procedure using PPh_3 and NBS.[1106]

Allylic and benzylic alcohols can also be converted to bromides or iodides with NaX-BF_3 etherate,[1107] and to iodides with AlI_3.[1108] A mixture of methanesulfonic acid and NaI also converts benzylic alcohols to benzylic iodides.[1109] Both (chlorophenylthio-methylene)dimethylammonium chloride[1110] and 2-chloro-1,3-dimethylimidazolinium chloride[1111] react with alcohols to give the corresponding chloride.

[1097]For reviews of reactions with these reagents, see Castro, B.R. *Org. React.* ***1983***, *29*, 1; Mackie, R.K., in Cadogan, J.I.G. *Organophosphorus Reagents in Organic Synthesis*, Academic Press, NY, ***1979***; pp. 433–466.

[1098]Furukawa, N.; Inoue, T.; Aida, T.; Oae, S. *J. Chem. Soc., Chem. Commun.* ***1973***, 212.

[1099]For reviews, see Appel, R. *Angew. Chem. Int. Ed.* ***1975***, *14*, 801; Appel, R.; Halstenberg, M., in Cadogan, J.I.G. *Organophosphorus Reagents in Organic Synthesis*, Academic Press, NY, ***1979***, pp. 387–431. For a discussion of the mechanism, see Slagle, J.D.; Huang, T.T.; Franzus, B. *J. Org. Chem.* ***1981***, *46*, 3526. For a similar reaction using hexachloroethane and bis-1,2-diphenylphosphinoethane see Pollastri, M.P.; Sagal, J.F.; Chang, G. *Tetrahedron Lett.* ***2001***, *42*, 2459.

[1100]Wagner, A.; Heitz, M.; Mioskowski, C. *Tetrahedron Lett.* ***1989***, *30*, 557. See also, Desmaris, L.; Percina, N.; Cottier, L.; Sinou, D. *Tetrahedron Lett.* ***2003***, *44*, 7589.

[1101]For a review of the conversion of allylic alcohols to allylic halides, see Magid, R.M. *Tetrahedron* ***1980***, *36*, 1901, pp. 1924–1926.

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[1103]Hrubiec, R.T.; Smith, M.B. *Synth. Commun.* ***1983***, *13*, 593.

[1104]Corey, E.J.; Kim, C.U.; Takeda, M. *Tetrahedron Lett.* ***1972***, 4339.

[1105]Li, Z.; Crosignani, S.; Linclau, B. *Tetrahedron Lett.* ***2003***, *44*, 8143; Crosignani, S.; Nadal, B.; Li, Z.; Linclau, B. *Chem. Commun.* ***2003***, 260.

[1106]Iranpoor, N.; Firouzabadi, H.; Aghapour, G. *Synlett* ***2001***, 1176.

[1107]Vankar, Y.D.; Rao, C.T. *Tetrahedron Lett.* ***1985***, *26*, 2717; Mandal, A.K.; Mahajan, S.W. *Tetrahedron Lett.* ***1985***, *26*, 3863; Bandgar, B.P.; Sadavarte, V.S.; Uppalla, L.S. *Tetrahedron Lett.* ***2001***, *42*, 951.

[1108]Sarmah, P.; Barua, N.C. *Tetrahedron* ***1989***, *45*, 3569.

[1109]Kamal, A.; Ramesh, G.; Laxman, N. *Synth. Commun.* ***2001***, *31*, 827.

[1110]Gomez, L.; Gellibert, F.; Wagner, A.; Mioskowski, C. *Tetrahedron Lett.* ***2000***, *41*, 6049.

[1111]Isobe, T.; Ishikawa, T. *J. Org. Chem.* ***1999***, *64*, 5832.

When the reagent is HX, the mechanism is S_N1cA or S_N2cA; that is, the leaving group is not ^-OH, but OH_2 (p. 496). The leaving group is not ^-OH with the other reagents either, since in these cases the alcohol is first converted to an inorganic ester, for example, ROSOCl with $SOCl_2$ (**10-22**). The leaving group is therefore ^-OSOCl or a similar group (**10-47**). These may react by the S_N1 or S_N2 mechanism and, in the case of ROSOCl, by the S_Ni mechanism[1112] (p. 468).

Trialkylsilyl ethers such as $ROSiMe_3$ are converted to the corresponding iodide with SiO_2—Cl/NaI.[1113]

OS **I**, 25, 36, 131, 142, 144, 292, 294, 533; **II**, 91, 136, 159, 246, 308, 322, 358, 399, 476; **III**, 11, 227, 370, 446, 698, 793, 841; **IV**, 106, 169, 323, 333, 576, 681; **V**, 1, 249, 608; **VI**, 75, 628, 634, 638, 781, 830, 835; **VII**, 210, 319, 356; **VIII**, 451. Also see, OS **III**, 818; **IV**, 278, 383, 597.

10-49 Formation of Alkyl Halides from Ethers

Halo-de-alkoxylation

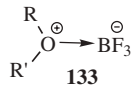
$$ROR' + HI \longrightarrow RI + R'OH$$

Ethers can be cleaved by heating with concentrated HI or HBr.[1114] Hydrogen chloride is seldom successful,[1115] and HBr reacts more slowly than HI, but is often a superior reagent, since it causes fewer side reactions. Phase-transfer catalysis has also been used,[1116] and 47% HBr in ionic liquids has proven effective.[1117] Dialkyl ethers and alkyl aryl ethers can be cleaved. In the latter case the alkyl–oxygen bond is the one broken. As in **10-48**, the actual leaving group is not OR'^-, but OHR′. Although alkyl aryl ethers always cleave so as to give an alkyl halide and a phenol, there is no general rule for dialkyl ethers. Often cleavage occurs from both sides, and a mixture of two alcohols and two alkyl halides is obtained. However, methyl ethers are usually cleaved so that methyl iodide or bromide is a product. An excess of HI or HBr converts the alcohol product into alkyl halide, so that dialkyl ethers (but not alkyl aryl ethers) are converted to 2 equivalents of alkyl halide. This procedure is often carried out so that a mixture of only two products is obtained instead of four. *O*-Benzyl ethers are readily cleaved to the alcohol and the hydrocarbon via hydrogenolysis, and the most common methods are hydrogenation[1118] or

[1112]Schreiner, P.R.; Schleyer, P.v.R.; Hill, R.K. *J. Org. Chem.* ***1993***, *58*, 2822.
[1113]Firouzabadi, H.; Iranpoor, N.; Hazarkhani, H. *Tetrahedron Lett.* ***2002***, *43*, 7139.
[1114]For reviews of ether cleavage in general, see Bhatt, M.V.; Kulkarni, S.U. *Synthesis* ***1983***, 249; Staude, E.; Patat, F., in Patai, S. *The Chemistry of the Ether Linkage*, Wiley, NY, ***1967***, p. 22. For a review of cleavage of aryl alkyl ethers, see Tiecco, M. *Synthesis* ***1988***, 749.
[1115]Cleavage with HCl has been accomplished in the presence of surfactants: Juršić, B. *J. Chem. Res. (S)* ***1989***, 284.
[1116]Landini, D.; Montanari, F.; Rolla, F. *Synthesis* ***1978***, 771.
[1117]In bmim BF_4, 1-*n*-butyl-3-methylimidazolium bromide: Boovanahalli, S.K.; Kim, D.W.; Chi, D.Y. *J. Org. Chem.* ***2004***, *69*, 3340.
[1118]Heathcock, C.H.; Ratcliffe, R. *J. Am. Chem. Soc.* ***1971***, *93*, 1746.

dissolving metal conditions (Na or K in ammonia).[1119] Heating in anisole with 3% $Sc(NTf_2)_3$[1120] or In metal in aqueous ethanol[1121] also cleaves benzyl ethers. Isoprenyl alkyl ethers are cleaved using iodine in dichloromethane,[1122] and allyl alkyl ethers are cleaved with Lewis acids under various conditions.[1123] The $OCH_2CH{=}CHPh$ unit of mixed allyl ethers (O-$CH_2CH{=}CH_2$ and $OCH_2CH{=}CHPh$) can be cleaved selectively under electrolytic conditions.[1124]

Cyclic ethers (usually tetrahydrofuran derivatives) can be similarly cleaved (see **10-50** for epoxides). Treatment of 2-methyltetrahydrofuran with acetyl chloride and $ZnCl_2$ gave primarily *O*-acetyl-4-chloro-1-pentanol.[1125] A mixture of Et_2NSiMe_3/2 MeI cleaved tetrahydrofuran to give the *O*-trimethylsilyl ether of 4-iodo-1-butanol.[1126] Ethers have also been cleaved with Lewis acids, such as BF_3, $Ce(OTf)_4$,[1127] $SiCl_4$/LiI/BF_3,[1128] BBr_3,[1129] or $AlCl_3$.[1130] In such cases, the departure of the OR is assisted by complex formation with the Lewis acid (see **133**).



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Lewis acids are also used. The reagent NaI—BF_3 etherate selectively cleaves ethers in the order benzylic ethers > alkyl methyl ethers > aryl methyl ethers.[1131]

Dialkyl and alkyl aryl ethers are cleaved with iodotrimethylsilane:[1132] $ROR' + Me_3SiI \rightarrow RI + Me_3SiOR$.[1133] A more convenient and less expensive alternative, which gives the same products, is a mixture of chlorotrimethylsilane and

[1119]McCloskey, C.M. *Adv. Carbohydr. Chem.* ***1957***, *12*, 137; Reist, E.J.; Bartuska, V.J.; Goodman, L. *J. Org. Chem.* ***1964***, *29*, 3725.
[1120]Ishihara, K.; Hiraiwa, Y.; Yamamoto, H. *Synlett* ***2000***, 80.
[1121]Moody, C.J.; Pitts, M.R. *Synlett* ***1999***, 1575.
[1122]Vatèle, J.-M. *Synlett* ***2001***, 1989. For a procedure using DDQ, see Vatèle, J.-M. *Synlett* ***2002***, 507
[1123]Examples include SmI_2 in the presence of H_2O-*i*$PrNH_2$: Dahlen, A.; Sundgren, A.; Lahmann, M.; Oscarson, S.; Hilmersson, G. *Org. Lett.* ***2003***, *5*, 4085. $CeCl_3$/NaI: Bartoli, G.; Cupone, G.; Dalpozzo, R.; DeNino, A.; Maiuolo, L.; Marcantoni, E.; Procopio, A. *Synlett* ***2001***, 1897. $ZnCl_2$-$Pd(PPh_3)_4$: Chandrasekhar, S.; Reddy, Ch.R.; Rao, R.J. *Tetrahedron* ***2001, 57***, 3435. A ruthenium-catalyzed protocol: Tanaka, S.; Saburi, H.; Ishibashi, Y.; Kitamura, M. *Org. Lett.* ***2004***, *6*, 1873. See also, Murakami, H.; Minami, T.; Ozawa, F. *J. Org. Chem.* ***2004***, *69*, 4482.
[1124]Solis-Oba, A.; Hudlicky, T.; Koroniak, L.; Frey, D. *Tetrahedron Lett.* ***2001***, *42*, 1241.
[1125]Mimero, P.; Saluzzo, C.; Amouroux, R. *Tetrahedron Lett.* ***1994***, *35*, 1553.
[1126]Ohshita, J.; Iwata, A.; Kanetani, F.; Kunai, A.; Yamamoto, Y.; Matui, C. *J. Org. Chem.* ***1999***, *64*, 8024.
[1127]Khalafi-Nezhad, A.; Alamdari, R.F. *Tetrahedron* ***2001***, *57*, 6805.
[1128]Zewge, D.; King, A.; Weissman, S.; Tschaen, D. *Tetrahedron Lett.* ***2004***, *45*, 3729.
[1129]Press, J.B. *Synth. Commun.* ***1979***, *9*, 407; Niwa, H.; Hida, T.; Yamada, K. *Tetrahedron Lett.* ***1981***, *22*, 4239.
[1130]For a review, see Johnson, F., in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 4, Wiley, NY, ***1965***, pp. 1–109.
[1131]Vankar, Y.D.; Rao, C.T. *J. Chem. Res. (S)* ***1985***, 232. See also, Mandal, A.K.; Soni, N.R.; Ratnam, K.R. *Synthesis* ***1985***, 274; Ghiaci, M.; Asghari, J. *Synth. Commun.* ***1999***, *29*, 973; Sharma, G.V.M.; Reddy, Ch.G.; Krishna, P.R. *J. Org. Chem.* ***2003***, *68*, 4574.
[1132]For a review of this reagent, see Olah, G.A.; Prakash, G.K.S.; Krishnamurti, R. *Adv. Silicon Chem.* ***1991***, *1*, 1.
[1133]Jung, M.E.; Lyster, M.A. *J. Org. Chem.* ***1977***, *42*, 3761; *Org. Synth.* ***VI***, 353.

NaI.[1134] Triphenyldibromophosphorane (Ph_3PBr_2) cleaves dialkyl ethers to give 2 moles of alkyl bromide.[1135] Alkyl aryl ethers can also be cleaved with LiI to give alkyl iodides and salts of phenols[1136] in a reaction similar to **10-51**. Allyl aryl ethers[1137] are efficiently cleaved with NaI/Me_3SiCl,[1138] $CeCl_3$/NaI[1139] or $ZrCl_4$/$NaBH_4$.[1140]

A closely related reaction is cleavage of oxonium salts.

$$R_3O^+X^- \longrightarrow RX + R_2O$$

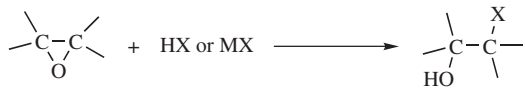
For these substrates, HX is not required, and X can be any of the four halide ions.

tert-Butyldimethylsilyl ethers ($ROSiMe_2CMe_3$) can be converted to bromides RBr by treatment with Ph_3PBr_2,[1141] $Ph_3P{-}CBr_4$,[1142] or BBr_3.[1143] Alcohols are often protected by conversion to this kind of silyl ether.[1144]

OS **I**, 150; **II**, 571; **III**, 187, 432, 586, 692, 753, 774, 813; **IV**, 266, 321; **V**, 412; **VI**, 353. See also, OS **VIII**, 161, 556.

10-50 Formation of Halohydrins from Epoxides

(3)*OC-seco*-Halo-de-alkoxylation



This is a special case of **10-49** and is frequently used for the preparation of halohydrins. In contrast to the situation with open-chain ethers and with larger rings, many epoxides react with all four hydrohalic acids, although with HF[1145] the reaction is unsuccessful with simple aliphatic and cycloalkyl epoxides.[1146] Hydrogen fluoride does react with more rigid epoxides, such as those in steroid systems. The reaction can applied to simple epoxides[1147] if polyhydrogen fluoride-pyridine

[1134]Morita, T.; Okamoto, Y.; Sakurai, H. *J. Chem. Soc., Chem. Commun.* ***1978***, 874; Olah, G.A.; Narang, S.C.; Gupta, B.G.B.; Malhotra, R. *J. Org. Chem.* ***1979***, *44*, 1247; Amouroux, R.; Jatczak, M.; Chastrette, M. *Bull. Soc. Chim. Fr.* ***1987***, 505.

[1135]Anderson Jr., A.G.; Freenor, F.J. *J. Org. Chem.* ***1972***, *37*, 626.

[1136]Harrison, I.T. *Chem. Commun.* ***1969***, 616.

[1137]For cleavage with Pd/C in KOH/MeOH, see Ishizaki, M.; Yamada, M.; Watanabe, S.-i.; Hoshino, O.; Nishitani, K.; Hayashida, M.; Tanaka, A.; Hara, H. *Tetrahedron* ***2004***, *60*, 7973.

[1138]Kamal, A.; Laxman, E.; Rao, N.V. *Tetrahedron Lett.* ***1999***, *40*, 371.

[1139]Thomas, R.M.; Reddy, G.S.; Iyengar, D.S. *Tetrahedron Lett.* ***1999***, *40*, 7293

[1140]Chary, K.P.; Mohan, G.H.; Iyengar, D.S. *Chem. Lett.* ***1999***, 1223.

[1141]Aizpurua, J.M.; Cossío, F.P.; Palomo, C. *J. Org. Chem.* ***1986***, *51*, 4941.

[1142]Mattes, H.; Benezra, C. *Tetrahedron Lett.* ***1987***, *28*, 1697.

[1143]Kim, S.; Park, J.H. *J. Org. Chem.* ***1988***, *53*, 3111.

[1144]See Corey, E.J.; Venkateswarlu, A. *J. Am. Chem. Soc.* ***1972***, *94*, 6190.

[1145]For a review of reactions HF with epoxides, see Sharts, C.M.; Sheppard, W.A. *Organic Fluorine Chemistry*, W.A. Benjamin, NY, ***1969***, pp. 52–184, 409–430. For a related review, see Yoneda, N. *Tetrahedron* ***1991***, *47*, 5329.

[1146]Shahak, I.; Manor, S.; Bergmann, E.D. *J. Chem. Soc. C* ***1968***, 2129.

[1147]Olah, G.A.; Meidar, D. *Isr. J. Chem.* ***1978***, *17*, 148.

is the reagent. The reagent NEt_3•3 HF converts epoxides to fluorohydrins with microwave irradiation.[1148] The epoxide-to-fluorohydrin conversion has also been carried out with SiF_4 and a tertiary amine.[1149] Chloro-, bromo-, and iodohydrins can also be prepared[1150] by treating epoxides with Ph_3P and X_2,[1151] with $InBr_3$/$NaBr/H_2O$,[1152] LiBr on Amberlyst-15 resin,[1153] $TiCl_4$-LiCl,[1154] $SiCl_4$,[1155] I_2 with a SmI_2 catalyst,[1156] and LiI on silica gel.[1157] Epoxides can be converted directly to 1,2-dichloro compounds by treatment with $SOCl_2$ and pyridine,[1158] or with Ph_3P and CCl_4.[1159] These are two-step reactions: a halohydrin is formed first and is then converted by the reagents to the dihalide (**10-48**). As expected, inversion is found at both carbons. Meso epoxides were cleaved enantioselectively with the chiral B-halodiisopinocampheylboranes (see **15-16**), where the halogen was Cl, Br, or I.[1160] Diatomic iodine gives an iodohydrin with a 2,6-bis[2-(*o*-aminophenoxy) methyl]-4-bromo-1-methoxybenzene catalyst.[1161]

Bicyclic epoxides are usually opened to the *trans*-halohydrin. Unsymmetrical epoxides are usually opened to give mixtures of regioisomers. In a typical reaction, the halogen is delivered to the less sterically hindered carbon of the epoxide. In the absence of this structural feature, and in the absence of a directing group, relatively equal mixtures of regioisomeric halohydrins are expected. The phenyl is such as group in 1-phenyl-2-alkyl epoxides, where reaction with $POCl_3$/DMAP leads to the chlorohydrin with the chlorine on the carbon bearing the phenyl.[1162]

[1148]Inagaki, T.; Fukuhara, T.; Hara, S. *Synthesis* ***2003***, 1157.

[1149]Shimizu, M.; Yoshioka, H. *Tetrahedron Lett.* ***1988***, *29*, 4101. For other methods, see Muehlbacher, M.; Poulter, C.D. *J. Org. Chem.* ***1988***, *53*, 1026; Ichihara, J.; Hanafusa, T. *J. Chem. Soc., Chem. Commun.* ***1989***, 1848.

[1150]Einhorn, C.; Luche, J. *J. Chem. Soc., Chem. Commun.* ***1986***, 1368; Ciaccio, J.A.; Addess, K.J.; Bell, T.W. *Tetrahedron Lett.* ***1986***, *27*, 3697; Spawn, C.; Drtina, G.J.; Wiemer, D.F. *Synthesis* ***1986***, 315. For reviews, see Bonini, C.; Righi, G. *Synthesis* ***1994***, 225; Chini, M.; Crotti, P.; Gardelli, C.; Macchia, F. *Tetrahedron* ***1992***, *48*, 3805.

[1151]Palumbo, G.; Ferreri, C.; Caputo, R. *Tetrahedron Lett.* ***1983***, *24*, 1307. See Afonso, C.A.M.; Vieira, N.M.L.; Motherwell, W.B. *Synlett* ***2000***, 382.

[1152]Amantini, D.; Fringulli, F.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.* ***2001***, *66*, 4463.

[1153]Bonini, C.; Giuliano, C.; Righi, G.; Rossi, L. *Synth. Commun.* ***1992***, *22*, 1863.

[1154]Shimizu, M.; Yoshida, A.; Fujisawa, T. *Synlett*, ***1992***, 204.

[1155]Denmark, S.E.; Barsanti, P.A.; Wong, K.-T.; Stavenger, R. *J. Org. Chem.* ***1998***, *63*, 2428; Tao, B.; Lo, M.M.-C.; Fu, G.C. *J. Am. Chem. Soc.* ***2001***, *123*, 353; Reymond, S.; Legrand, O.; Brunel, J.M.; Buono, G. *Eur. J. Org. Chem.* ***2001***, 2819.

[1156]Kwon, D.W.; Cho, M.S.; Kim, Y.H. *Synlett* ***2003***, 959.

[1157]Kotsuki, H.; Shimanouchi, T. *Tetrahedron Lett.* ***1996***, *37*, 1845.

[1158]Campbell, J.R.; Jones, J.K.N.; Wolfe, S. *Can. J. Chem.* ***1966***, *44*, 2339.

[1159]Isaacs, N.S.; Kirkpatrick, D. *Tetrahedron Lett.* ***1972***, 3869.

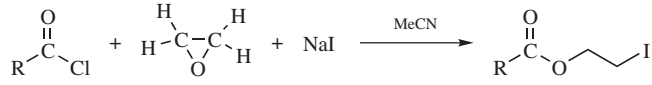
[1160]Srebnik, M.; Joshi, N.N.; Brown, H.C. *Isr. J. Chem.* ***1989***, *29*, 229.

[1161]Nikam, K.; Nashi, T. *Tetrahedron*, ***2002***, *58*, 10259. For an alternative reaction of iodine and a pyridine-containing macrocycle, see Sharghi, H.; Niknam, K.; Pooyan, M. *Tetrahedron* ***2001***, *57*, 6057. For the reaction of iodine with a Mn–salen catalyst see Sharghi, H.; Naeimi, H. *Bull. Chem. Soc. Jpn.* ***1999***, *72*, 1525.

[1162]Sartillo-Piscil, F.; Quinero, L.; Villegas, C.; Santacruz-Juárez, E.; de Parrodi, C.A. *Tetrahedron Lett.* ***2002***, *43*, 15.

When done in an ionic liquid with Me_3SiCl, styrene epoxide gives 2-chloro-2-phenylethanol.[1163] The reaction of thionyl chloride and poly(vinylpyrrolidinone) converts epoxides to the corresponding 2-chloro-1-carbinol.[1164] Bromine with a phenylhydrazine catalyst, however, converts epoxides to the 1-bromo-2-carbinol.[1165] An alkenyl group also leads to a halohydrin with the halogen on the carbon bearing the C=C unit.[1166] Epxoy carboxylic acids are another example. When NaI reacts at pH 4, the major regioisomer is the 2-iodo-3-hydroxy compound, but when $InCl_3$ is added, the major product is the 3-iodo-2-hydroxy carboxylic acid.[1167]

Acyl chlorides react with ethylene oxide in the presence of NaI to give 2-iodoethyl esters.[1168]



Acyl chlorides react with epoxides in the presence of a $Eu(dpm)_3$ catalyst[1169] [dpm = 1,1-bis(diphenylphosphino)methane] or a YCp_2Cl catalyst[1170] to give chloro esters.

A related reaction with epi-sulfides leads to 2-chlorothio-esters.[1171] Aziridines have been opened with $MgBr_2$ to give 2-haloamides in a related reaction.[1172] *N*-Tosyl aziridines react with KF•2 H_2O to give the 2-fluorotosylamine product.[1173]

OS **I**, 117; **VI**, 424; **IX**, 220.

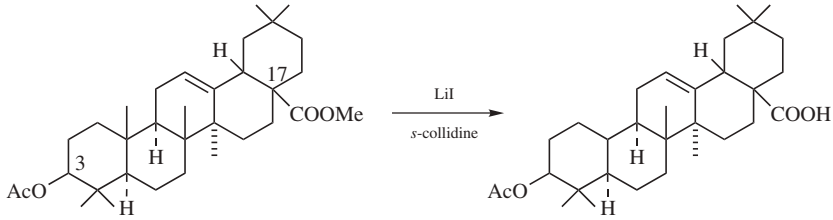
10-51 Cleavage of Carboxylic Esters With Lithium Iodide

Iodo-de-acyloxy-substitution

$$\text{R'COOR} + \text{LiI} \xrightarrow[\Delta]{\text{pyridine}} \text{RI} + \text{R'COOLi}$$

[1163]Xu, L.-W.; Li, L.; Xia, C.-G.; Zhao, P.-Q. *Tetrahedron Lett.* ***2004***, *45*, 2435.
[1164]Tamami, B.; Ghazi, I.; Mahdavi, H. *Synth. Commun.* ***2002***, *32*, 3725.
[1165]Sharghi, H.; Eskandari, M.M. *Synthesis* ***2002***, 1519.
[1166]Ha, J.D.; Kim, S.Y.; Lee, S.J.; Kang, S.K.; Ahn, J.H.; Kim, S.S.; Choi, J.-K. *Tetrahedron Lett.* ***2004***, *45*, 5969.
[1167]Fringuelli, F.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.* ***2001***, *66*, 4719. For a related SmI_2 ring opening of epoxy amides to give the 3-iodo-2-hydroxy compound, see Concellón, J.M.; Bardales, E.; Concellón, C.; García-Granda, S.; Díaz, M.R. *J. Org. Chem.* ***2004***, *69*, 6923.
[1168]Belsner, K.; Hoffmann, H.M.R. *Synthesis* ***1982***, 239. See also, Roloff, A. *Chimia*, ***1985***, *39*, 392; Iqbal, J.; Khan, M.A.; Srivastava, R.R. *Tetrahedron Lett.* ***1988***, *29*, 4985.
[1169]Taniguchi, Y.; Tanaka, S.; Kitamura, T.; Fujiwara, Y. *Tetrahedron Lett.* ***1998***, *39*, 4559.
[1170]Qian, C.; Zhu, D. *Synth. Commun.* ***1994***, *24*, 2203.
[1171]Kameyama, A.; Kiyota, M.; Nishikubo, T. *Tetrahedron Lett.* ***1994***, *35*, 4571.
[1172]Righi, G.; D'Achille, R.; Bonini, C. *Tetrahedron Lett.* ***1996***, *37*, 6893.
[1173]Fan, R.-H.; Zhou, Y.-G.; Zhang, W.-X.; Hou, X.-L.; Dai, L.-X. *J. Org. Chem.* ***2004***, *69*, 335.

Carboxylic esters, where R is methyl or ethyl, can be cleaved by heating with lithium iodide in refluxing pyridine or a higher boiling amine.[1174] The reaction is useful where a molecule is sensitive to acid and base (so that **16-59** cannot be used) or where it is desired to cleave selectively only one ester group in a molecule containing two or more. For example, refluxing *O*-acetyloleanolic acid methyl ester



with LiI in *s*-collidine cleaved only the 17-carbomethoxy group, not the 3-acetyl group.[1175] Esters RCOOR′ and lactones can also be cleaved with a mixture of Me_3SiCl and NaI to give R′I and RCOOH.[1176] The reaction of acetyl chloride and allylic acetate leads to the allylic chloride.[1177]

10-52 Conversion of Diazo Ketones to α-halo Ketones

Hydro, halo-de-diazo-bisubstitution

$$RCOCHN_2 + HBr \longrightarrow RCOCH_2Br$$

When diazo ketones are treated with HBr or HCl, they give the respective α-halo ketones. HI does not give the reaction, since it reduces the product to a methyl ketone (**19-67**). α-Fluoro ketones can be prepared by addition of the diazo ketone to polyhydrogen fluoride–pyridine.[1178] This method is also successful for diazoalkanes.

Diazotization of α-amino acids in the above solvent at room temperature gives α-fluoro carboxylic acids.[1179] If this reaction is run in the presence of excess KCl or KBr, the corresponding α-chloro or α-bromo acid is obtained instead.[1180]

OS **III**, 119.

[1174]Taschner, E.; Liberek, B. *Rocz. Chem.* ***1956***, *30*, 323 [*Chem. Abstr.*, ***1957***, *51*, 1039]. For a review, see McMurry, J. *Org. React.* ***1976***, *24*, 187–224.

[1175]Elsinger, F.; Schreiber, J.; Eschenmoser, A. *Helv. Chim. Acta* ***1960***, *43*, 113.

[1176]Olah, G.A.; Narang, S.C.; Gupta, B.G.B.; Malhotra, R. *J. Org. Chem.* ***1979***, *44*, 1247. See also, Kolb, M.; Barth, J. *Synth. Commun.* ***1981***, *11*, 763.

[1177]Yadav, V.K.; Babu, K.G. *Tetrahedron* ***2003***, *59*, 9111.

[1178]Olah, G.A.; Welch, J. *Synthesis* ***1974***, 896; Olah, G.A.; Welch, J.; Vankar, Y.D.; Nojima, M.; Kerekes, I.; Olah, J.A. *J. Org. Chem.* ***1979***, *44*, 3872.

[1179]Olah, G.A.; Prakash, G.K.S.; Chao, Y.L. *Helv. Chim. Acta* ***1981***, *64*, 2528; Faustini, F.; De Munary, S.; Panzeri, A.; Villa, V.; Gandolfi, C.A. *Tetrahedron Lett.* ***1981***, *22*, 4533; Barber, J.; Keck, R.; Rétey, J. *Tetrahedron Lett.* ***1982***, *23*, 1549.

[1180]Olah, G.A.; Shih, J.; Prakash, G.K.S. *Helv. Chim. Acta* ***1983***, *66*, 1028.

10-53 Conversion of Amines to Halides

Halo-de-amination

$$RNH_2 \longrightarrow RNTs_2 \xrightarrow[DMF]{I^-} RI$$

Primary alkyl amines RNH_2 can be converted[1181] to alkyl halides by (*1*) conversion to $RNTs_2$ (p. 498) and treatment of this with I^- or Br^- in DMF,[385] or to N(Ts)—NH_2 derivatives followed by treatment with *N*-bromosuccinimide under photolysis conditions;[1182] (*2*) diazotization with *tert*-butylnitrite and a metal halide such as $TiCl_4$ in DMF;[1183] or (*3*) the Katritzky pyrylium–pyridinium method (p. 498).[1184] Alkyl groups can be cleaved from secondary and tertiary aromatic amines by concentrated HBr in a reaction similar to **10-49**, for example,[1185]

$$ArNR_2 + HBr \longrightarrow RBr + ArNHR$$

Tertiary aliphatic amines are also cleaved by HI, but useful products are seldom obtained. Tertiary amines can be cleaved by reaction with phenyl chloroformate:[1186] $R_3N + ClCOOPh \rightarrow RCl + R_2NCOOPh$. α-Chloroethyl chloroformate behaves similarly.[1187] Alkyl halides may be formed when quaternary ammonium salts are heated: $R_4N^+ X^- \rightarrow R_3N + RX$.[1188]

OS **VIII**, 119. See also, OS **I**, 428.

10-54 Conversion of Tertiary Amines to Cyanamides: The von Braun Reaction

Bromo-de-dialkylamino-substitution

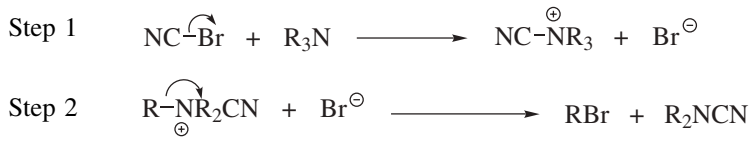
$$R_3NH + BrCN \longrightarrow R_2NCN + RBr$$

The *von Braun reaction* involves the cleavage of tertiary amines by cyanogen bromide to give an alkyl bromide and a disubstituted cyanamide, and can be applied to many tertiary amines.[1189] Usually, the R group that cleaves is the one that gives the most reactive halide (e.g., benzyl or allyl). For simple alkyl groups, the smallest

[1181]For another method, see Lorenzo, A.; Molina, P.; Vilaplana, M.J. *Synthesis* ***1980***, 853.
[1182]Collazo, L.R.; Guziec, Jr., F.S.; Hu, W.-X.; Pankayatselvan, R. *Tetrahedron Lett.* ***1994***, *35*, 7911.
[1183]Doyle, M.P.; Bosch, R.J.; Seites, P.G. *J. Org. Chem.* ***1978***, *43*, 4120.
[1184]Katritzky, A.R.; Chermprapai, A.; Patel, R.C. *J. Chem. Soc. Perkin Trans. 1* ***1980***, 2901.
[1185]Chambers, R.A.; Pearson, D.E. *J. Org. Chem.* ***1963***, *28*, 3144.
[1186]Hobson, J.D.; McCluskey, J.G. *J. Chem. Soc. C* ***1967***, 2015. For a review, see Cooley, J.H.; Evain, E.J. *Synthesis* ***1989***, 1.
[1187]Olofson, R.A.; Martz, J.T.; Senet, J.; Piteau, M.; Malfroot, T. *J. Org. Chem.* ***1984***, *49*, 2081; Olofson, R.A.; Abbott, D.E. *J. Org. Chem.* ***1984***, *49*, 2795. See also, Campbell, A.L.; Pilipauskas, D.R.; Khanna, I.K.; Rhodes, R.A. *Tetrahedron Lett.* ***1987***, *28*, 2331.
[1188]For examples, see Ko, E.C.F.; Leffek, K.T. *Can. J. Chem.* ***1970***, *48*, 1865; ***1971***, *49*, 129; Deady, L.W.; Korytsky, O.L. *Tetrahedron Lett.* ***1979***, 451.
[1189]For a review, see Cooley, J.H.; Evain, E.J. *Synthesis* ***1989***, 1.

are the most readily cleaved. One or two of the groups on the amine may be aryl, but they do not cleave. Cyclic amines have been frequently cleaved by this reaction. Secondary amines also give the reaction, but the results are usually poor.[1190]

The mechanism consists of two successive nucleophilic substitutions, with the tertiary amine as the first nucleophile and the liberated bromide ion as the second:



The intermediate *N*-cyanoammonium bromide has been trapped, and its structure confirmed by chemical, analytical, and spectral data.[1191] The BrCN in this reaction has been called a *counterattack reagent*; that is, a reagent that accomplishes, in one flask, two transformations designed to give the product.[1192]

OS **III**, 608.

CARBON NUCLEOPHILES

In any heterolytic reaction in which a new carbon–carbon bond is formed,[1193] one carbon atoms attacks as a nucleophile and the other as an electrophile. The classification of a given reaction as nucleophilic or electrophilic is a matter of convention and is usually based on analogy. Although not discussed in this chapter, **11-8**–**11-25** and **12-16**–**12-21** are nucleophilic substitutions with respect to one reactant, though, following convention, we classify them with respect to the other. Similarly, all the reactions in this section would be called electrophilic substitution (aromatic or aliphatic) if we were to consider the reagent as the substrate.

In **10-56**–**10-65** the nucleophile is a ''carbanion'' part of an organometallic compound, often a Grignard reagent. There is much that is still not known about the mechanisms of these reactions and many of them are not nucleophilic substitutions at all. In those reactions that are nucleophilic substitutions, the attacking carbon brings a pair of electrons with it to the new C—C bond, whether or not free carbanions are actually involved. The connection of two alkyl or aryl groups is called *coupling*. Reactions **10-56**–**10-65** include both symmetrical and unsymmetrical coupling reactions. The latter are also called *cross-coupling reactions*. Other coupling reactions are considered in later chapters.

[1190]For a detailed discussion of the scope of the reaction and of the ease of cleavage of different groups, see Hageman, H.A. *Org. React.* ***1953***, 205.

[1191]Fodor, G.; Abidi, S. *Tetrahedron Lett.* ***1971***, 1369; Fodor, G.; Abidi, S.; Carpenter, T.C. *J. Org. Chem.* ***1974***, *39*, 1507. See also, Paukstelis, J.V.; Kim, M. *J. Org. Chem.* ***1974***, *39*, 1494.

[1192]For a review of counterattack reagents, see Hwu, J.R.; Gilbert, B.A. *Tetrahedron* ***1989***, *45*, 1233.

[1193]For a monograph that discusses most of the reactions in this section, see Stowell, J.C. *Carbanions in Organic Synthesis*, Wiley, NY, ***1979***. For a review, see Noyori, R., in Alper, H. *Transition Metal Organometallics in Organic Synthesis*, Vol. 1, Academic Press, NY, ***1976***, pp. 83–187.

10-55 Coupling With Silanes

De-silylalkyl-coupling

$$R{-}X + R^1_3Si{-}CH_2CH{=}CH_2 \longrightarrow R{-}CH_2CH{=}CH_2$$

Organosilanes $RSiMe_3$ or $RSiMe_2F$ (where R can be vinylic, allylic, or alkynyl) couple with vinylic, allylic, and aryl bromides and iodides R′X, in the presence of certain catalysts, to give RR′ in good yields.[1194] Allylsilanes react with allylic acetates in the presence of iodine.[1195] The transition-metal catalyzed coupling of silanes, particularly allyl silanes, is a mild method for incorporating alkyl fragments into a molecule.[1196] $PhSiMe_2Cl$ couples to give biphenyl in the presence of CuI and Bu_4NF,[1197] and vinyl silanes react with allylic carbonates and a palladium catalyst to give dienes.[1198] Allylsilanes have been coupled to substrates containing a benzotriazole unit, in the presence of BF_3•etherate.[1199] One variation used a silylmethyltin derivative in a palladium-catalyzed coupling with aryl iodides.[1200] Homoallyl silanes coupled to Ph_3BiF_2 in the presence of BF_3•OEt_2 to give the phenyl coupling product.[1201]

α-Silyloxy methoxy derivatives, $RCH(OMe)OSiR^1_3$, react with allyltrimethylsilane ($Me_3SiCH_2CH{=}CH_2$) in the presence of TiX_4 derivatives to give displacement of the OMe group and $RCH(OSiR^1_3)CH_2CH{=}CH_2$).[1202] A tertiary silyloxy group was displaced by allyl in the presence of $ZnCl_2$.[1203] Electrolysis with allyltrimethylsilane and RCH(OMe)SPh leads to $RCH(OMe)CH_2CH{=}CH_2$.[1204] Similar reaction with a dithioacetal leads to the allylic silane.[1205] Allylic acetates react with $Me_3SiSiMe_3$ and LiCl with a palladium catalyst to give the allyl silane.[1206] $RSiF_3$ reagents can also be used in coupling reaction with aryl halides.[1207]

[1194]Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* ***1988***, *53*, 918; ***1989***, *54*, 268; Cho, Y.S.; Kang, S.-H.; Han, J.-S.; Yoo, B.R.; Jung, I.N. *J. Am. Chem. Soc.* ***2001***, *123*, 5584.

[1195]Yadav, J.S.; Reddy, B.V.S.; Rao, K.V.; Raj, K.S.; Rao, P.P.; Prasad, A.R.; Gunasekar, D. *Tetrahedron Lett.* ***2004***, *45*, 6505.

[1196]For a ruthenium-catalyzed reaction, see Kakiuchi, F.; Tsuchiya, K.; Matsumoto, M.; Mizushima, E.; Chatani, N. *J. Am. Chem. Soc.* ***2004***, *126*, 12792. For a Cp_2TiCl_2-catalyzed reaction with allyl phenyl ether and chlorotrialkylsilanes, see Nii, S.; Terao, J.; Kambe, N. *Tetrahedron Lett.* ***2004***, *45*, 1699.

[1197]Kang, S.-K.; Kim, T.H.; Pyun, S.-J. *J. Chem. Soc. Perkin Trans. 1* ***1997***, 797.

[1198]Matsuhashi, H.; Hatanaka, Y.; Kuroboshi, M.; Hiyama, T. *Tetrahedron Lett.* ***1995***, *36*, 1539; Matsuhashi, H.; Asai, S.; Hirabayashi, K.; Hatanaka, Y.; Mori, A.; Hiyama, T. *Bull. Chem. Soc. Jpn.* ***1997***, *70*, 1943.

[1199]Katritzky, A.R.; Mehta, S.; He, H.-Y.; Cui, X. *J. Org. Chem.* ***2000***, *65*, 4364.

[1200]Itami, K.; Kamei, T.; Yoshida, J.-i. *J. Am. Chem. Soc.* ***2001***, *123*, 8773.

[1201]Matano, Y.; Yoshimune, M.; Suzuki, H. *Tetrahedron Lett.* ***1995***, *36*, 7475.

[1202]Maeda, K.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* ***1997***, *62*, 6429.

[1203]Yokozawa, T.; Furuhashi, K.; Natsume, H. *Tetrahedron Lett.* ***1995***, *36*, 5243.

[1204]Yoshida, J.; Sugawara, M.; Kise, N. *Tetrahedron Lett.* ***1996***, *37*, 3157.

[1205]Fujiwara, T.; Takamori, M.; Takeda, T. *Chem. Commun.* ***1998***, 51.

[1206]Tsuji, Y.; Funato, M.; Ozawa, M.; Ogiyama, H.; Kajita, S.; Kawamura, T. *J. Org. Chem.* ***1996***, *61*, 5779.

[1207]Hatanaka, Y.; Goda, K.; Hiyama, T. *Tetrahedron Lett.* ***1994***, *35*, 6511; Matsuhashi, H.; Kuroboshi, M.; Hatanaka, Y.; Hiyama, T. *Tetrahedron Lett.* ***1994***, *35*, 6507.

Allyl silanes react with epoxides, in the presence of BF_3•OEt_2 to give 2-allyl alcohols.[1208] The reaction of α-bromo lactones and CH_2=$CHCH_2Si(SiMe_3)_3$ and AIBN leads to the α-allyl lactone.[1209] On the other hand, silyl epoxides have been prepared from epoxides via reaction with *sec*-butyllithium and chlorotrimethylsilane.[1210] α-Silyl-*N*-Boc-amines were prepared in a similar manner from the *N*-Boc-amine.[1211] Arylsilanes were prepared by reaction of an aryllithium intermediate with $TfOSi(OEt)_3$.[1212] In the presence of BF_3•etherate, allyl silane and α-methoxy *N*-Cbz amines were coupled.[1213] Benzyl silanes coupled with allyl silanes to give $ArCH_2$—R derivatives in the presence of $VO(OEt)Cl_2$[1214] and allyltin compounds couple with allyl silanes in the presence of $SnCl_4$.[1215] Allyl silanes couple to the α-carbon of amines under photolysis conditions.[1216]

The reaction of a vinyl iodide with $(EtO)_3SiH$ with a palladium catalyst generated a good yield of the corresponding vinylsilane.[1217]

OSCV 10, 531.

10-56 Coupling of Alkyl Halides: The Wurtz Reaction

De-halogen-coupling

$$2\,RX + Na \longrightarrow RR$$

The coupling of alkyl halides by treatment with sodium to give a symmetrical product is called the *Wurtz reaction*. Side reactions (elimination and rearrangement) are so common that the reaction is seldom used. Mixed Wurtz reactions of two alkyl halides are even less feasible because of the number of products obtained. A somewhat more useful reaction (though still not very good) takes place when a mixture of an alkyl and an aryl halide is treated with sodium to give an alkylated aromatic compound (the *Wurtz–Fittig reaction*).[1218]

[1208]Burgess, L.E.; Gross, E.K.M.; Jurka, J. *Tetrahedron Lett.* ***1996***, *37*, 3255; Prestat, G.; Baylon, C.; Heck, M.-P.; Mioskowski, C. *Tetrahedron Lett.* ***2000***, *41*, 3829.

[1209]Chatgilialoglu, C.; Ferreri, C.; Ballestri, M.; Curran, D.P. *Tetrahedron Lett.* ***1996***, *37*, 6387; Chatgilialoglu, C.; Alberti, A.; Ballestri, M.; Macciantelli, D.; Curran, D.P. *Tetrahedron Lett.* ***1996***, *37*, 6391.

[1210]Hodgson, D.M.; Norsikian, S.L.M. *Org. Lett.* ***2001***, *3*, 461.

[1211]Harrison, J.R.; O'Brien, P.; Porter, D.W.; Smith, N.W. *Chem. Commun.* ***2001***, 1202.

[1212]Seganish, W.M.; DeShong, P. *J. Org. Chem.* ***2004***, *69*, 6790.

[1213]Matos, M.R.P.N.; Afonso, C.A.M.; Batey, R.A. *Tetrahedron Lett.* ***2001***, *42*, 7007.

[1214]Hirao, T.; Fujii, T.; Ohshiro, Y. *Tetrahedron Lett.* ***1994***, *35*, 8005.

[1215]Takeda, T.; Takagi, Y.; Takano, H.; Fujiwara, T. *Tetrahedron Lett.* ***1992***, *33*, 5381.

[1216]Pandey, G.; Rani, K.S.; Lakshimaiah, G. *Tetrahedron Lett.* ***1992***, *33*, 5107. See Gelas-Mialhe, Y.; Gramain, J.-C.; Louvet, A.; Remuson, R. *Tetrahedron Lett.* ***1992***, *33*, 73 for an internal coupling reaction of an allyl silane and an α-hydoxy lactam.

[1217]Murata, M.; Watanabe, S.; Masuda, Y. *Tetrahedron Lett.* ***1999***, *40*, 9255.

[1218]For an example, see Kwa, T.L.; Boelhouwer, C. *Tetrahedron* ***1970***, *25*, 5771.

However, the coupling of two aryl halides with sodium is impractical (but see **13-11**). Other metals have also been used to effect Wurtz reactions,[1219] notably silver, zinc,[1220] iron,[1221] activated copper,[1222] In,[1223] La,[1224] and manganese compounds.[1225] Lithium, under the influence of ultrasound, has been used to couple alkyl, aryl, and benzylic halides.[1226] Metallic nickel, prepared by the reduction of nickel halides with Li, dimerizes benzylic halides to give $ArCH_2CH_2Ar$.[1227] The coupling of alkyl halides has also been achieved electrochemically[1228] and photochemically.[1229] In a related reaction, Grignard reagents (**12-38**) have been coupled in the presence of trifluorosulfonic anhydride.[1230]

Tosylates and other sulfonates and sulfates couple with Grignard reagents,[1231] most often those prepared from aryl or benzylic halides.[1232] Alkyl sulfates and sulfonates generally make better substrates in reactions with Grignard reagents than the corresponding halides (**10-57**). The method is useful for primary and secondary R.

One type of Wurtz reaction that is quite useful is the closing of small rings, especially three-membered rings.[1233] For example, 1,3-dibromopropane can be converted to cyclopropane by Zn and NaI.[1234] Two highly strained molecules that

[1219]For a list of reagents, including metals and other reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 83–84.

[1220]See, for example, Nosek, J. *Collect. Czech. Chem. Commun.* ***1964***, *29*, 597.

[1221]Nozaki, H.; Noyori, R. *Tetrahedron* ***1966***, *22*, 2163; Onsager, O. *Acta Chem. Scand. Ser. B*, ***1978***, *32*, 15.

[1222]Ginah, F.O.; Donovan, T.A.; Suchan, S.D.; Pfennig, D.R.; Ebert, G.W. *J. Org. Chem.* ***1990***, *55*, 584.

[1223]Ranu, B.C.; Dutta, P.; Sarkar, A. *Tetrahedron Lett.* ***1998***, *39*, 9557.

[1224]Nishino, T.; Watanabe, T.; Okada, M.; Nishiyama, Y.; Sonoda, N. *J. Org. Chem.* ***2002***, *67*, 966.

[1225]$Mn/CuCl_2$: Ma, J.; Chan, T.-H. *Tetrahedron Lett.* ***1998***, *39*, 2499. $Mn_2(CO)_{10}/h\nu$: Gilbert, B.C.; Lindsay, C.I.; McGrail, P.T.; Parsons, A.F.; Whittaker, D.T.E. *Synth. Commun.* ***1999***, *29*, 2711.

[1226]Han, B.H.; Boudjouk, P. *Tetrahedron Lett.* ***1981***, *22*, 2757.

[1227]Inaba, S.; Matsumoto, H.; Rieke, R.D. *J. Org. Chem.* ***1984***, *49*, 2093. For some other reagents that accomplish this, see Sayles, D.C.; Kharasch, M.S. *J. Org. Chem.* ***1961***, *26*, 4210; Cooper, T.A. *J. Am. Chem. Soc. 1973*, *95*, 4158; Ho, T.; Olah, G.A. *Synthesis* ***1977***, 170; Ballatore, A.; Crozet, M.P.; Surzur, J. *Tetrahedron Lett.* ***1979***, 3073; Yamada, Y.; Momose, D. *Chem. Lett.* ***1981***, 1277; Iyoda, M.; Sakaitani, M.; Otsuka, H.; Oda, M. *Chem. Lett.* ***1985***, 127.

[1228]Folest, J.C.; Nédélec, J.Y.; Perichon, J. *J. Chem. Res. (S)* ***1989***, 394.

[1229]Ouchi, A.; Yabe, A. *Tetrahedron Lett.* ***1992***, *33*, 5359.

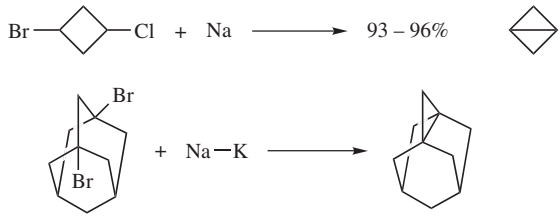
[1230]Nishiyama, T.; Seshita, T.; Shodai, H.; Aoki, K.; Kameyama, H.; Komura, K. *Chem. Lett.* ***1996***, 549.

[1231]For a review, see Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood Cliffs, NJ, ***1954***, pp. 1277–1286.

[1232]For an example involving an allylic rearrangement (conversion of a silylalkyne to a silylallene), see Danheiser, R.L.; Tsai, Y.; Fink, D.M. *Org. Synth. 66*, 1.

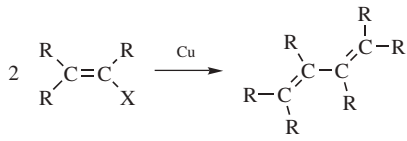
[1233]For a review, see Freidlina, R.Kh.; Kamyshova, A.A.; Chukovskaya, E.Ts. *Russ. Chem. Rev.* ***1982***, *51*, 368. For reviews of methods of synthesizing cyclopropane rings, see, in Rappoport *The Chemistry of the Cyclopropyl Group*, pt. 1; Wiley, NY, ***1987***, the reviews by Tsuji, T.; Nishida, S. pp. 307–373, and Verhé, R.; De Kimpe, N. pp. 445–564.

[1234]For a discussion of the mechanism, see Applequist, D.E.; Pfohl, W.F. *J. Org. Chem.* ***1978***, *43*, 867.



Tetracyclo[3.3.1.13,7.01,3]decane

have been prepared this way are bicyclobutane[1235] and tetracyclo[3.3.1.1^{3,7}.0^{1,3}]decane.[1236] Three- and four-membered rings can also be closed in this manner with certain other reagents,[1237] including benzoyl peroxide,[1238] *t*-BuLi,[1239] and lithium amalgam,[1240] as well as electrochemically.[1241]



134

Vinylic halides can be coupled to give 1,3-butadienes (**134**) by treatment with activated copper powder in a reaction analogous to the Ullmann reaction (**13-11**).[1242] This reaction is stereospecific, with retention of configuration at both carbons. Vinylic halides can also be coupled[1243] with Zn—$NiCl_2$,[1244] and with *n*-BuLi in ether in the presence of $MnCl_2$.[1245] The coupling reaction with vinyltin reagents and vinyl halides occurs with a palladium catalyst.[1246]

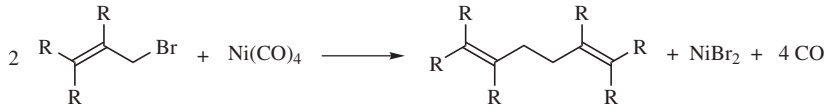
[1235]Wiberg, K.B.; Lampman, G.M. *Tetrahedron Lett.* ***1963***, 2173; Lampman, G.M.; Aumiller, J.C. *Org. Synth.* ***VI***, 133.
[1236]Pincock, R.E.; Schmidt, J.; Scott, W.B.; Torupka, E.J. *Can. J. Chem.* ***1972***, *50*, 3958.
[1237]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 175–184.
[1238]Kaplan, L. *J. Am. Chem. Soc.* ***1967***, *89*, 1753; *J. Org. Chem.* ***1967***, *32*, 4059.
[1239]Bailey, W.F.; Gagnier, R.P. *Tetrahedron Lett.* ***1982***, *23*, 5123.
[1240]Connor, D.S.; Wilson, E.R. *Tetrahedron Lett.* ***1967***, 4925.
[1241]Rifi, M.R. *J. Am. Chem. Soc.* ***1967***, *89*, 4442; *Org. Synth.* ***VI***, 153.
[1242]Cohen, T.; Poeth, T. *J. Am. Chem. Soc.* ***1972***, *94*, 4363.
[1243]See Wellmann, J.; Steckhan, E. *Synthesis* ***1978***, 901; Miyahara, Y.; Shiraishi, T.; Inazu, T.; Yoshino, T. *Bull. Chem. Soc. Jpn.* ***1979***, *52*, 953; Grigg, R.; Stevenson, P.; Worakun, T. *J. Chem. Soc., Chem. Commun.* ***1985***, 971; Vanderesse, R.; Fort, Y.; Becker, S.; Caubere, P. *Tetrahedron Lett.* ***1986***, *27*, 3517.
[1244]Takagi, K.; Mimura, H.; Inokawa, S. *Bull. Chem. Soc. Jpn.* ***1984***, *57*, 3517.
[1245]Cahiez, G.; Bernard, D.; Normant, J.F. *J. Organomet. Chem.* ***1976***, *113*, 99.
[1246]Paley, R.S.; de Dios, A.; de la Pradilla, R.F. *Tetrahedron Lett.* ***1993***, *34*, 2429.

Treatment of conjugated ketones with SmI_2 in HMPA gave the coupled diketone via Wurtz-type coupling.[1247]

It seems likely that the mechanism of the Wurtz reaction consists of two basic steps. The first is halogen-metal exchange to give an organometallic compound ($RX + M \rightarrow RM$), which in many cases can be isolated (**12-38**). Following this, the organometallic compound reacts with a second molecule of alkyl halide ($RX + RM \rightarrow RR$). This reaction and its mechanism are considered in the next section (**10-57**).

OS **III**, 157; **V**, 328, 1058; **VI**, 133, 153.

A variation of the Wurtz coupling uses other metals to mediate or facilitate the coupling. In certain cases, such variations can be synthetically useful.



Because of the presence of the 1,5-diene moiety in many naturally occurring compounds, methods that couple[1248] allylic groups[1249] are quite important. In one of these methods, allylic halides, tosylates, and acetates can be symmetrically coupled by treatment with nickel carbonyl[1250] at room temperature in a solvent, such as THF or DMF to give 1,5-dienes.[1251] The order of halide reactivity is $I > Br > Cl$. With unsymmetrical allylic substrates, coupling nearly always takes place at the less-substituted end. The reaction can be performed intramolecularly; large (11–20 membered) rings can be made in good yields (60–80%) by the use of high dilution.[1252] The mechanism of coupling likely involves reaction of the allylic compound with $Ni(CO)_4$ to give one or more π-allyl complexes, one of which may be the η^3-complex **135**. Loss of CO to give a π-allylnickel bromide (**136**) and ligand transfer leads to coupling and the final product. In some cases, the η^3-complexes **136** can be isolated from the solution and

[1247]Cabrera, A.; Rosas, N.; Sharma, P.; LeLagadec, R.; Velasco, L.; Salmón, M. *Synth. Commun.* ***1998***, *28*, 1103.

[1248]For a review of some allylic coupling reactions, see Magid, R.M. *Tetrahedron* ***1980***, *36*, 1901, see pp. 1910–1924.

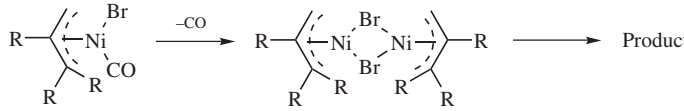
[1249]In this section are discussed methods in which one molecule is a halide. For other allylic coupling reactions, see **10-57**, **10-63**, and **10-60**.

[1250]For a review of the use of organonickel compounds in organic synthesis, see Tamao, K.; Kumada, M., in Hartley, F.R. *The Chemistry of the Metal-Carbon Bond*, Vol. 4, Wiley, NY, ***1987***, pp. 819–887.

[1251]For reviews, see Collman, J.P. ; Hegedus, L.; Norton, J.R.; Finke, R. *Principles and Applications of Organotransition Metal Chemsitry*, 2nd ed., University Science Books, Mill Valley, CA, ***1987***, pp. 739–748; Billington, D.C. *Chem. Soc. Rev.* ***1985***, *14*, 93; Kochi, J.K. *Organometallic Mechanisms and Catalysis*, Academic Press, NY, ***1978***, pp. 398–408; Semmelhack, M.F. *Org. React.* ***1972***, *19*, 115, see pp. 162–170; Baker, R. *Chem. Rev.* ***1973***, *73*, 487, see pp. 512–517; Heimbach, P.; Jolly, P.W.; Wilke, G. *Adv. Organomet. Chem.* ***1970***, *8*, 29, see pp. 30–39.

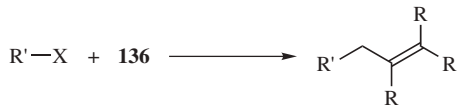
[1252]Corey, E.J.; Wat, E.K.W. *J. Am. Chem. Soc.* ***1967***, *89*, 2757. See also, Corey, E.J.; Helquist, P. *Tetrahedron Lett.* ***1975***, 4091; Reijnders, P.J.M.; Blankert, J.F.; Buck, H.M. *Recl. Trav. Chim. Pays-Bas* ***1978***, *97*, 30.

crystallized as stable solids.



135 **136**

Unsymmetrical coupling can be achieved by treating an alkyl halide directly with **136**, in a polar aprotic solvent, [1253] where coupling occurs at the less substituted end. There is evidence that free radicals are involved in such couplings.[1254] Hydroxy or carbonyl groups in the alkyl halide do not interfere. When **136** reacts with an allylic halide, a mixture of three products is obtained because of halogen–metal interchange. For example, allyl bromide treated with **136** prepared from methallyl bromide gave an approximately statistical mixture of 1,5-hexadiene, 2-methyl-1,5-hexadiene, and 2,5-dimethyl-1,5-hexadiene.[1255] Allylic tosylates can be symmetrically coupled with $Ni(CO)_4$.



Symmetrical coupling of allylic halides can prepared by heating with magnesium in ether,[1256] with a cuprous iodide–dialkylamide complex,[1257] or electrochemically.[1258] The coupling of two different allylic groups has been achieved by treatment of an allylic bromide with an allylic Grignard reagent in THF containing HMPA,[1259] or with an allylic tin reagent.[1260] This type of coupling can be achieved with almost no allylic rearrangement in the substrate (and almost complete allylic rearrangement in the reagent) by treatment of allylic halides with lithium allylic boron ate complexes ($RCH{=}CHCH_2B^{\ominus}\ R_3^2\ Li^+$).[1261] The reaction between primary and secondary halides and allyltributylstannane provides another method for unsymmetrical coupling

[1253]Corey, E.J.; Semmelhack, M.F. *J. Am. Chem. Soc.* ***1967***, *89*, 2755. For a review, see Semmelhack, M.F. *Org. React.* ***1972***, *19*, 115, see pp. 147–162. For a discussion of the preparation and handling of π-allylnickel halides, see Semmelhack, M.F. *Org. React.* ***1972***, *199*, 115, see pp. 144–146.

[1254]Hegedus, L.S.; Thompson, D.H.P. *J. Am. Chem. Soc.* ***1985***, *107*, 5663.

[1255]Corey, E.J.; Semmelhack, M.F.; Hegedus, L.S. *J. Am. Chem. Soc.* ***1968***, *90*, 2416.

[1256]Turk, A.; Chanan, H. *Org. Synth.* ***III***, 121.

[1257]Kitagawa, Y.; Oshima, K.; Yamamoto, H.; Nozaki, H. *Tetrahedron Lett.* ***1975***, 1859.

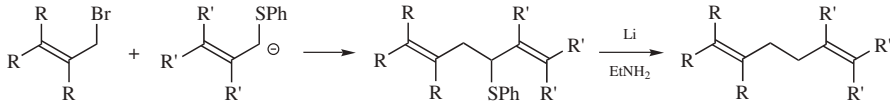
[1258]Tokuda, M.; Endate, K.; Suginome, H. *Chem. Lett.* ***1988***, 945.

[1259]Stork, G.; Grieco, P.A.; Gregson, M. *Tetrahedron Lett.* ***1969***, 1393; Grieco, P.A. *J. Am. Chem. Soc.* ***1969***, *91*, 5660.

[1260]Godschalx, J.; Stille, J.K. *Tetrahedron Lett.* ***1980***, *21*, 2599; ***1983***, *24*, 1905; Hosomi, A.; Imai, T.; Endo, M.; Sakurai, H. *J. Organomet. Chem.* ***1985***, *285*, 95. See also, Yanagisawa, A.; Norikate, Y.; Yamamoto, H. *Chem. Lett.* ***1988***, 1899.

[1261]Yamamoto, Y.; Yatagai, H.; Maruyama, K. *J. Am. Chem. Soc.* ***1981***, *103*, 1969.

$RX + CH_2{=}CHCH_2SnBu_3 \rightarrow RCH_2CH{=}CH_2$.[1262]



137

In another method for the coupling of two different allylic groups,[1263] a carbanion derived from a β,γ-unsaturated thioether couples with an allylic halide to give **137**.[1264] The product **137** contains an SPh group that must be removed (with Li in ethylamine) to give the 1,5-diene. Unlike most of the methods previously discussed, this method has the advantage that the coupling preserves the original positions and configurations of the two double bonds; no allylic rearrangements take place.

OS **III**, 121; **IV**, 748; **VI**, 722.

10-57 The Reaction of Alkyl Halides and Sulfonate Esters With Group I and II Organometallic Reagents[1265]

Alkyl-de-halogenation

$$R{-}Na(K)(Li) + R'X \longrightarrow R{-}R'$$

A variety of organometallic compounds[1266] have been used to couple with alkyl halides.[1267] Organosodium and organopotassium compounds are more reactive than Grignard reagents and couple even with less reactive halides. Organolithium reagents react with ether solvents, and their half-life in such solvents is known.[1268] The difficulty is in preparing and keeping them long enough for the alkyl halide to be added. Alkenes can be prepared by the coupling of vinylic lithium compounds with primary halides[1269] or of vinylic halides with alkyllithium reagents in the presence of a Pd or

[1262]See Keck, G.E.; Yates, J.B. *J. Am. Chem. Soc.* ***1982***, *104*, 5829; Migita, T.; Nagai, K.; Kosugi, M. *Bull. Chem. Soc. Jpn* ***1983***, *56*, 2480.

[1263]For other procedures, see Axelrod, E.H.; Milne, G.M.; van Tamelen, E.E. *J. Am. Chem. Soc.* ***1970***, *92*, 2139; Morizawa, Y.; Kanemoto, S.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* ***1982***, *23*, 2953.

[1264]Biellmann, J.F.; Ducep, J.B. *Tetrahedron Lett.* ***1969***, 3707.

[1265]For a review of the reactions in this section, see Naso, F.; Marchese, G., in Patai, S.; Rappoport, Z. *The Chemstry of Functional Groups, Supplement D*, pt. 2, Wiley, NY, ***1983***, pp. 1353–1449.

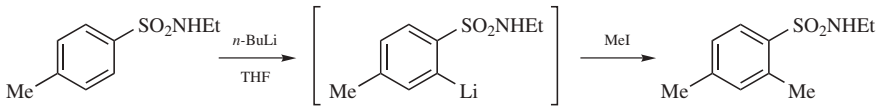
[1266]For lists of reagents and substrates, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 101–127.

[1267]For a review of the coupling of organic halides with organotin, mercury, and copper compounds catalyzed by palladium complexes, see Beletskaya, I.P. *J. Organomet. Chem.* ***1983***, *250*, 551. For a review of palladium-assisted coupling, see Larock, R.C. *Organomercury Compounds in Organic Synthesis*; Springer, NY, ***1985***, pp. 249–262.

[1268]Stanetty, P.; Mihovilovic, M.D. *J. Org. Chem.* ***1997***, *62*, 1514.

[1269]Millon, J.; Lorne, R.; Linstrumelle, G. *Synthesis* ***1975***, 434; Duhamel, L.; Poirier, J. *J. Am. Chem. Soc.* ***1977***, *99*, 8356.

Ru catalyst.[1270] Propargyl lithium reagents formed in the presence of mercuric salts couple with halides.[1271] Coupling of organolithium compounds with alkyl halides[1272] or aryl halides[1273] is possible.[1274] Unactivated aryl halides couple with alkyllithium reagents in THF.[1275] The reaction of *n*-butyllithium–TMEDA with a homoallylic alcohol [CH_2=C(Me)CH_2CH_2OH] leads to the allyllithium reagent, and subsequent reaction with an alkyl halide gives the substituted homoallylic alcohol [CH_2=C(CH_2R)CH_2CH_2OH].[1276] α-Lithioepoxides can also be formed, and reaction with an alkyl halide gives the substituted epoxide.[1277] Arylsilanes, such as 2-trimethylsilylpyridine, undergo a deprotonation reaction of a silyl methyl group when treated with *tert*-butyllithium to give the corresponding $ArMe_2SiCH_2Li$ reagent.[1278] Subsequent reaction with an alkyl halide leads to the substituted silane. Organolithium reagents formed by Li—H exchange in the presence of (−)-sparteine couple with alkyl halides with high asymmetric induction.[1279] The dianion of PhC(=Se)$NHCH_2Ph$ was generated with *n*-butyllithium and reaction with bromocyclohexane gave the C-substituted derivative.[1280] Exchange of organotin compounds with organolithium reagents generates a new organolithium, and in one case intramolecular coupling in the presence of (−)-sparteine led to chiral pyrrolidine derivatives.[1281] It is noted that 1-lithioalkynes were coupled to alkyl halides in the presence of a palladium catalyst.[1282]

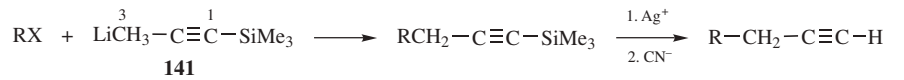


138 **139** **140**

Aryllithium reagents are formed by metal–halogen exchange with aryl halides or H-metal exchange with various aromatic compounds, and they react with alkyl halides. The reaction of **138** with *n*-butyllithium, for example, generated the

[1270]Murahashi, S.; Yamamura, M.; Yanagisawa, K.; Mita, N.; Kondo, K. *J. Org. Chem.* ***1979***, *44*, 2408.
[1271]Ma, S.; Wang, L. *J. Org. Chem.* ***1998***, *63*, 3497.
[1272]Snieckus, V.; Rogers-Evans, M.; Beak, P.; Lee, W.K.; Yum, E.K.; Freskos, J. *Tetrahedron Lett.* ***1994***, *35*, 4067.
[1273]Dieter, R.K.; Li, S.J. *J. Org. Chem.* ***1997***, *62*, 7726; Dieter, R.K.; Dieter, J.W.; Alexander, C.W.; Bhinderwala, N.S. *J. Org. Chem.* ***1996***, *61*, 2930. Also see, Beak, P.; Du, H. *J. Am. Chem. Soc.* ***1993***, *115*, 2516; Beak, P.; Wu, S.; Yum, E.K.; Jun, Y.M. *J. Org. Chem.* ***1994***, *59*, 276.
[1274]For example, see Brimble, M.A.; Gorsuch, S. *Aust. J. Chem.* ***1999***, *52*, 965.
[1275]Merrill, R.E.; Negishi, E. *J. Org. Chem.*, ***1974***, *39*, 3452. For another method, see Hallberg, A.; Westerlund, C. *Chem. Lett.*, ***1982***, 1993.
[1276]Yong, K.H.; Lotoski, J.A.; Chong, J.M. *J. Org. Chem.* ***2001***, *66*, 8248.
[1277]Marié, J.-C.; Curillon, C.; Malacria, M. *Synlett* ***2002***, 553.
[1278]Itami, K.; Kamei, T.; Mitsudo, K.; Nokami, T.; Yoshida, J.-i. *J. Org. Chem.* ***2001***, *66*, 3970.
[1279]Basu, A.; Beak, P. *J. Am. Chem. Soc.* ***1996***, *118*, 1575; Wu, S.; Lee, S.; Beak, P. *J. Am. Chem. Soc.* ***1996***, *118*, 715; Dieter, R.K.; Sharma, R.R. *Tetrahedron Lett.* ***1997***, *38*, 5937.
[1280]Murai, T.; Aso, H.; Kato, S. *Org. Lett.* ***2002***, *4*, 1407.
[1281]Serino, C.; Stehle, N.; Park, Y.S.; Florio, S.; Beak, P. *J. Org. Chem.* ***1999***, *64*, 1160.
[1282]Yang, L.-M.; Huang, L.-F.; Luh, T.-Y. *Org. Lett.* ***2004***, *6*, 1461.

aryllithium (**139**), which reacted with iodomethane to give **140**.[1283] When an aromatic ring has an attached heteroatom or an heteroatom-containing substituent, reaction with a strong base, such as an organolithium reagent, usually leads to an ortho lithiated species.[1284] Subsequent reaction with an electrophilic species gives the ortho substituted product. This phenomenon is known as *directed ortho metalation* (see **13-17**). This selectivity was discovered independently by Gilman and by Wittig in 1939–1940, when anisole was found to give ortho deprotonation in the presence of butyllithium.[1285] Alkylation ortho to a carbonyl is possible, and treatment of the acyl hydrazide $PhC(=O)NHNMe_2$ with *sec*-butyllithium and then iodoethane gave the ortho ethyl derivative.[1286] It is noted that aminonaphthalene derivatives were reacted with *tert*-butyllithium and aryllithium formation occurred on the ring distal to the amino group, and subsequent reaction with iodomethane gave methylation on that ring.[1287]



In a method for propargylating an alkyl halide without allylic rearrangement, the halide is treated with lithio-1-trimethylsilylpropyne (**141**), which is a lithium compound protected by an $SiMe_3$ group.[1288] Attack by the ambident nucleophile at its 1 position (which gives an allene) takes place only to a small extent, because of steric blockage by the large $SiMe_3$ group. The $SiMe_3$ group is easily removed by treatment with Ag^+ followed by CN^-. **141** is prepared by treating propynyllithium with Me_3SiCl to give $MeC{=}CSiMe_3$ from which a proton is removed with BuLi. R may be primary or allylic.[1289] On the other hand, propargylic halides can be alkylated with essentially complete allylic rearrangement, to give allenes, by treatment with Grignard reagents and metallic salts,[1290] or with dialkylcuprates R_2Cu.[1291]

Grignard reagents can be made to couple with alkyl halides in good yields by the use of certain catalysts,[1292] and stereocontrol is possible in these reactions.[1293] Among these are Cu(I) salts (see **10-58**), which permit the coupling of Grignard reagents with

[1283]MacNeil, S.L.; Familoni, O.B.; Snieckus, V. *J. Org. Chem.* ***2001***, *66*, 3662.
[1284]For reviews, see Snieckus, V. *Chem. Rev.* ***1990***, *90*, 879; Gschwend, H.W.; Rodriguez, H.R. *Org. React.* ***1979***, *26*, 1. See also, Green, L.; Chauder, B.; Snieckus, V. *J. Heterocyclic Chem.* ***1999***, *36*, 1453; Puterbaugh, W.H.; Hauser, C.R. *J. Org. Chem.* ***1964***, *29*, 853;
[1285]Gilman, H.; Bebb, R.L. *J. Am. Chem. Soc.* ***1939***, *61*, 109; Wittig, G.; Fuhrman, G. *Chem. Ber.* ***1940***, *73*, 1197.
[1286]McCombie, S.W.; Lin, S.-I.; Vice, S.F. *Tetrahedron Lett.* ***1999***, *40*, 8767.
[1287]Kraus, G.A.; Kim, J. *J. Org. Chem.* ***2002***, *67*, 2358.
[1288]Corey, E.J.; Kirst, H.A.; Katzenellenbogen, J.A. *J. Am. Chem. Soc.* ***1970***, *92*, 6314.
[1289]For an alternative procedure, see Ireland, R.E.; Dawson, M.I.; Lipinski, C.A. *Tetrahedron Lett.* ***1970***, 2247.
[1290]Pasto, D.J.; Chou, S.; Waterhouse, A.; Shults, R.H.; Hennion, G.F. *J. Org. Chem.* ***1978***, *43*, 1385; Jeffery-Luong, T.; Linstrumelle, G. *Tetrahedron Lett.* ***1980***, *21*, 5019.
[1291]Pasto, D.J.; Chou, S.; Fritzen, E.; Shults, R.H.; Waterhouse, A.; Hennion, G.F. *J. Org. Chem.* ***1978***, *43*, 1389. See also, Tanigawa, Y.; Murahashi, S. *J. Org. Chem.* ***1980***, *45*, 4536.
[1292]For reviews, see Erdik, E. *Tetrahedron* ***1984***, *40*, 641; Kochi, J.K. *Organometallic Mechanisms and Catalysis*, Academic Press, NY, ***1978***, pp. 374–398.
[1293]Bäckvall, J.-E.; Persson, E.S.M.; Bombrun, A. *J. Org. Chem.* ***1994***, *59*, 4126.

primary alkyl halides in good yield[1294] (organocopper salts are probably intermediates here). Allylic halides are more reactive than aliphatic alkyl halides, but copper salts have been used to facilitate coupling with alkylmagnesiumhalides.[1295] Iron(III)[1296] or palladium[1297] complexes are also used, and the latter allows the coupling of Grignard reagents and vinylic halides. Vinyl halides[1298] and aryl halides[1299] also couple with alkyl Grignard reagents in the presence of a catalytic amount of $Fe(acac)_3$, where acac = acetylacetonate, as do vinyl triflates with CuI[1300] or vinyl halides with a cobalt catalyst.[1301] Grignard reagents prepared from primary or secondary[1302] alkyl or aryl halides can be coupled with vinylic or aryl halides (see **13-9**) in high yields in the presence of a nickel(II) catalyst.[1303] When a chiral nickel(II) catalyst is used, optically active hydrocarbons can be prepared from achiral reagents.[1304] Neopentyl iodides also couple with aryl Grignard reagents in the presence of a nickel(II) catalyst.[1305]

Aryl halides, even when activated, generally do not couple with Grignard reagents, although certain transition-metal catalysts do effect this reaction in variable yields.[1306] The reaction with Grignard reagents proceeds better when OR can be the leaving group, providing that activating groups are present in the ring. The oxazoline group actives *o*-methoxy and *o*-fluoro groups to reaction with Grignard

[1294]Tamura, M.; Kochi, J.K. *J. Am. Chem. Soc.* ***1971***, *93*, 1485; Derguini-Boumechal, F.; Linstrumelle, G. *Tetrahedron Lett.* ***1976***, 3225; Mirviss, S.B. *J. Org. Chem.* ***1989***, *54*, 1948; Terao, J.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* ***2003***, *125*, 5646.

[1295]Tissot-Croset, K.; Alexakis, A. *Tetrahedron Lett.* ***2004***, *45*, 7375; Tissot-Croset, K.; Polet, D.; Alexakis, A. *Angew. Chem. Int. Ed.* ***2004***, *43*, 2426.

[1296]Smith, R.S.; Kochi, J.K. *J. Org. Chem.* ***1976***, *41*, 502; Walborsky, H.M.; Banks, R.B. *J. Org. Chem.* ***1981***, *46*, 5074; Molander, G.A.; Rahn, B.J.; Shubert, D.C.; Bonde, S.E. *Tetrahedron Lett.* ***1983***, *24*, 5449. An iron–salen catalyst has been used: see Bedford, R.B.; Bruce, D.W.; Frost, R.M.; Goodby, J.W.; Hird, M. *Chem. Commun.* ***2004***, 2822.

[1297]Ratovelomanana, V.; Linstrumelle, G.; Normant, J. *Tetrahedron Lett.* ***1985***, *26*, 2575; Minato, A.; Suzuki, K.; Tamao, K. *J. Am. Chem. Soc.* ***1987***, *109*, 1257; Frisch, A.C.; Shaikh, N.; Zapf, A.; Beller, M. *Angew. Chem. Int. Ed.* ***2002***, *41*, 4056. For other references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 386–392.

[1298]Cahiez, G.; Avedissian, H. *Synthesis* ***1998***, 1199; Nagano, T.; Hayashi, T. *Org. Lett.* ***2004***, *6*, 1297.

[1299]Fürstner, A.; Leitner, A. *Angew. Chem. Int. Ed.* ***2002***, *41*, 609; Martin, R.; Fürstner, A. *Angew. Chem. Int. Ed.* ***2004***, *43*, 3955.

[1300]Karlström, A.S.E.; Rönn, M.; Thorarensen, A. ; Bäckvall, J.-E. *J. Org. Chem.* ***1998***, *63*, 2517.

[1301]Cahiez, G.; Avedissian, H. *Tetrahedron Lett.* ***1998***, *39*, 6159.

[1302]Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* ***1984***, *106*, 158.

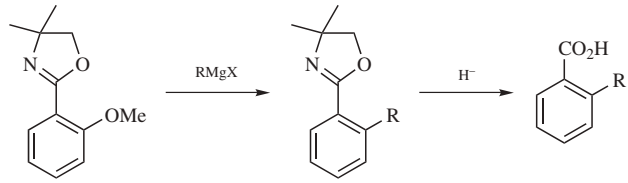
[1303]Corriu, R.J.P.; Masse, J.P. *J. Chem. Soc., Chem. Commun.* ***1972***, 144; Böhm, V.P.W.; Gstöttmayr, C.W.K.; Weskamp, T.; Hermann, W.A. *Angew. Chem. Int. Ed.* ***2001***, *40*, 3387; Terao, J.; Watanabe, H.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* ***2002***, *124*, 4222. For a review, see Kumada, M. *Pure Appl. Chem.* ***1980***, *52*, 669.

[1304]For a review, see Hayashi, T.; Kumada, M., in Morrison, J.D. *Asymmetic Synthesis*, Vol. 5, Academic Press, NY, ***1985***, pp. 147–169. See also, Cross, G.A.; Kellogg, R.M. *J. Chem. Soc., Chem. Commun.* ***1987***, 1746; Iida, A.; Yamashita, M. *Bull. Chem. Soc. Jpn.* ***1988***, *61*, 2365.

[1305]Yuan, K.; Scott, W.J. *Tetrahedron Lett.* ***1991***, *32*, 189.

[1306]See, for example, Sekiya, A.; Ishikawa, N. *J. Organomet. Chem.*, ***1976***, *118*, 349; ***1977***, *125*, 281; Tiecco, M.; Testaferri, L.; Tingoli, M.; Chianelli, D.; Wenkert, E. *Tetrahedron Lett.*, ***1982***, *23*, 4629; Bell, T.W.; Hu, L.; Patel, S.V. *J. Org. Chem.*, ***1987***, *52*, 3847; Bumagin, N.A.; Andryukhova, N.L.; Beletskaya, I.P. *Doklad. Chem.*, ***1987***, *297*, 524; Ozawa, F.; Kurihara, K.; Fujimori, M.; Hidaka, T.; Toyoshima, T.; Yamamoto, A. *Organometallics* ***1989***, *8*, 180.

reagents and organolithiums; the product **142** can be hydrolyzed after coupling[1307] (see **10-74**):



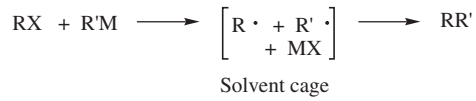
142

gem-Dichlorides have been prepared by coupling alkyl halides to $RCCl_3$ compounds electrochemically, in an undivided cell with a sacrificial anode:[1308]

$$RCCl_3 + R'X + 2\,e^- \longrightarrow RCCl_2R' + Cl^- + X^-$$

R′ could also be Cl, in which case the product bears a CCl_3 group.[1309]

Much study has been devoted to the mechanisms of these reactions,[1310] but firm conclusions are still lacking, in part because the mechanisms vary depending on the metal, the R group, the catalyst, if any, and the reaction conditions. Two basic pathways can be envisioned: a nucleophilic substitution process (which might be S_N1 or S_N2) and a free-radical mechanism. This could be an SET pathway, or some other route that provides radicals. In either case the two radicals R• and R′• would be in a solvent cage:



It is necessary to postulate the solvent cage because, if the radicals were completely free, the products would be about 50% RR′, 25% RR, and 25% R′R′. This is generally not the case; in most of these reactions RR′ is the predominant or exclusive product.[1311] An example where an S_N2 mechanism has been demonstrated (by the finding of inversion of configuration at R) is the reaction between allylic or benzylic lithium reagents with secondary halides.[1312] The fact that in some of these cases the

[1307]For a review of oxazolines in aromatic substitutions, see Reuman, M.; Meyers, A.I. *Tetrahedron*, ***1985***, *41*, 837. For the similar use of oxazoles, see Cram, D.J.; Bryant, J.A.; Doxsee, K.M. *Chem. Lett.*, ***1987***, 19.
[1308]Nédélec, J.; Aït Haddou Mouloud, H.; Folest, J.; Périchon, J. *J. Am. Chem. Soc.* ***1988***, *53*, 4720.
[1309]For the transformation $RX \rightarrow RCF_3$, see Chen, Q.; Wu, S. *J. Chem. Soc., Chem. Commun.* ***1989***, 705.
[1310]For a review, see Beletskaya, I.P.; Artamkina, G.A.; Reutov, O.A. *Russ. Chem. Rev.* ***1976***, *45*, 330.
[1311]When a symmetrical distribution of products *is* found, this is evidence for a free-radical mechanism: the solvent cage is not efficient and breaks down.
[1312]Sauer, J.; Braig, W. *Tetrahedron Lett.* ***1969***, 4275; Sommer, L.H.; Korte, W.D. *J. Org. Chem.* ***1970***, *35*, 22; Korte, W.D.; Kinner, L.; Kaska, W.C. *Tetrahedron Lett.* ***1970***, 603. See also, Schlosser, M.; Fouquet, G. *Chem. Ber.* ***1974***, *107*, 1162, 1171.

reaction can be successfully applied to aryl and vinylic substrates indicates that a simple S_N process cannot be the only mechanism. One possibility is that the reagents first undergo an exchange reaction: $ArX + RM \rightarrow RX + ArM$, and then a nucleophilic substitution takes place. On the other hand, there is much evidence that many coupling reactions involving organometallic reagents with simple alkyl groups occur by free-radical mechanisms. Among the evidence[1313] is the observation of CIDNP in reactions of alkyl halides with simple organolithium reagents[1314] (see p. 269), the detection of free radicals by esr spectroscopy[1315] (p. 277), and the formation of 2,3-dimethyl-2,3-diphenylbutane when the reaction was carried out in the presence of cumene[1316] (this product is formed when a free-radical abstracts a hydrogen from cumene to give $PhCMe_2$, which dimerizes). Evidence for free-radical mechanisms has also been found for the coupling of alkyl halides with simple organosodium compounds (Wurtz),[1317] with Grignard reagents,[1318] and with lithium dialkylcopper reagents (see **10-58**).[1319] Free radicals have also been implicated in the metal-ion-catalyzed coupling of alkyl and aryl halides with Grignard reagents.[1320]

A much older reaction is the coupling of alkyl halides with Grignard reagents.[1321] Grignard reagents have the advantage that they are usually simpler to prepare than the corresponding R'_2CuLi (see **10-58**), but the reaction is much narrower in scope. Grignard reagents couple only with active halides: allylic (though allylic rearrangements are common) and benzylic. They also couple with tertiary alkyl halides, but generally in low or moderate yields.[1322]

Aryl Grignard reagents usually give better yields in these reactions than alkyl Grignard reagents. Aryl triflates couple with arylmagnesium halides in the presence

[1313]For other evidence, see Muraoka, K.; Nojima, M.; Kusabayashi, S.; Nagase, S. *J. Chem. Soc. Perkin Trans. 2* ***1986***, 761.

[1314]Ward, H.R.; Lawler, R.G.; Cooper, R.A. *J. Am. Chem. Soc.* ***1969***, *91*, 746; Lepley, A.R.; Landau, R.L. *J. Am. Chem. Soc.* ***1969***, *91*, 748; Podoplelov, A.V.; Leshina, T.V.; Sagdeev, R.Z.; Kamkha, M.A.; Shein, S.M. *J. Org. Chem. USSR* ***1976***, *12*, 488. For a review, see Ward, H.R.; Lawler, R.G.; Cooper, R.A., in Lepley, A.R.; Closs, G.L. *Chemically Induced Magnetic Polarization*, Wiley, NY, ***1973***, pp. 281–322.

[1315]Russell, G.A.; Lamson, D.W. *J. Am. Chem. Soc.* ***1969***, *91*, 3967.

[1316]Bryce-Smith, D. *Bull. Soc. Chim. Fr.* ***1963***, 1418.

[1317]Garst, J.F.; Cox, R.H. *J. Am. Chem. Soc.* ***1970***, *92*, 6389; Kasukhin, L.F.; Gragerov, I.P. *J. Org. Chem. USSR* ***1971***, *7*, 2087; Garst, J.F.; Hart, P.W. *J. Chem Soc. Chem. Commun.* ***1975***, 215.

[1318]Gough, R.G.; Dixon, J.A. *J. Org. Chem.* ***1968***, *33*, 2148; Ward, H.R.; Lawler, R.G.; Marzilli, T.A. *Tetrahedron Lett.* ***1970***, 521; Kasukhin, L.F.; Ponomarchuk, M.P.; Buteiko, Zh.F. *J. Org. Chem. USSR* ***1972***, *8*, 673; Singh, P.R.; Tayal, S.R.; Nigam, A. *J. Organomet. Chem.* ***1972***, *42*, C9.

[1319]Ashby, E.C.; Coleman, D. *J. Org. Chem.* ***1987***, *52*, 4554; Bertz, S.H.; Dabbagh, G.; Mujsce, A.M. *J. Am. Chem. Soc.* ***1991***, *113*, 631.

[1320]Norman, R.O.C.; Waters, W.A. *J. Chem. Soc.* ***1957***, 950; Frey Jr., F.W. *J. Org. Chem.* ***1961***, *26*, 5187; Slaugh, L.H. *J. Am. Chem. Soc.* ***1961***, *83*, 2734; Davies, D.I.; Done, J.N.; Hey, D.H. *J. Chem. Soc. C* ***1969***, 1392, 2021, 2056; Abraham, M.H.; Hogarth, M.J. *J. Organomet. Chem.* ***1968***, *12*, 1, 497; Tamura, M.; Kochi, J.K. *J. Am. Chem. Soc.* ***1971***, *93*, 1483, 1485, 1487; *J. Organomet. Chem.* ***1971***, *31*, 289; ***1972***, *42*, 205; Lehr, G.F.; Lawler, R.G. *J. Am. Chem. Soc.* ***1986***, *106*, 4048.

[1321]For reviews, see Raston, C.L.; Salem, G., in Hartley, F.R. *The Chemistry of the Metal-Carbon Bond*, Vol. 4, Wiley, NY, ***1987***, pp. 161–306, 269–283; Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood Cliffs, NJ, ***1954***, pp. 1046–1165.

[1322]See, for example, Ohno, M.; Shimizu, K.; Ishizaki, K.; Sasaki, T.; Eguchi, S. *J. Org. Chem.* ***1988***, *53*, 729.

of a palladium catalyst,[1323] as do vinyl halides with RMgX with a palladium[1324] or nickel catalyst.[1325] It is also possible to couple alkynylmagnesium halides with aryl iodides in the presence of palladium catalysts.[1326] A silica-supported phosphine–palladium (0) medium was used to couple arylmagnesium halides with aryl iodides.[1327] Aryl Grignard reagents couple with alkyl halides, including neopentyl iodide, in the presence of $ZnCl_2$ and a nickel catalyst.[1328]

In some cases, vinyl halides can be coupled. An aryl Grignard reagent was coupled to a vinyl iodide in the presence of an iron catalyst.[1329] Butylmagnesium chloride was coupled to vinyl triflates with $Fe(acac)_3$.[1330] The palladium-catalyzed coupling of arylmagnesium halides and vinyl bromides has also been reported.[1331]

Because Grignard reagents react with the C=O group (**16-24**, **16-82**), they cannot be used to couple with halides containing ketone, COOR, or amide functions. Although the coupling of Grignard reagents with ordinary alkyl halides is usually not useful for synthetic purposes, small amounts of symmetrical coupling product are commonly formed while Grignard reagents are being prepared.

For symmetrical coupling of organometallic reagents (2RM → RR), see **14-24** and **14-25**.

OS **I**, 186; **III**, 121; **IV**, 748; **VI**, 407; **VII**, 77, 172, 326, 485; **VIII**, 226, 396; **IX**, 530; **X**, 332, 396.

10-58 Reaction of Alkyl Halides and Sulfonate Esters with Organocuprates

Alkyl-de-halogenation

$$RX + R'_2CuLi \longrightarrow R{-}R'$$

The reagents lithium dialkylcopper[1332] (dialkyl cuprates, also called *Gilman reagents*)[1333] react with alkyl bromides, chlorides, and iodides in ether or THF to

[1323]Kamikawa, T.; Hayashi, T. *Synlett*, ***1997***, 163.
[1324]Hoffmann, R.W.; Gieson, V.; Fuest, M. *Liebigs Ann. Chem.* ***1993***, 629.
[1325]Babudri, F.; Fiandanese, V.; Mazzone, L.; Naso, F. *Tetrahedron Lett.* ***1994***, *35*, 8847.
[1326]Negishi, E.; Kotora, M.; Xu, C. *J. Org. Chem.* ***1997***, *62*, 8957.
[1327]Cai, M.-Z.; Song, C.-S.; Huang, X. *J. Chem. Res. (S)* ***1998***, 264.
[1328]Kondo, S.; Ohira, M.; Kawasoe, S.; Kunisada, H.; Yuki, Y. *J. Org. Chem.* ***1993***, *58*, 5003.
[1329]Dohle, W.; Kopp, F.; Cahiez, G.; Knochel, P. *Synlett* ***2001***, 1901.
[1330]Scheiper, B.; Bonnekessel, M.; Krause, H.; Fürstner, A. *J. Org. Chem.* ***2004***, *69*, 3943.
[1331]Rathore, R.; Deselnicu, M.I.; Burns, C.L. *J. Am. Chem. Soc.* ***2002***, *124*, 14832.
[1332]For the structure of Me_2CuLi (a cyclic dimer), see Pearson, R.G.; Gregory, C.D. *J. Am. Chem. Soc.* ***1976***, *98*, 4098. See also, Lipshutz, B.H.; Kozlowski, J.A.; Breneman, C.M. *Tetrahedron Lett.* ***1985***, *26*, 5911. For a review of the structure and reactions of organocopper compounds, see Collman, J.P.; Hegedus, L.S.; Norton, J.R.; Finke, R.G. *Principles and Applications of Organotransition Metal Chemistry*, 2nd ed., University Science Books, Mill Valley, CA, ***1987***, pp. 682–698.
[1333]See Stemmler, T.L.; Barnhart, T.M.; Penner-Hahn, J.E.; Tucker, C.E.; Knochel, P.; Böhme, M.; Frenking, G. *J. Am. Chem. Soc.* ***1995***, *117*, 12489 for a discussion concerning the structure of organocuprate reagents. Solution compositions of Gilman reagents have also been studied. See Lipshutz, B.H.; Kayser, F.; Siegmann, K. *Tetrahedron Lett.* ***1993***, *34*, 6693.

give good yields of the cross-coupling products.[1334] They are prepared (see **12-36**) by the reaction of an organolithium compound with CuI or CuBr, typically, most other Cu(I) compounds can be used. They are usually generated at temperatures $<0°C$ due to the thermal instability of many dialkyl cuprates. The reaction with alkyl halides is of wide scope[1335] and R in R_2CuLi may be primary alkyl, allylic, benzylic, aryl, vinylic, or allenic, and may contain keto, COOH, COOR, or $CONR_2$ groups.[1336] Inversion of configuration has been shown in the reaction of 2-bromobutane with Ph_2CuLi,[1337] but the same reaction with 2-iodobutane has been reported to proceed with racemization.[1338] The reaction at a vinylic substrate occurs stereospecifically, with retention of configuration.[1339] When the reagent and substrate are both vinylic, yields are low, but the reaction can be pushed to give 1,3-butadienes, stereospecifically and in high yields by the use of $ZnBr_2$ and a Pd(0) complex.[1340] Many *gem*-dihalides do not react, but when the two halogens are on a carbon α to an aromatic ring[1341] or on a cyclopropane ring,[1342] both halogens can be replaced by R, for example, $PhCHCl_2 \rightarrow PhCHMe_2$. However, 1,2-dibromides give exclusive elimination[1337] (**17-22**). Vinylmagnesium halides, upon addition of a catalytic amount of Li_2CuCl_4, couple to alkyl halide.[1343]

Lithium dialkylcopper reagents couple with alkyl tosylates.[1344] High yields are obtained with primary tosylates; secondary tosylates give lower yields.[1345] Aryl tosylates do not react. Vinylic triflates[1346] couple very well to give alkenes[1347] and they

[1334]Corey, E.J.; Posner, G.H. *J. Am. Chem. Soc.* ***1968***, *90*, 5615; Bergbreiter, D.E.; Whitesides, G.M. *J. Org. Chem.* ***1975***, *40*, 779. See Bertz, S.H.; Eriksson, M.; Miao, G.; Snyder, J.P. *J. Am. Chem. Soc.* ***1998***, *118*, 10906 for the reactivity of β-silyl organocuprates.

[1335]For reviews see Posner, G.H. *Org. React.* ***1975***, *22*, 253; Normant, J.F. *Synthesis* ***1972***, 63; Lipshutz, B.H. *Accts. Chem. Res*. ***1997***, *30*, 277; Posner, G.H. *An Introduction to Synthesis Using Organocopper Reagents*, Wiley, NY, ***1980***. For lists of substrates and reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 392–399, 599–604, 1564.

[1336]For a discussion of the mechansim of S_N2 alkylation with organocuprates see Mori, S.; Nakamura, E.; Morokuma, K. *J. Am. Chem. Soc.* ***2000***, *122*, 7294.

[1337]Cahiez, G.; Chaboche, C.; Jézéquel, M. *Tetrahedron* ***2000***, *56*, 2733.

[1338]Lipshutz, B.H.; Wilhelm, R.S.; Nugent, S.T.; Little, R.D.; Baizer, M.M. *J. Org. Chem.* ***1983***, *48*, 3306.

[1339]Corey, E.J.; Posner, G.H. *J. Am. Chem. Soc.* ***1967***, *89*, 3911; Klein, J.; Levene, R. *J. Am. Chem. Soc.* ***1972***, *94*, 2520. For a discussion of the mechanism, see Yoshikai, N.; Nakamura, E. *J. Am. Chem. Soc.* ***2004***, *126*, 12264.

[1340]Jabri, N.; Alexakis, A.; Normant, J.F. *Tetrahedron Lett.* ***1981***, *22*, 959; ***1982***, *23*, 1589; *Bull. Soc. Chim. Fr.* ***1983***, II-321, II-332.

[1341]Posner, G.H.; Brunelle, D.J. *Tetrahedron Lett.* ***1972***, 293.

[1342]See, for example, Kitatani, K.; Hiyama, T.; Nozaki, H. *Bull. Chem. Soc. Jpn.* ***1977***, *50*, 1600.

[1343]Posner, G.H.; Ting, J. *Synth. Commun.* ***1973***, *3*, 281.

[1344]Johnson, C.R.; Dutra, G.A. *J. Am. Chem. Soc.* ***1973***, *95*, 7777, 7783. For examples, see Posner, G.H. *An Introduction to Synthesis Using Organocopper Reagents*, Wiley, NY, ***1980***, pp. 85–90.

[1345]Secondary tosylates give higher yields when they contain an O or S atom: Hanessian, S.; Thavonekham, B.; DeHoff, B. *J. Org. Chem.* ***1989***, *54*, 5831.

[1346]For a review of coupling reactions of vinylic triflates, see Scott, W.J.; McMurry, J.E. *Acc. Chem. Res.* ***1988***, *21*, 47.

[1347]McMurry, J.E.; Scott, W.J. *Tetrahedron Lett.* ***1980***, *21*, 4313; Tsushima, K.; Araki, K.; Murai, A. *Chem. Lett.* ***1989***, 1313.

also couple with allylic cuprates, to give 1,4-dienes.[1348] Propargylic tosylates couple with vinylic cuprates to give vinylic allenes.[1349]

The R′ in R'_2CuLi may be primary alkyl, vinylic, allylic, or aryl. Thus, in the reaction as so far described, the alkyl groups on the organocuprate or the alkyl halide may *not* be secondary or tertiary alkyl. However, secondary and tertiary alkyl coupling can be achieved (on primary RX) by the use of $R'_2CuLi{\bullet}PBu_3$[1350] (though this procedure introduces problems in the workup) or by the use of PhS(R′)CuLi,[1351] which selectively couples a secondary or tertiary R′ with a primary iodide RI to give RR′.[1352] It is possible to prepare mixed cuprates, where one ligand is tightly bound to the copper, allowing the other ligand to be transferred in a coupling reaction. A common example is adds a 2-thienyl group to the cuprate to give R(Th)CuLi, where the R group is transferred in lieu of the thienyl unit.[1353] A lithium neopentyl aryl cuprate selectively transferred to aryl group to an allylic halide.[1354]

Coupling to a secondary alkyl halide (R in RX above = secondary) can be achieved in high yield with the reagents $R'_2Cu(CN)Li_2$,[1355] where R′ is primary alkyl or vinylic (but not aryl).[1356] This modified reagent is commonly known as a higher order mixed cuprate. The reagents $RCu(PPh_2)Li$, $RCu(NR'_2)Li$, and $RCu(PR'_2)Li$ (R′ = cyclohexyl) are more stable than R_2CuLi and can be used at higher temperatures.[1357] However, these reagents are quite reactive. Unactivated aryl triflates[1358] $ArOSO_2CF_3$ react to give ArR in good yields when treated with $R_2Cu(CN)Li_2$,[1359] with R_3Al,[1360] or with R'_3SnR and a Pd complex catalyst.[1361] See section **10-59** for other examples involving Al, Sn and Pd coupling reactions.

[1348]Lipshutz, B.H.; Elworthy, T.R. *J. Org. Chem.* ***1990***, *55*, 1695.

[1349]Baudouy, R.; Goré, J. *J. Chem. Res. (S)* ***1981***, 278. See also, Elsevier, C.J.; Vermeer, P. *J. Org. Chem.* ***1989***, *54*, 3726.

[1350]Whitesides, G.M.; Fischer, Jr., W.F.; San Filippo, Jr., J.; Bashe, R.W.; House, H.O., *J. Am. Chem. Soc.* ***1969***, *91*, 4871.

[1351]Prepared as in Ref. 1371 or treatment of PhSCu with RLi: Posner, G.H.; Brunelle, D.J.; Sinoway, L. *Synthesis* ***1974***, 662.

[1352]Posner, G.H.; Whitten, C.E.; Sterling, J.J. *J. Am. Chem. Soc.* ***1973***, *95*, 7788.

[1353]For an example, see Malmberg, H.; Nilsson, M.; Ullenius, C. *Tetrahedron Lett.* ***1982***, *23*, 3823. For an example involving higher order cuprates, see Lipshutz, B.H.; Kozlowski, J.A.; Parker, D.A.; Nguyen, S.L.; McCarthy, K.E. *J. Organomet. Chem.* ***1985***, *285*, 437.

[1354]Piazza, C.; Knochel, P. *Angew. Chem. Int. Ed.* ***2002***, *41*, 3263.

[1355]For reviews of these and other "higher order" organocuprates, see Lipshutz, B.H.; Wilhelm, R.S.; Kozlowski, J.A. *Tetrahedron* ***1984***, *40*, 5005; Lipshutz, B.H. *Synthesis* ***1987***, 325; *Synlett* ***1990***, 119. See also, Bertz, S.H. *J. Am. Chem. Soc.* ***1990***, *112*, 4031; Lipshutz, B.H.; Sharma, S.; Ellsworth, E.L. *J. Am. Chem. Soc.* ***1990***, *112*, 4032.

[1356]Lipshutz, B.H.; Wilhelm, R.S.; Floyd, D.M. *J. Am. Chem. Soc.* ***1981***, *103*, 7672.

[1357]Bertz, S.H.; Dabbagh, G.; Villacorta, G.M. *J. Am. Chem. Soc.* ***1982***, *104*, 5824; Bertz, S.H.; Dabbagh, G. *J. Org. Chem.* ***1984***, *49*, 1119.

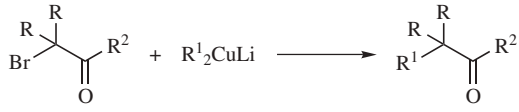
[1358]For another coupling reaction of aryl triflates, see Aoki, S.; Fujimura, T.; Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.*, ***1988***, *110*, 3296.

[1359]McMurry, J.E.; Mohanraj, S. *Tetrahedron Lett.*, ***1983***, *24*, 2723.

[1360]Hirota, K.; Isobe, Y.; Maki, Y. *J. Chem. Soc., Perkin Trans. 1*, ***1989***, 2513.

[1361]Echevarren, E.M.; Stille, J.K. *J. Am. Chem. Soc.*, ***1987***, *109*, 5478. For a similar reaction with aryl fluorosulfonates, see Roth, G.P.; Fuller, C.E. *J. Org. Chem.*, ***1991***, *56*, 3493.

Both OTf units in $RCH(OTf)_2$ can be replaced with $Me_2(CN)CuLi_2$.[1362] With an allenic substrate, reaction with R(CN)CuLi can give ordinary displacement (with retention of configuration)[1363] or an S_N2' reaction to produce an alkyne.[1364] In the latter case, a chiral allene gave a chiral alkyne. The structures of these "higher order mixed" cuprates has been called into question[1365] by Bertz, who suggested the reagent actually existed as $R_2CuLi{\bullet}LiCN$ in THF.[1366] This was contradicted by Lipshutz.[1367]



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The fact that R'_2CuLi do not react with ketones provides a method for the alkylation of ketones via the organocuprate coupling with α-halokeotones, such as **143**[1368] (see also, **10-68** and **10-73**). Note that halogen–metal exchange (**12-39**) is a side reaction and can become the main reaction.[1369] When α,α′-dibromo ketones are treated with Me_2CuLi in ether at −78°C and the mixture quenched with methanol, *mono*methylation takes place[1370] (no dimethylation is observed). It has been suggested that the reaction involves cyclization (**10-56**) to a cyclopropanone followed by nucleophilic attack to give the enolate anion, which is protonated by the methanol. If methyl iodide is added instead of methanol, an α,α′-dimethyl ketone is obtained, presumably from S_N2 attack (**10-68**). Primary, secondary, *and tertiary* monoalkylation can be achieved with a lithium *tert*-butoxy (alkyl)copper reagent[1371] instead of Me_2CuLi, one of the few methods for introducing a tertiary alkyl group a to a carbonyl group.

When dialkylcopperzinc reagents $R_2CuZnCl$ couple with allylic halides, almost complete allylic rearrangement occurs (S_N2'), and the reaction is diastereoselective if the allylic halide contains a δ alkoxy group.[1372] Another type of copper reagent

[1362]Martínez, A.G.; Barcina, J.O.; Díez, B.R.; Subramanian, L.R. *Tetrahedron* ***1994***, *50*, 13231.
[1363]Mooiweer, H.H.; Elsevier, C.J.; Wijkens, P.; Vermeer, P. *Tetrahedron Lett.* ***1985***, *26*, 65.
[1364]Corey, E.J.; Boaz, N.W. *Tetrahedron Lett.* ***1984***, *25*, 3059, 3063. For the reaction of these reagents with haloalkynes, see Yeh, M.C.P.; Knochel, P. *Tetrahedron Lett.* ***1989***, *30*, 4799.
[1365]Bertz, S.H.; Miao, G.; Eriksson, M. *Chem. Commun.* ***1996***, 815; Snyder, J.P.; Bertz, S.H. *J. Org. Chem.* ***1995***, *60*, 4312. Also see, Snyder, J.P.; Tipsword, G.E.; Spangler, D.P. *J. Am. Chem. Soc.* ***1992***, *114*, 1507.
[1366]Bertz, S.H. *J. Am. Chem. Soc.* ***1990***, *112*, 4031.
[1367]Lipshutz, B.H.; James, B. *J. Org. Chem.* ***1994***, *59*, 7585; Lipshutz, B.H.; Sharma, S.; Ellsworth, E.L. *J. Am. Chem. Soc.* ***1990***, *112*, 4032.
[1368]Dubois, J.E.; Lion, C.; Moulineau, C. *Tetrahedron Lett.* ***1971***, 177; Dubois, J.E.; Fournier, P.; Lion, C. *Bull. Soc. Chim. Fr.* ***1976***, 1871.
[1369]See Corey, E.J.; Posner, G.H. *J. Am. Chem. Soc.* ***1967***, *89*, 3911; Wakselman, C.; Mondon, M. *Tetrahedron Lett.* ***1973***, 4285.
[1370]Posner, G.H.; Sterling, J.J. *J. Am. Chem. Soc.* ***1973***, *95*, 3076. See also, Posner, G.H.; Sterling, J.J.; Whitten, C.E.; Lentz, C.M.; Brunelle, D.J. *J. Am. Chem. Soc.* ***1975***, *97*, 107; Lion, C.; Dubois, J.E. *Tetrahedron* ***1975***, *31*, 1223. The compound Ph_2CuLi behaves similarly: see Lei, X.; Doubleday Jr., C.; Turro, N.J. *Tetrahedron Lett.* ***1986***, *27*, 4671.
[1371]Prepared by treating CuI with *t*-BuOLi in THF at 0°C and adding RLi to this solution.
[1372]Nakamura, E.; Sekiya, K.; Arai, M.; Aoki, S. *J. Am. Chem. Soc.* ***1989***, *111*, 3091.

was prepared from RZnI/CuCN, and this was shown to couple with alkenyl halides,[1373] and diethylzinc in the presence of a catalytic amount of CuBr coupled to allylic chlorides.[1374] When treated with organocopper compounds and Lewis acids (e.g., *n*-BuCu•BF_3), allylic halides give substitution with almost complete allylic rearrangement, irrespective of the degree of substitution at the two ends of the allylic system.[1375]

$$ArI + R_2CuLi \longrightarrow ArR$$

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10-59 Reaction of Alkyl Halides and Sulfonate Esters With Other Organometallic Reagents

Alkyl-de-halogenation

$$RX + R'{-}M \longrightarrow R{-}R'$$

Many other metals and metal complexes can be used to catalyze or mediate coupling reactions. Organoaluminum compounds couple very well with tertiary (to give products containing a quaternary carbon) and benzylic halides at −78°C.[1376] This reaction can also be applied to allylic, secondary, and some primary halides, but several days standing at room temperature is required (see also **10-63**). Vinylic aluminum compounds (in the presence of a suitable transition-metal catalyst) couple with allylic halides, acetates, and alcohol derivatives to give 1,4-dienes,[1377] and with vinylic and benzylic halides to give 1,3-dienes and allylic arenes, respectively.[1378] An interesting transformation treated a vinyl nitro compound ($PhCH{=}CHNO_2$) with Et_3Al and a large excess of 2-iodopropane, in the presence of 2 equivalents of dibenzoyl peroxide, to give the coupling product, PhCH=CH*i*-Pr.[1379] Note that alkylboronic acids are coupled in the presence of Ag_2O and a catalytic amount of $CrCl_2$ to give the symmetrical alkyl derivative.[1380]

[1373]Marquais, S.; Cahiez, G.; Knochel, P. *Synlett*, ***1994***, 849.
[1374]Malda, H.; van Zijl, A.W.; Arnold, L.A.; Feringa, B.L. *Org. Lett.* ***2001***, *3*, 1169.
[1375]Yamamoto, Y.; Yamamoto, S.; Yatagai, H.; Maruyama, K. *J. Am. Chem. Soc.* ***1980***, *102*, 2318. See also, Lipshutz, B.H.; Ellsworth, E.L.; Dimock, S.H. *J. Am. Chem. Soc.* ***1990***, *112*, 5869.
[1376]Miller, D.B. *J. Org. Chem.* ***1966***, *31*, 908; Kennedy, J.P. *J. Org. Chem.* ***1970***, *35*, 532. See also, Kennedy, J.P.; Sivaram, S. *J. Org. Chem.* ***1973***, *38*, 2262; Sato, F.; Kodama, H.; Sato, M. *J. Organomet. Chem.* ***1978***, *157*, C30.
[1377]Lynd, R.A.; Zweifel, G. *Synthesis* ***1974***, 658; Matsushita, H.; Negishi, E. *J. Am. Chem. Soc.* ***1981***, *103*, 2882; *J. Chem. Soc., Chem. Commun.* ***1982***, 160. For similar reactions with other metals, see Larock, R.C.; Bernhardt, J.C.; Driggs, R.J. *J. Organomet. Chem.* ***1978***, *156*, 45; Brown, H.C.; Campbell, Jr., J.B. *J. Org. Chem.* ***1980***, *45*, 550; Baeckström, P.; Björkling, F.; Högberg, H.; Norin, T. *Acta Chem. Scand. Ser. B*, ***1984***, *38*, 779.
[1378]Negishi, E.; Takahashi, T.; Baba, S.; Van Horn, D.E.; Okukado, N. *J. Am. Chem. Soc.* ***1987***, *109*, 2393; Negishi, E.; Takahashi, T.; Baba, S. *Org. Synth. 66*, 60.
[1379]Liu, J.-Y.; Liu, J.-T.; Yao, C.-F. *Tetrahedron Lett.* ***2001***, *42*, 3613.
[1380]Falck, J.R.; Mohaptra, S.; Bondlela, M.; Venkataraman, S.K. *Tetrahedron Lett.* ***2002***, *43*, 8149.

Products containing a quaternary carbon can also be obtained by treatment of tertiary halides with dialkyl or diaryl zinc reagents in CH_2Cl_2,[1381] with Me_4Si and $AlCl_3$,[1382] or with alkyltitanium reagents $RTiCl_3$ and R_2TiCl_2.[1383] Dialkylzinc compounds can be coupled to alkyl iodides in the presence of a nickel catalyst,[1384] but with geminal diiodo compounds without a catalyst.[1385] Copper compounds can also be used as catalysts with dialkylzinc reagents.[1386] The reaction of aryl halides with Me_4ZnLi_2, and then $VO(OEt)Cl_2$ leads to the methylated aryl.[1387] Isopropylzinc (*i*PrZn) displaces the iodide in γ-iodo ketones to give the alkyl substitution product, without reaction at the carbonyl.[1388] Reactions of organozinc reagents with a carbonyl compound via acyl addition is presented in **16-31**, the Reformatsky reaction. The titanium method can also be used with secondary halides ($R_2CHCl \rightarrow R_2CHMe$), tertiary ethers ($R_3COR' \rightarrow R_3CMe$), and *gem*-dihalides ($R_2CCl_2 \rightarrow R_2CMe_2$).[1389] Tertiary halides have also been coupled to allyltin reagents in the presence of AIBN.[1390] Alkyl halides can be treated with SmI_2 and then CuBr to give a reactive species that couples with other alkyl halides.[1391] Trialkylindium compounds couple to allylic bromides in the presence of $Cu(OTf)_2$•$P(OEt)_3$[1392] and vinyl indium compounds are coupled to α-halo esters with a BEt_3 catalyst.[1393] Arylsulfonyl chlorides couple with allyl halides in the presence of bismuth to give allyl-aryls.[1394] Vinyl iodides couple with RMnCl with an iron catalyst[1395] and $Bu_3MnMgBr$ reacted with a geminal dibromocyclopropane to give a dialkylated cyclopropane.[1396] α-Haloketones are coupled with aryl halides using a nickel catalyst.[1397] Allylgallium reagents have been coupled to α-bromo esters in the presence of BEt_3/O_2.[1398]

Arylpalladium salts ''ArPdX'' prepared from arylmercury compounds and lithium palladium chloride couple with allylic chlorides in moderate yields,

[1381]Reetz, M.T.; Wenderoth, B.; Peter, R.; Steinbach, R.; Westermann, J. *J. Chem. Soc., Chem. Commun.* ***1980***, 1202. See also, Klingstedt, T.; Frejd, T. *Organometallics* ***1983***, *2*, 598.
[1382]Bolestova, G.I.; Parnes, Z.N.; Latypova, F.M.; Kursanov, D.N. *J. Org. Chem. USSR* ***1981***, *17*, 1203.
[1383]Reetz, M.T.; Westermann, J.; Steinbach, R. *Angew. Chem. Int. Ed.* ***1980***, *19*, 900, 901.
[1384]Giovannini, R.; Stüdemann, T.; Devasagayaraj, A.; Dussin, G.; Knochel, P. *J. Org. Chem.* ***1999***, *64*, 3544; Jensen, A.E.; Knochel, P. *J. Org. Chem.* ***2002***, *67*, 79; Zhou, J.; Fu, G.C. *J. Am. Chem. Soc.* ***2003***, *125*, 14726; Terao, J.; Todo, H.; Watanabe, H.; Ikumi, A.; Kambe, N. *Angew. Chem. Int. Ed.* ***2004***, *43*, 6180.
[1385]Shibli, A.; Varghese, J.P.; Knochel, P.; Marek, I. *Synlett* ***2001***, 818.
[1386]Shi, W.J.; Wang, L.-X.; Fu, Y.; Zhu, S.-F.; Zhou, Q.-L. *Tetrahedron Asymmetry* ***2003***, *14*, 3867.
[1387]Hu, J.-b.; Zhao, G.; Yang, G.-s.; Ding, Z.-d. *J. Org. Chem.* ***2001***, *66*, 303.
[1388]Jensen, A.E.; Knochel, P. *J. Org. Chem.* ***2002***, *67*, 79.
[1389]Reetz, M.T.; Steinbach, R.; Wenderoth, B. *Synth. Commun.* ***1982***, *11*, 261.
[1390]Kraus, G.A.; Ansersh, B.; Su, Q.; Shi, J. *Tetrahedron Lett.* ***1993***, *34*, 1741.
[1391]Berkowitz, W.F.; Wu, Y. *Tetrahedron Lett.* ***1997***, *38*, 3171.
[1392]Rodríguez, D.; Sestelo, J.P.; Sarandeses, L.A. *J. Org. Chem.* ***2003***, *68*, 2518.
[1393]Takami, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* ***2004***, *6*, 4555.
[1394]Baruah, M.; Boruah, A.; Prajapati, D.; Sandu, J.S. *Synlett*, ***1998***, 1083.
[1395]Cahiez, G.; Marquais, S. *Tetrahedron Lett.* ***1996***, *37*, 1773.
[1396]Kakiya, H.; Inoue, R.; Shinokubo, H.; Oshima, K. *Tetrahedron* ***2000***, *56*, 2131.
[1397]Durandetti, M.; Sibille, S.; Nédélec, J.-Y.; Périchon, J. *Synth. Commun.* ***1994***, *24*, 145.
[1398]Usugi, S.-i.; Yorimitsu, H.; Oshima, K. *Tetrahedron Lett.* ***2001***, *42*, 4535.

although allylic rearrangements can occur.[1399] The advantage of this procedure is that the aryl group may contain nitro, ester, or aldehyde groups, and so on, which cannot be present in a Grignard reagent. In most cases, a palladium(0) complex is added to the substrate, sometimes in conjunction with another metal, to facilitate coupling. Any arylpalladium species is therefore generated *in situ*. Allylic, benzylic, vinylic, and aryl halides or triflates (trifluoromethylsulfonates) couple with organotin reagents in a reaction catalyzed by palladium complexes.[1400] Such functional groups as COOR, CN, OH, and CHO may be present in either reagent, but the substrate may not bear a β hydrogen on an sp^3 carbon, because that results in elimination. Indium metal has been used to mediate the coupling of an allylic halide and an arylpalladium complex,[1401] and organoindium compounds were coupled to 1-iodonaphthalene with a palladium catalyst.[1402] Dimethylzinc was coupled to aryl halides with a palladium catalyst,[1403] and Reformatsky-type zinc derivatives (**16–28**) have been coupled to aryl halides using a palladium catalyst and microwave irradiation.[1404]

In many cases, the organometallic reagent is prepared from the corresponding organolithium reagent (**10-57**), as in the conversion of an aryllithium to an arylzirconium reagent, which was subsequently coupled to a aryl halide in the presence of a palladium catalyst.[1405] Alkyl or aryl triflates (halides) couple with alkyl or ArZn(halide) reagents in the presence of a palladium catalyst.[1406] This organozinc coupling reaction has been done in ionic liquids.[1407] Vinyl halides coupled with vinyltin reagents in the presence of CuI,[1408] and aryl tin compounds couple with vinyl halides[1409] or vinyl triflates when a palladium catalyst is present.[1410] When the vinyltin reagent is coupled with a vinyl triflate in the presence of a palladium catalyst, the reaction is known as the *Stille reaction* (**12-15**). These latter reactions are obviously related, but the Stille reaction is placed in Chapter 14 for mechanistic reasons related

[1399]Heck, R.F. *J. Am. Chem. Soc.* ***1968***, *90*, 5531. See **13-10**. For a review of palladium-assisted coupling, see Heck, R.F. *Palladium Reagents in Organic Syntheses*, Academic Press, NY, ***1985***, pp. 208–214, 242–249.

[1400]For a review, see Stille, J.K. *Angew. Chem. Int. Ed.* ***1986***, *25*, 508. For a review of the mechanism, see Bumagin, N.A.; Beletskaya, I.P. *Russ. Chem. Rev.* ***1990***, *59*, 1174. See also, Stille, J.K.; Simpson, J.H. *J. Am. Chem. Soc.* ***1987***, *109*, 2138; Martínez, A.G.; Barcina, J.O.; Heras, Md.R.C.; Cerezo, A.d.F. *Org. Lett.* ***2000***, *2*, 1377.

[1401]Lee, P.H.; Sung, S.-y.; Lee, K. *Org. Lett.* ***2001***, *3*, 3201.

[1402]Lee, P.H.; Lee, S.W.; Seomoon, D. *Org. Lett.* ***2003***, *5*, 4963; Rodríguez, D.; Sestelo, J.P.; Sarandeses, L.A. *J. Org. Chem.* ***2004***, *69*, 8136.

[1403]Herbert, J.M. *Tetrahedron Lett.* ***2004***, *45*, 817.

[1404]Bentz, E.; Moloney, M.G.; Westaway, S.M. *Tetrahedron Lett.* ***2004***, *45*, 7395.

[1405]Frid, M.; Pérez, D.; Peat, A.J.; Buchwald, S.L. *J. Am. Chem. Soc.* ***1999***, *121*, 9469. See also, Villiers, P.; Vicart, N.; Ramondenc, Y.; Plé, G. *Tetrahedron Lett.* ***1999***, *40*, 8781.

[1406]Piber, M.; Jensen, A.E.; Rottländer, M.; Knochel, P. *Org. Lett.* ***1999***, *1*, 1323; Hossain, K.M.; Shibata, T.; Takagi, K. *Synlett* ***2000***, 1137; Zhou, J.; Fu, G.C. *J. Am. Chem. Soc.* ***2003***, *125*, 12527.

[1407]Sirieix, J.; Oßberger, M.; Betzemeier, B.; Knochel, P. *Synlett* ***2000***, 1613.

[1408]Kang, S.-K.; Kim, J.-S.; Choi, S.-C. *J. Org. Chem.* ***1997***, *62*, 4208.

[1409]Shen, W.; Wang, L. *J. Org. Chem.* ***1999***, *64*, 8873.

[1410]Fouquet, E.; Rodriguez, A.L. *Synlett* ***1998***, 1323; Lipshutz, B.H.; Alami, M. *Tetrahedron Lett.* ***1993***, *34*, 1433.

to similar palladium-catalyzed coupling reactions. Vinylic triflates, in the presence of $Pd(Ph_3P)_4$ and LiCl, couple with organotin compounds $R'SnMe_3$, where R′ can be alkyl, allylic, vinylic, or alkynyl.[1411] The reaction has been performed intramolecularly, to prepare large-ring lactones.[1412] Alkyl halides couple with ArMnCl or RMnCl in the presence of a palladium catalyst.[1413] The coupling of aryl substrates to form biaryls is discussed in **13-9**.

Alkenylboranes ($R'_2C{=}CHBZ_2$; Z = various groups) couple in high yields with vinylic,[1414] alkynyl, aryl, benzylic, and allylic halides or triflates in the presence of a palladium catalyst and a base to give $R'_2C{=}CHR$.[1415] 9-Alkyl-9-BBN compounds (**15–16**) also couple with vinylic and aryl halides,[1416] as well as with α-halo ketones, nitriles, and esters.[1417] Another palladium-catalyzed coupling of vinyl halides and alkylboronic acids[1418] gives substituted alkenes, in a reaction that is related to the Suzuki coupling (**13-12**). Arylboronic acids can also be coupled to alkyl halides with a palladium catalyst,[1419] alkylboronic acids can be coupled to aryl halides in a similar manner,[1420] and a cyclopropylboronic acid was coupled to an allylic bromide with silver oxide/KOH and a palladium catalyst.[1421] Vinyl zirconium reagents were coupled to alkyl halides with a palladium catalyst.[1422]

Potassium aryl- and 1-alkenyltrifluoroborates ($ArBF_3K$ and RBF_3K) are easily prepared from organoboronic acids or esters. In general, the trifluoroborates have greater air stability and greater nucleophilicity[1423] when compared to the

[1411]Kwon, H.B.; McKee, B.H.; Stille, J.K. *J. Org. Chem.* ***1990***, *55*, 3114. For discussions of the mechanism, see Stang, P.J.; Kowalski, M.H.; Schiavelli, M.D.; Longford, D. *J. Am. Chem. Soc.* ***1989***, *111*, 3347; Stang, P.J.; Kowalski, M.H. *J. Am. Chem. Soc.* ***1989***, *111*, 3356.

[1412]Stille, J.K.; Tanaka, M. *J. Am. Chem. Soc.* ***1987***, *109*, 3785.

[1413]Riquet, E.; Alami, M.; Cahiez, G. *Tetrahedron Lett.* ***1997***, *38*, 4397; Cahiez, G.; Marquais, S. *Synlett*, ***1993***, 45.

[1414]Occhiato, E.G.; Trabocchi, A.; Guarna, A. *Org. Lett.* ***2000***, *2*, 1241.

[1415]Brown, H.C.; Molander, G.A. *J. Org. Chem.* ***1981***, *46*, 645; Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc.* ***1985***, *107*, 972; Sato, M.; Miyaura, N.; Suzuki, A. *Chem. Lett.* ***1989***, 1405; Rivera, I.; Soderquist, J.A. *Tetrahedron Lett.* ***1991***, *32*, 2311; and references cited therein. For a review, see Matteson, D.S. *Tetrahedron* ***1989***, *45*, 1859.

[1416]Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* ***1989***, *111*, 314. See also, Soderquist, J.A.; Santiago, B. *Tetrahedron Lett.* ***1990***, *31*, 5541.

[1417]Ishiyama, T.; Abe, S.; Miyaura, N.; Suzuki, A. *Chem. Lett.* ***1992***, 691; Brown, H.C.; Joshi, N.N.; Pyun, C.; Singaram, B. *J. Am. Chem. Soc.* ***1989***, *111*, 1754. For another such coupling, see Matteson, D.S.; Tripathy, P.B.; Sarkar, A.; Sadhu, K.M. *J. Am. Chem. Soc.* ***1989***, *111*, 4399.

[1418]Bellina, F.; Anselmi, C.; Rossi, R. *Tetrahedron Lett.* ***2001***, *42*, 3851. See also, Yoshida, H.; Yamaryo, Y.; Oshita, J.; Kunai, A. *Tetrahedron Lett.* ***2003***, *44*, 1541.

[1419]Nobre, S.M.; Monteiro, A.L. *Tetrahedron Lett.* ***2004***, *45*, 8225; Liu, X.-x.; Deng, M.-z. *Chem. Commun.* ***2002***, 622; Langle, S.; Abarbri, M.; Duchêne, A. *Tetrahedron Lett.* ***2003***, *44*, 9255.

[1420]Kondolff, I.; Doucet, H.; Santelli, M. *Tetrahedron* ***2004***, *60*, 3813. For a variation involving a borate complex, see Zou, G.; Falck, J.R. *Tetraahedron Lett.* ***2001***, *42*, 5817.

[1421]Chen, H.; Deng, M.-Z. *J. Org. Chem.* ***2000***, *65*, 4444.

[1422]Wiskur, S.L.; Lorte, A.; Fu, G.C. *J. Am. Chem. Soc.* ***2004***, *126*, 82.

[1423]Batey, R.A.; Thadani, A.N.; Smil, D.V.; Lough, A.J. *Synthesis* ***2000***, 990; Batey R.A.; Thadani, A.N.; Smil, D.V. *Org. Lett.* ***1999***, *1*, 1683; Batey, R.A.; Thadani, A.N.; Smil, D.V. *Tetrahedron Lett.* ***1999***, *40*, 4289; Batey, R.A.; MacKay, D.B.; Santhakumar, V. *J. Am. Chem. Soc.* ***1999***, *121*, 5075.

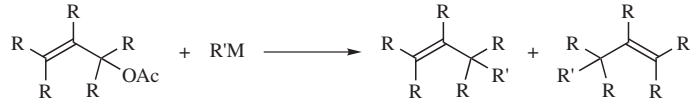
corresponding organoboranes and organoboronic acid derivatives. Potassium alkyltrifluoroborates undergo the palladium-catalyzed coupling reaction with arenediazonium tetrafluoroborates,[1424] diaryliodonium salts,[1425] aryl halides,[1426] as well as with aryl triflates. An example of the latter reaction converted **144** to diphenylmethane via coupling with phenyl triflate.[1427] Alkenyltrifluoroborates can be coupled to aryl halides.[1428]

$$\underset{\mathbf{144}}{\mathrm{PhCH_2BF_3K}} + \mathrm{PhOTf} \xrightarrow[9\%\ \mathrm{PdCl_2(dppf)\bullet CH_2Cl_2}]{3\ \mathrm{equiv}\ \mathrm{Cs_2CO_3},\ \mathrm{aq.\ THF}} \mathrm{PhCH_2Ph}$$

OS **VII**, 245; **VIII**, 295; **X**, 391.

10-60 Coupling of Organometallic Reagents With Carboxylic Esters

Alkyl-de-acyloxy-substitution



Several organometallic reagents react with allylic esters and carbonates to give the coupling product. Lithium dialkylcopper reagents couple with allylic acetates to give normal coupling products or those resulting from allylic rearrangement, depending on the substrate.[1429] A mechanism involving a σ-allylic copper(III) complex has been suggested.[1430] Silyl cuprates have also been used, with benzoate esters, to give allyl silanes.[1431] Interestingly, allylic silanes have been coupled to acetates using $B(C_6F_5)_3$[1432] or BF_3.[1433] With propargyl substrates, the products are allenes.[1434]

$$\mathrm{RC{\equiv}C{-}CR_2{-}OAc} + \mathrm{R'_2CuLi} \longrightarrow \mathrm{RR'C{=}C{=}CR_2}$$

[1424]Darses, S.; Michaud, G.; Genêt, J.-P. *Eur. J. Org. Chem.* ***1999***, 1875; Darses, S.; Michaud, G.; Genêt, J.-P. *Tetrahedron Lett.* ***1998***, *39*, 5045; Darses, S.; Genêt, J.-P.; Brayer, J.-L.; Demoute, J.-P. *Tetrahedron Lett.* ***1997***, *38*, 4393.

[1425]Xia, M.; Chen, Z.-C. *Synth. Commun.* ***1999***, *29*, 2457.

[1426]Ishikura, M.; Agata, I.; Katagiri, N. *J. Heterocylic Chem.* ***1999***, *36*, 873; Molander, G.A.; Biolatto, B. *Org. Lett.* ***2002***, *4*, 1867.

[1427]Molander, G.A.; Ito, T. *Org. Lett.* ***2001***, *3*, 393.

[1428]Molander, G.A.; Rivero, M.R. *Org. Lett.* ***2002***, *4*, 107.

[1429]Rona, P.; Tökes, L.; Tremble, J.; Crabbé, P. *Chem. Commun.* ***1969***, 43; Goering, H.L.; Kantner, S.S. *J. Org. Chem.* ***1984***, *49*, 422; Purpura, M.; Krause, N. *Eur. J. Org. Chem.* ***1999***, 267.

[1430]Goering, H.L.; Kantner, S.S.; Seitz Jr., E.P. *J. Org. Chem.* ***1985***, *50*, 5495.

[1431]Fleming, I.; Higgins, D.; Lawrence, N.J.; Thomas, A.P. *J. Chem. Soc. Perkin Trans. 1* ***1992***, 3331.

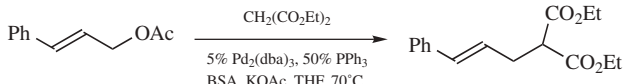
[1432]Rubin, M.; Gevorgyan, V. *Org. Lett.* ***2001***, *3*, 2705. For a reaction of a propargyl ester ($-O_2CCH_2Cl$) with an allylic silane and a catalytic amount of $B(C_6F_5)_3$, see Schwier, T.; Rubin, M.; Gevorgyan, V. *Org. Lett.* ***2004***, *6*, 1999.

[1433]Smith, D.M.; Tran, M.B.; Woerpel, K.A. *J. Am. Chem. Soc.* ***2003***, *125*, 14149; Ayala, L.; Lucero, C.G.; Romero, J.A.C.; Tabacco, S.A.; Woerpel, K.A. *J. Am. Chem. Soc.* ***2003***, *125*, 15521.

[1434]Crabbé, P.; Barreiro, E.; Dollat, J.; Luche, J. *J. Chem. Soc., Chem. Commun.* ***1976***, 183, and references cited therein.

Allenes are also obtained when propargyl acetates are treated with methylmagnesium iodide.[1435] Lithium dialkylcopper reagents also give normal coupling products with enol acetates of β-dicarbonyl compounds.[1436] It is also possible to carry out the coupling of allylic acetates with Grignard reagents, if catalytic amounts of cuprous salts are present.[1437] With this method yields are better and regioselectivity can be controlled by a choice of cuprous salts.

Allylic, benzylic, and cyclopropylmethyl acetates couple with trialkylaluminums,[1438] and allylic acetates couple with aryl and vinylic tin reagents, in the presence of a palladium catalyst[1439] (see below). Allylic acetates can be symmetrically coupled by treatment with $Ni(CO)_4$ (reaction **10-56**) or with Zn and a palladium-complex catalyst,[1440] or converted to unsymmetrical 1,5-dienes by treatment with an allylic stannane $R_2C{=}CHCH_2SnR_3$ in the presence of a palladium complex.[1441] Aryl halides can be coupled to allylic acetates with $CoBr_2$/Mn/$FeBr_2$.[1442] Lactones can be coupled at carbon by an alkylpalladium reagent in the presence of a silane[1443] or by a Grignard reagent with CuBr.[1444]



145 **146**

The most common method now in the literature is the reaction of η^3-π-allyl palladium complexes[1445] (see p. 117) with various nucleophiles,[1446] where the complex is obtained from allylic esters (acetate is the most common) or allylic

[1435]Roumestant, M.; Gore, J. *Bull. Soc. Chim. Fr.* ***1972***, 591, 598.

[1436]Casey, C.P.; Marten, D.F. *Synth. Commun.* ***1973***, *3*, 321, *Tetrahedron Lett.* ***1974***, 925. See also, Posner, G.H.; Brunelle, D.J. *J. Chem. Soc., Chem. Commun.* ***1973***, 907; Kobayashi, S.; Takei, H.; Mukaiyama, T. *Chem. Lett.* ***1973***, 1097.

[1437]Paisley, S.D.; Schmitter, J.; Lesheski, L.; Goering, H.L. *J. Org. Chem.* ***1989***, *54*, 2369; Karlström, A.S.E.; Huerta, F.F.; Muezelaar, G.J.; Bäckvall, J.-E. *Synlett* ***2001***, 923; Alexakis, A.; Malan, C.; Lea, L.; Benhaim, C.; Fournioux, X. *Synlett* ***2001***, 927.

[1438]Itoh, A.; Oshima, K.; Sasaki, S.; Yamamoto, H.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* ***1979***, 4751; Gallina, C. *Tetrahedron Lett.* ***1985***, *26*, 519; Tolstikov, G.A.; Dzhemilev, U.M. *J. Organomet. Chem.* ***1985***, *292*, 133; van Klaveren, M.; Persson, E.S.M.; del Villar, A.; Grove, D.M.; Bäckvall, J.-E.; van Koten, G. *Tetrahedron Lett.* ***1995***, *36*, 3059.

[1439]Del Valle, L.; Stille, J.K.; Hegedus, L.S. *J. Org. Chem.* ***1990***, *55*, 3019. For another method, see Legros, J.; Fiaud, J. *Tetrahedron Lett.* ***1990***, *31*, 7453.

[1440]Sasaoka, S.; Yamamoto, T.; Kinoshita, H.; Inomata, K.; Kotake, H. *Chem. Lett.* ***1985***, 315.

[1441]Trost, B.M.; Keinan, E. *Tetrahedron Lett.* ***1980***, *21*, 2595.

[1442]Gomes, P.; Gosmini, C.; Périchon, J. *Org. Lett.* ***2003***, *5*, 1043.

[1443]Iwata, A.; Ohshita, J.; Tang, H.; Kunai, A.; Yamamoto, Y.; Matui, C. *J. Org. Chem.* ***2002***, *67*, 3927.

[1444]Nelson, S.G.; Wan, Z.; Stan, M.A. *J. Org. Chem.* ***2002***, *67*, 4680.

[1445]For a review of the use of η^3-allylpalladium complexes to form C–C bonds, see Tsuji, J., in Hartley, F.R.; Patai, S. *The Chemistry of the Metal-Carbon Bond*, Vol. 3, Wiley, NY, ***1985***, pp. 163–199.

[1446]For a review related to synthetic applications see Trost, B.M.; Crawley, M.L. *Chem. Rev.* ***2003***, *103*, 2921. For a discussion of the mechanism see Tsurugi, K.; Nomura, N.; Aoi, K. *Tetrahedron Lett.* ***2002***, *43*, 469.

carbonates.[1447] The mechansim of such π-allyl palladium reactions has been discussed.[1448] A typical transformation is shown for the reaction of **145** with diethyl malonate, BSA and potassium acetate, which gives coupling product **146** in the presence of the palladium catalyst.[1449] This reaction is a variation of the basic transformation reported several years ago by Trost.[1450] Sulfone anions were also used as nucleophiles.[1451] The palladium catalyst used, the reaction conditions, and the nature of the organometallic compounds varies widely. Although two allylic coupling products are possible via the π-allyl intermediate, attack at the less substituted position is generally favored. In most reported cases the R′M species is the anion of an active methylene compound (such as sodium, potassium or lithium dimethylmalonate) or Knoevenagel-type carbanions (**16–38**) or amino acid surrogates.[1452] The use of chiral ligands[1453] or chiral additives that may act as ligands[1454]

[1447]For reviews, see Trost, B.M. *Angew. Chem. Int. Ed.* ***1989***, *28*, 1173; *Aldrichimica Acta* ***1981***, *14*, 43; *Acc. Chem. Res.* ***1980***, *13*, 385; *Tetrahedron* ***1977***, *33*, 2615; Tsuji, J.; Minami, I. *Acc. Chem. Res.* ***1987***, *20*, 140; Tsuji, J. *Tetrahedron* ***1986***, *42*, 4361, *Organic Synthesis with Palladium Compounds*, Springer, Berlin, ***1981***, pp. 45, 125; Heck, R.F. *Palladium Reagents in Organic Synthesis*, Academic Press, NY, ***1985***, pp. 130–166; Hegedus, L.S., in Buncel, E.; Durst, T. *Comprehensive Carbanion Chemistry*, Vol. 5, pt. B, Elsevier, NY, ***1984***, pp. 30–44.

[1448]Trost, B.M.; Strege, P.E.; Weber, L.; Fullerton, T.J.; Dietsche, T.J. *J. Am. Chem. Soc.* ***1978***, *100*, 3407; Organ, M.G.; Miller, M.; Konstantinou, Z. *J. Am. Chem. Soc.* ***1998***, *120*, 9283; Trost, B.M.; Toste, F.D. *J. Am. Chem. Soc.* ***1999***, *121*, 4545

[1449]Poli, G.; Giambastiani, G.; Mordini, A. *J. Org. Chem.* ***199***, *64*, 2962.

[1450]Trost, B.M.; Weber, L.; Strege, P.E.; Fullerton, T.J.; Dietsche, T.J. *J. Am. Chem. Soc.* ***1978***, *100*, 3416, 3426. These papers include a discussion of the mechanism of this reaction.

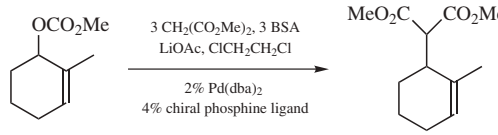
[1451]Manchand, P.S.; Wong, H.S.; Blount, J.F. *J. Org. Chem.* ***1978***, *43*, 4769.

[1452]Nakoji, M.; Kanayama, T.; Okino, T.; Takemoto, Y. *Org. Lett.* ***2001***, *3*, 3329.

[1453]For example see Kodama, H.; Taiji, T.; Ohta, T.; Furkawa, I. *Tetrahedron Asymmetry* ***2000***, *11*, 4009; Gong, L.; Chen, G.; Mi, A.; Jiang, Y.; Fu, F.; Cui, X.; Chan, A.S.C. *Tetrahedron Asymmetry* ***2000***, *11*, 4297; Mino, T.; Shiotsuki, M.; Yamamoto, N.; Suenaga, T.; Sakamoto, M.; Fujita, T.; Yamashita, M. *J. Org. Chem.* ***2001***, *66*, 1795; Zhang, R.; Yu, L.; Xu, L.; Wang, Z.; Ding, K. *Tetrahedron Lett.* ***2001***, *42*, 7659; Arena, C.G.; Drommi, D.; Faraone, F. *Tetrahedron Asymmetry* ***2000***, *11*, 4753; Kang, J.; Lee, J.H.; Choi, J.S. *Tetrahedron Asymmetry* ***2001***, *12*, 33; Mino, T.; Tanaka, Y.; Sakamoto, M.; Fujita, T. *Tetrahedron Asymmetry* ***2001***, *12*, 2435; Hu, X.; Dai, H.; Hu, X.; Chen, H.; Wang, J.; Bai, C.; Zheng, Z. *Tetrahedron Asymmetry* ***2002***, *13*, 1687; Tollabi, M.; Framery, E.; Goux-Henry, C.; Sinou, D. *Tetrahedron Asymmetry* ***2003***, *14*, 3329; Boaz, N.W.; Ponaskik, Jr., J.A.; Large, S.E.; Debenham, S.D. *Tetrahedron Asymmetry* ***2004***, *15*, 2151.

[1454]Rabeyrin, C.; Nguefack, C.; Sinou, D. *Tetrahedron Lett.* ***2000***, *41*, 7461; Jansat, S.; Gómez, M.; Muller, G.; Diéguez, M.; Aghmiz, A.; Claver, C.; Masdeu-Bultó, A.M.; Flores-Santos, L.; Martin, E.; Maestro, M.A.; Mahía, J. *Tetrahedron Asymmetry* ***2001***, *12*, 1469; Fukuda, T.; Takehara, A.; Iwao, M. *Tetrahedron Asymmetry* ***2001***, *12*, 2793; Abrunhosa, I.; Gulea, M.; Levillain, J.; Masson, S. *Tetrahedron Asymmetry* ***2001***, *12*, 2851; Stranne, R.; Moberg, C. *Eur. J. Org. Chem.* ***2001***, 2191; Mancheño, O.G.; Priego, J.; Cabera, S.; Arrayás, R.G.; Llamas, T.; Carretero, J.C. *J. Org. Chem.* ***2003***, *68*, 3679; Molander, G.A.; Burke, J.P.; Carroll, P.J. *J. Org. Chem.* ***2004***, *69*, 8062; Hou, X.-L.; Sun, N. *Org. Lett.* ***2004***, *6*, 4399; Jin, M.-J.; Kim, S.-H.; Lee. S.-J.; Kim, Y.-M. *Tetrahedron Lett.* ***2002***, *43*, 7409; Okuyama, Y.; Nakano, H.; Takahashi, K.; Hongo, H.; Kubuto, C. *Chem. Commun.* ***2003***, 524; Chen, G.; Li, X.; Zhang, H.; Gong, L.; Mi, A.; Cui, X.; Jiang, Y.; Choi, M.C.K.; Chan, A.S.C. *Tetrahedron Asymmetry* ***2002***, *13*, 809; Kloetzing, R.J.; Lotz, M.; Knochel, P. *Tetrahedron Asymmetry* ***2003***, *14*, 255; Nakano, H.; Yokayama, J.-i.; Koiyama, Y.; Fujita, R.; Hongo, H. *Tetrahedron Asymmetry* ***2003***, *14*, 2361; Mercier, F.; Brebion, F.; Dupont, R.; Mathey, F. *Tetrahedron Asymmetry* ***2003***, *14*, 3137.

lead to asymmetric induction in the coupling product.[1455] Enolate anions (see **10–68**) have also been used.[1456] This transformation has been done in ionic liquids[1457] and ionic liquids have been used as additives in catalytic amounts in other solvents.[1458] Palladium nanoparticles have been used to catalyze the reaction.[1459] Other nucleophiles can be used to displace allylic acetates.[1460] S_N2' reactions with allylic acetates have been reported.[1461] Benzoate esters have been used successfully in lieu of the acetate.[1462] Catalyst systems other than palladium have been used for this reaction with allylic acetates.[1463]



147 **148**

As mentioned above, a common variation is to replace the acetate leaving group with a carbonate ($-OCO_2R$), where methyl carbonate ($-OCO_2Me$) is most common.[1464] A typical reaction is the transformation of **147** to **148**,[1465] where the use of a chiral ligand led to modest asymmetric induction. As with allylic acetates, chiral ligands and chiral additives lad to asymmetric induction.[1466] A variety of active methylene compounds can be used as nucleophiles,[1467] including enolate anions.[1468] Other nucleophiles can be used to

[1455]For a review, see Consiglio, G.; Waymouth, R.M. *Chem. Rev.* ***1989***, *89*, 257.
[1456]Braun, M.; Laicher, F.; Meier, T. *Angew. Chem. Int. Ed.* ***2000***, *39*, 3494.
[1457]For a reaction in bmim BF_4, 1-butyl-3-methylimidazolium tetrafluoroborate, see Chen, W.; Xu, L.; Chatterton, C.; Xiao, J. *Chem. Commun.* ***1999***, 1247.
[1458]Sato, Y.; Yoshino, T.; Mori, M. *Org. Lett.* ***2003***, *5*, 31.
[1459]Jansat, S.; Gómez, M.; Philippot, K.; Muller, G.; Guiu, E.; Claver, C.; Castillón, S.; Chaudret, B. *J. Am. Chem. Soc.*, ***2004***, *126*, 1592.
[1460]**$NaN(CHO)_2$:** Wang, Y.; Ding, K. *J. Org. Chem.* ***2001***, *66*, 3238. **Indene**: Hayashi, T.; Suzuka, T.; Okada, A.; Kawatsura, M. *Tetrahedron Asymmetry* ***2004***, *15*, 545.
[1461]Belelie, J.L.; Chong, J.M. *J. Org. Chem.* ***2002***, *67*, 3000.
[1462]Krafft, M.E.; Sugiura, M.; Abboud, K.A. *J. Am. Chem. Soc.* ***2001***, *123*, 9174.
[1463]**Pt**: Blacker, A.J.; Clarke, M.L.; Loft, M.S.; Mahon, M.F.; Humphries, M.E.; Williams, J.M.J. *Chem. Eur. J.* ***2000***, *6*, 353. **Ir**: Kinoshita, N.; Marx, K.H.; Tanaka, K.; Tsubaki, K.; Kawabata, T.; Yoshikai, N.; Nakamura, E.; Fuji, K. *J. Org. Chem.* ***2004***, *69*, 7960; Bartels, B.; García-Yebra, C.; Helmchen, G. *Eur. J. Org. Chem.* ***2003***, 1097. **Ru**: Renaud, J.-L.; Bruneau, C.; Demerseman, B. *Synlett* ***2003***, 408.
[1464]For a $-OCO_2Ph$ leaving group, see Ito, K.; Kashiwagi, R.; Hayashi, S.; Uchida, T.; Katsuki, T. *Synlett* ***2001***, 284.
[1465]Hamada, Y.; Sakaguchi, K.-e.; Hatano, K.; Hara, O. *Tetrahedron Lett.* ***2001***, *42*, 1297.
[1466]Kuwano, R.; Kondo, Y.; Matsuyama, Y. *J. Am. Chem. Soc.* ***2003***, *125*, 12104; Faller, J.W.; Wilt, J.C. *Tetrahedron Lett.* ***2004***, *45*, 7613.
[1467]**Amide esters:** Kazmaier, U.; Zumpe, F.L. *Angew. Chem. Int. Ed.* ***1999***, *38*, 1468.
[1468]You, S.-L.; Hou, X.-L.; Dai, L.-X.; Zhu, X.-Z. *Org. Lett.* ***2001***, *3*, 149; Evans, P.A.; Leahy, D.K. *J. Am. Chem. Soc.* ***2003***, *125*, 7882; Evans, P.A.; Lawler, M.J. *J. Am. Chem. Soc.* ***2004***, *126*, 8642. For a reaction of a silyl enol ether, see Muraoka, T.; Matsuda, I.; Itoh, K. *Tetrahedron Lett.* ***2000***, *41*, 8807.

displace allylic carbonates,[1469] often in conjunction with chiral ligands to give the product with enantioselectivity. Polymer-supported phosphine ligands have been used successfully.[1470] Catalyst systems other than palladium have been used for this reaction with allylic carbonates.[1471]

Intramolecular cyclization is possible when the active methylene compound and an allylic acetate or carbonate is incorporated into the same molecule.[1472]

Allylic phosphonates have been used as substrates for displacement by higher order cuprates[1473] (see **10-58**) or dialkylzinc reagents.[1474]

10-61 Coupling of Organometallic Reagents With Esters of Sulfates, Sulfoxides, Sulfones, Nitro, and Acetals

Alkyl-de-sulfonyl and de-sulfonyloxy-substitution, and so on; **Alkyl-de-alkoxy-substitution**, and so on; **Alkyl-de-nitration**, and so on.

$$RSO_2X + R'M \longrightarrow R{-}R'$$

Leaving groups other than halide, esters or carbonate, or sulfonate esters are sometimes used. Sulfates, sulfonates, and epoxides give the expected products. The reaction of sodium sulfonates and alkyl halides in ionic liquids have been reported.[1475] Acetals can behave as substrates, one OR group being replaced by ZCHZ′ in a reaction similar to **10-64**.[1476] Ortho esters behave similarly, but the product loses R′OH to give an enol ether.[1477] The SO_2Ph group of allylic sulfones can

[1469]**Aryllithium reagents:** Evans, P.A.; Uraguchi, D. *J. Am. Chem. Soc.* ***2003***, *125*, 7158. **Alkoxides**: Evans, P.A.; Leahy, D.K.; Slieker, L.M. *Tetrahedron Asymmetry* ***2003***, *14*, 3613. **Phenoxide anions**: Evans, P.A.; Leahy, D.K. *J. Am. Chem. Soc.* ***2000***, *122*, 5012; López, F.; Ohmura, T.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2003***, *125*, 3426. **Secondary amines**: Matsushima, Y.; Onitsuka, K.; Kondo, T.; Mitsudo, T.-A.; Takahashi, S. *J. Am. Chem. Soc.* ***2001***, *123*, 10405. **Primary amines**: Ohmura, T.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2002***, *124*, 15164. ***N*-Lithio-sulfonamides**: Evans, P.A.; Robinson, J.E.; Baum, E.W.; Fazal, A.N. *J. Am. Chem. Soc.* ***2002***, *124*, 8782. ***C*-Alkylation with an indole**: Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Org. Lett.* ***2004***, *6*, 3199. **Michael addition of conjugated esters**: Muraoka, T.; Matsuda, I.; Itoh, K. *J. Am. Chem. Soc.* ***2000***, *122*, 9552.

[1470]Uozumi, Y.; Shibatmoi, K. *J. Am. Chem. Soc.* ***2001***, *123*, 2919.

[1471]**Ruthenium**: Trost, B.M.; Fraisse, P.L.; Ball, Z.T. *Angew. Chem. Int. Ed.* ***2002***, *41*, 1059. **Molybdenum**: Glorius, F.; Pfaltz, A. *Org. Lett.* ***1999***, *1*, 141; Malkov, A.V.; Spoor, P.; Vinader, V.; Kočovský, P. *Tetrahedron Lett.* ***2001***, *42*, 509. **Iridium**: Alexakis, A.; Polet, D. *Org. Lett.* ***2004***, *6*, 3529; Lee, P.H.; Sung, S.-y.; Lee, K.; Chang, S. *Synlett* ***2002***, 146.

[1472]Castaño, A.M.; Méndez, M.; Ruano, M.; Echavarren, A.M. *J. Org. Chem.* ***2001***, *66*, 589. See also, Zhang, Q.; Lu, X.; Han, X. *J. Org. Chem.* ***2001***, *66*, 7676.

[1473]Belelie, J.L.; Chong, J.M. *J. Org. Chem.* ***2001***, *66*, 5552.

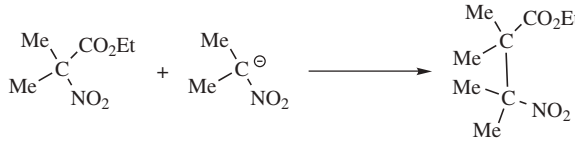
[1474]Kacprzynski, M.A.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***2004***, *126*, 10676.

[1475]In bmim BF_4, 1-butyl-3-methylimidazolium tetrafluoroborate: Hu, Y.; Chen, Z.-C.; Le, Z.-G.; Zheng, Q.G. *Synth. Commun.* ***2004***, *34*, 4031.

[1476]Yufit, S.S.; Krasnaya, Zh.A.; Levchenko, T.S.; Kucherov, V.F. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1967***, 123; Aleskerov, M.A.; Yufit, S.S.; Kucherov, V.F. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1972***, *21*, 2279.

[1477]For a review, see DeWolfe, R.H. *Carboxylic Ortho Acid Derivatives*, Academic Press, NY, ***1970***, pp. 231–266.

be a leaving group if a palladium(0) complex is present.[1478] The NR_2 group from Mannich bases, such as $RCOCH_2CH_2NR_2$, can also act as a leaving group in this reaction (elimination–addition mechanism, p. 474). A nitro group can be displaced[1479] from α-nitro esters, ketones, nitriles, and α,α-dinitro compounds,[1480] and even from simple tertiary nitro compounds of the form R_3CNO_2[1481] or ArR_2C-NO_2[1482] by salts of nitroalkanes, for example,



These reactions take place by SET mechanisms.[1483] However, with α-nitro sulfones it is the sulfone group that is displaced, rather than the nitro group.[1484] The SO_2R group of allylic sulfones can be replaced by CHZZ′ ($C{=}CCH_2{-}SO_2R \rightarrow C{=}CCH_2{-}CHZZ'$) if an $Mo(CO)_6$ catalyst is used.[1485]

tert-Butylsulfones react with organolithium reagents, in the presence of a catalytic amount of iron complex, to give coupling.[1486] In this case, the *t*-$BuSO_2$ unit becomes a ''leaving group.'' A sulfoxide was a ''leaving group'' in the cyclization of a carboxylic acid contain a sulfoxide unit at C-4. Treatment with phenyliodonium bis(trifluoroacetate) gave the five-membered ring lactone.[1487] Similar displacement of $TolSO_2$ was observed with tolylsulfones and diethylzinc.[1488] Biaryl can be prepared by the reaction of diarylsulfones and arylmagnesium halides, n the presence of a nickel catalyst.[1489]

Phosphonic esters, $ROPO(OR)_2$, react with allylic Grignard reagents to give the coupling product.[1490]

OS **I**, 471; **II**, 47, 360; **VII**, 351; **VIII**, 97, 471.

[1478]Trost, B.M.; Schmuff, N.R.; Miller, M.J. *J. Am. Chem. Soc.* ***1980***, *102*, 5979.

[1479]For reviews, see Kornblum, N., in Patai, S. *The Chemistry of Functional Groups, Supplement F*, pt. 1, Wiley, NY, ***1982***, pp. 361–393; Kornblum, N. *Angew. Chem. Int. Ed.* ***1975***, *14*, 734. For reviews of aliphatic S_N reactions in which NO_2 is a leaving group, see Tamura, R.; Kamimura, A.; Ono, N. *Synthesis* ***1991***, 423; Kornblum, N., in Feuer, H.; Nielsen, A.T. *Nitro Compunds: Recent Advances in Synthesis and Chemisry*, VCH, NY, ***1990***, pp. 46–85.

[1480]Kornblum, N.; Kelly, W.J.; Kestner, M.M. *J. Org. Chem.* ***1985***, *50*, 4720.

[1481]Kornblum, N.; Erickson, A.S. *J. Org. Chem.* ***1981***, *46*, 1037.

[1482]Kornblum, N.; Carlson, S.C.; Widmer, J.; Fifolt, M.J.; Newton, B.N.; Smith, R.G. *J. Org. Chem.* ***1978***, *43*, 1394.

[1483]For a review of the mechanism, see Beletskaya, I.P.; Drozd, V.N. *Russ. Chem. Rev.* ***1979***, *48*, 431. See also, Kornblum, N.; Wade, P.A. *J. Org. Chem.* ***1987***, *52*, 5301; Bowman, W.R. *Chem. Soc. Rev.* ***1988***, *17*, 283; Ref. 1479.

[1484]Kornblum, N.; Boyd, S.D.; Ono, N. *J. Am. Chem. Soc.* ***1974***, *96*, 2580.

[1485]Trost, B.M.; Merlic, C.A. *J. Org. Chem.* ***1990***, *55*, 1127.

[1486]Jin, L.; Julia, M.; Verpeaux, J.N. *Synlett* ***1994***, 215.

[1487]Casey, M.; Manage, A.C.; Murphy, P.J. *Tetrahedron Lett.* ***1992***, *33*, 965.

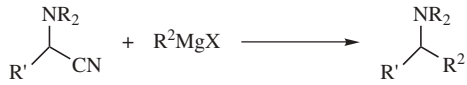
[1488]Dahmen, S.; Bräse, S. *J. Am. Chem. Soc.* ***2002***, *124*, 5940.

[1489]Cho, C.-H.; Yun, H.-S.; Park, K. *J. Org. Chem.* ***2003***, *68*, 3017.

[1490]Yanagisawa, A.; Hibino, H.; Nomura, N.; Yamamoto, H. *J. Am. Chem. Soc.* ***1993***, *115*, 5879.

10-62 The Bruylants Reaction

Alkyl-de-cyanation



The *Bruylants reaction* is the reaction of an aminonitrile with a Grignard reagent to give a substituted amine.[1491] This reaction is most often used for the preparation of aliphatic amines via aliphatic Grignard reagents. In a few cases, vinylic Grignard reagents can be used to prepare allylic amines.[1492] The use of $AgBF_4$ to convert amino nitriles to the corresponding iminium ion facilitates the Bruylants reaction with vinylic Grignard reagents.[1493]

Displacement of a cyano group in α-cyanoketones is possible. Treatment of the α-cyanoketone with SmI_2 followed by addition of an excess of allyl bromide gave the α-allyl ketone derivative.[1494] α-Cyano amines react with allyl bromide and then zinc metal to give homoallylic amines after treatment with dilute acetic acid in THF.[1495]

10-63 Coupling Involving Alcohols

De-hydroxyl-coupling

$$\mathrm{ROH} + \mathrm{R'M} \longrightarrow \mathrm{R{-}R'}$$

In some cases, it is possible to couple an alcohol with an organometallic compound. Allylic alcohols are coupled with alkylmagnesium bromides in the presence of $Ti(OiPr)_4$, for example.[1496] Allylic alcohols can be coupled with arylboronic acids in ionic liquid solvent and a rhodium catalyst.[1497] The palladium-catalyzed reaction of active methylene compounds with allylic alcohols[1498] or benzylic alcohols[1499] is also known. The coupling of an alcohol to the α-carbon of a ketone

[1491]Bruylants, P. *Bull. Soc. Chem. Belg.* ***1924***, *33*, 467.
[1492]Ahlbrecht, H.; Dollinger, H. *Synthesis* ***1985***, 743; Trost, B.M.; Spagnol, M.D. *J. Chem. Soc., Perkin Trans. 1* ***1995***, 2083.
[1493]Agami, C.; Couty, F.; Evano, G. *Org. Lett.* ***2000***, *2*, 2085.
[1494]Zhu, J.-L.; Shia, K.-S.; Liu, H.-J. *Tetrahedron Lett.* ***1999***, *40*, 7055.
[1495]Bernardi, L.; Bonini, B.F.; Capitò, E.; Dessole, G.; Fochi, M.; Comes-Franchini, M.; Ricci, A. *Synlett* ***2003***, 1778.
[1496]Kulinkovich, O.G.; Epstein, OL.; Isakov, V.E.; Khmel'nitskaya, E.A. *Synlett* ***2001***, 49.
[1497]Kabalka, G.W.; Dong, G.; Venkataish, B. *Org. Lett.* ***2003***, *5*, 893.
[1498]Manabe, K.; Kobayashi, S. *Org. Lett.* ***2003***, *5*, 3241; Kinoshita, H.; Shinokubo, H.; Oshima, K. *Org. Lett.* ***2004***, *6*, 4085; Horino, Y.; Naito, M.; Kimura, M. Tanaka, S.; Tamaru, Y. *Tetrahedron Lett.* ***2001***, *42*, 3113.
[1499]Bisaro, F.; Prestat, G.; Vitale, M.; Poli, G. *Synlett* ***2002***, 1823.

(RCOMe + R′OH) to give a β-substituted alcohol ($RCH(OH)CH_2R'$) is possible in the presence of a ruthenium catalyst.[1500]

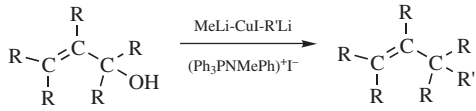
$$2\,ROH \xrightarrow[-78^\circ C]{MeLi-TiCl_3} RR$$

Allylic or benzylic alcohols can be symmetrically coupled[1501] by treatment with methyllithium and titanium trichloride at −78°C[1502] or by refluxing with $TiCl_3$ and $LiAlH_4$.[1503] When the substrate is an allylic alcohol, the reaction is not regiospecific, but a mixture of normal coupling and allylically rearranged products is found. A free-radical mechanism is involved.[1504] The $TiCl_3$–$LiAlH_4$ reagent can also convert 1,3-diols to cyclopropanes, provided that at least one a phenyl is present.[1505]

Tertiary alcohols react with trimethylaluminum at 80–200°C to give methylation.[1506] The presence of side products from elimination and rearrangement, as well as the lack of stereospecificity,[1507] indicate an

$$R_3COH + Me_3Al \xrightarrow{80-200^\circ C} R_3CMe$$

S_N1 mechanism. The reaction can also be applied to primary and secondary alcohols if these contain an aryl group in the a position. Higher trialkylaluminums are far less suitable, because reduction competes with alkylation (see also, reactions of Me_3Al with ketones, **16-24**, and with carboxylic acids, **16-82**). The compound Me_2TiCl_2 also reacts with tertiary alcohols in the same way.[1508] Allylic alcohols couple with a reagent prepared from MeLi, CuI, and R′Li in the presence of $(Ph_3PNMePh)^+ I^-$ to give alkenes, such as **149**, that are products of allylic rearrangement.[1509]



149

[1500]Cho, C.S.; Kim, B.T.; Kim. T.-J.; Shim. S.C. *J. Org. Chem.* ***2001***, *66*, 9020.
[1501]For a review, see Lai, Y. *Org. Prep. Proceed. Int.* ***1980***, *12*, 363, pp. 377–388.
[1502]Sharpless, K.B.; Hanzlik, R.P.; van Tamelen, E.E. *J. Am. Chem. Soc.* ***1968***, *90*, 209.
[1503]McMurry, J.E.; Silvestri, M.G.; Fleming, M.P.; Hoz, T.; Grayston, M.W. *J. Org. Chem.* ***1978***, *43*, 3249. For another method, see Nakanishi, S.; Shundo, T.; Nishibuchi, T.; Otsuji, Y. *Chem. Lett.* ***1979***, 955.
[1504]van Tamelen, E.E.; Åkermark, B.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1969***, *91*, 1552.
[1505]Baumstark, A.L.; McCloskey, C.J.; Tolson, T.J.; Syriopoulos, G.T. *Tetrahedron Lett.* ***1977***, 3003; Walborsky, H.M.; Murati, M.P. *J. Am. Chem. Soc.* ***1980***, *102*, 426.
[1506]Meisters, A.; Mole, T. *J. Chem. Soc., Chem. Commun.* ***1972***, 595; Harney, D.W.; Meisters, A.; Mole, T. *Aust. J. Chem.* ***1974***, *27*, 1639.
[1507]Salomon, R.G.; Kochi, J.K. *J. Org. Chem.* ***1973***, *38*, 3715.
[1508]Reetz, M.T.; Westermann, J.; Steinbach, R. *J. Chem. Soc., Chem. Commun.* ***1981***, 237.
[1509]Tanigawa, Y.; Ohta, H.; Sonoda, A.; Murahashi, S. *J. Am. Chem. Soc.* ***1978***, *100*, 4610; Goering, H.L.; Tseng, C.C. *J. Org. Chem.* ***1985***, *50*, 1597. For another procedure, see Yamamoto, Y.; Maruyama, K. *J. Organomet. Chem.* ***1978***, *156*, C9.

The reaction gives good yields with primary, secondary, and tertiary alcohols, and with alkyl and aryllithium reagents.[1510] Allylic alcohols also couple with certain Grignard reagents[1511] in the presence of a nickel complex to give both normal products and the products of allylic rearrangement.

Allenic alcohols couple with allyl indium reagents at 140°C to give allylic alcohol products.[1512] Similarly, ω-hydroxy lactones couple with organoindium reagents.[1513] Phenols react with vinyl boronates and a copper catalyst to give aryl vinyl ethers.[1514]

Alcohols react with allylsilanes, in the presence of an $InCl_3$[1515] or $InBr_3$[1516] catalyst to give the corresponding coupling product ($R_2CHOH \rightarrow R_2CH{-}CH_2CH{=}CH_2$).

10-64 Coupling of Organometallic Reagents With Compounds Containing the Ether Linkage[1517]

Alkyl-de-alkoxy-substitution

$$R_2C(OR')_2 + R''MgX \longrightarrow R_2CR''(OR') + R'OMgX$$

$$RC(OR')_3 + R''MgX \longrightarrow RCR''(OR')_2 + R'OMgX$$

Acetals,[1518] ketals, and ortho esters[1519] react with Grignard reagents to give, respectively, ethers and acetals (or ketals). The latter can be hydrolyzed to aldehydes or ketones (**10-6**). This procedure is a way of converting a halide R″X (which may be alkyl, aryl, vinylic, or alkynyl) to an aldehyde R″CHO, increasing the length of the carbon chain by one carbon (see also, **10-76**). The ketone synthesis generally gives lower yields. Acetals, including allylic acetals, also give this reaction with organocopper compounds and BF_3.[1520] Dihydropyrans react with Grignard reagents in the

[1510]For the allylation of benzylic alcohols, see Cella, J.A. *J. Org. Chem.* ***1982***, *47*, 2125.

[1511]Buckwalter, B.L.; Burfitt, I.R.; Felkin, H.; Joly-Goudket, M.; Naemura, K.; Salomon, M.F.; Wenkert, E.; Wovkulich, P.M. *J. Am. Chem. Soc.* ***1978***, *100*, 6445; Felkin, H.; Joly-Goudket, M.; Davies, S.G. *Tetrahedron Lett.* ***1981***, *22*, 1157; Consiglio, G.; Morandini, F.; Piccolo, O. *J. Am. Chem. Soc.* ***1981***, *103*, 1846, and references cited therein. For a review, see Felkin, H.; Swierczewski, G. *Tetrahedron* ***1975***, *31*, 2735. For other procedures, see Mukaiyama, T.; Imaoka, M.; Izawa, T. *Chem. Lett.* ***1977***, 1257; Fujisawa, T.; Iida, S.; Yukizaki, H.; Sato, T. *Tetrahedron Lett.* ***1983***, *24*, 5745.

[1512]Araki, S.; Usui, H.; Kato, M.; Butsugan, Y. *J. Am. Chem. Soc*, ***1996***, *118*, 4699.

[1513]Bernardelli, P.; Paquette, L.A. *J. Org. Chem.* ***1997***, *62*, 8284.

[1514]McKinley, N.F.; O'Shea, D.F. *J. Org. Chem.* ***2004***, *69*, 5087.

[1515]Yasuda, M.; Saito, T.; Ueba, M.; Baba, A. *Angew. Chem. Int. Ed.* ***2004***, *43*, 1414.

[1516]Kim, S.H.; Shin, C.; Pae, A.N.; Koh, H.Y.; Chang, M.H.; Chung, B.Y.; Cho, Y.S. *Synthesis* ***2004***, 1581.

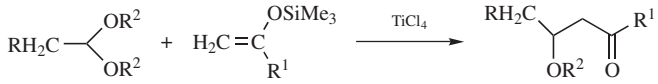
[1517]For a review, see Trofimov, B.A.; Korostova, S.E. *Russ. Chem. Rev.* ***1975***, *44*, 41.

[1518]For a review of coupling reactions of acetals, see Mukaiyama, T.; Murakami, M. *Synthesis* ***1987***, 1043. For a discussion of the mechanism, see Abell, A.D.; Massy-Westropp, R.A. *Aust. J. Chem.* ***1985***, *38*, 1031. For a list of substrates and reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 934–942.

[1519]For a review of the reaction with ortho esters, see DeWolfe, R.H. *Carboxylic Ortho Acid Derivatives*, Academic Press, NY, ***1970***, pp. 44–45, 224–230.

[1520]Normant, J.F.; Alexakis, A.; Ghribi, A.; Mangeney, P. *Tetrahedron* ***1989***, *45*, 507; Alexakis, A.; Mangeney, P.; Ghribi, A.; Marek, I.; Sedrani, R.; Guir, C.; Normant, J.F. *Pure Appl. Chem.* ***1988***, *60*, 49.

presence of a nickel catalyst.[1521] Acetals also undergo substitution when treated with silyl enol ethers or allylic silanes, with a Lewis acid catalyst,[1522] for example,

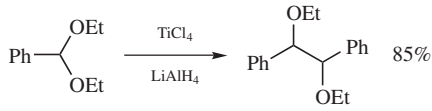


ω-Ethoxy lactams react with Grignard regents to give ω-substituted lactams.[1523] Tertiary amines can be prepared by the reaction of amino ethers with Grignard reagents,[1524] ($R_2NCH_2{-}OR' + R^2MgX \rightarrow R_2NCH_2{-}R^2$) or with lithium dialkylcopper reagents.[1525]

Ordinary ethers are not cleaved by Grignard reagents (in fact, diethyl ether and THF are the most common solvents for Grignard reagents), although more active organometallic compounds often do cleave them.[1526] Oxetanes have been opened with organolithium reagents and $BF_3{\bullet}OEt_2$[1527] and also with excess lithium metal with a biphenyl catalyst.[1528] Allylic ethers can be cleaved by Grignard reagents in THF if CuBr is present.[1529] The reaction takes place either with or without allylic rearrangement.[1530] Propargylic ethers give allenes.[1531] Vinylic ethers can also be cleaved by Grignard reagents in the presence of a catalyst, in this case, a nickel complex.[1532] Silyl enol ethers $R_2C{=}CROSiMe_3$ behave similarly.[1533] Bicyclic benzofurans can be opened by dialkylzinc reagents in the presence of a palladium catalyst.[1534]

[1521]Ducoux, J.-P.; LeMénez, P.; Kunesch, N.; Wenkert, E. *J. Org. Chem.* ***1993***, *58*, 1290.
[1522]See Mori, I.; Ishihara, K.; Flippen, L.A.; Nozaki, K.; Yamamoto, H.; Bartlett, P.A.; Heathcock, C.H. *J. Org. Chem.* ***1990***, *55*, 6107, and references cited therein.
[1523]Wei, Z.Y.; Knaus, E.E. *Org. Prep. Proceed. Int.* ***1993***, *25*, 255.
[1524]For example, see Miginiac, L.; Mauzé, B. *Bull. Soc. Chim. Fr.* ***1968***, 2544; Eisele, G.; Simchen, G. *Synthesis* ***1978***, 757; Kapnang, H.; Charles, G. *Tetrahedron Lett.* ***1983***, *24*, 1597; Morimoto, T.; Takahashi, T.; Sekiya, M. *J. Chem. Soc., Chem. Commun.* ***1984***, 794; Mesnard, D.; Miginiac, L. *J. Organomet. Chem.* ***1989***, *373*, 1. See also, Bourhis, M.; Bosc, J.; Golse, R. *J. Organomet. Chem.* ***1983***, *256*, 193.
[1525]Germon, C.; Alexakis, A.; Normant, J.F. *Bull. Soc. Chim. Fr.* ***1984***, II-377.
[1526]For a review of the reactions of ethers with Grignard Reagents, see Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood Cliffs, NJ, ***1954***, pp. 1013–1045.
[1527]Bach, T.; Eilers, F. *Eur. J. Org. Chem.* ***1998***, 2161.
[1528]Rama, K.; Pasha, M.A. *Tetrahedron Lett.* ***2000***, *41*, 1073.
[1529]Commercon, A.; Bourgain, M.; Delaumeny, M.; Normant, J.F.; Villieras, J. *Tetrahedron Lett.* ***1975***, 3837; Claesson, A.; Olsson, L. *J. Chem. Soc., Chem. Commun.* ***1987***, 621.
[1530]Normant, J.F.; Commercon, A.; Gendreau, Y.; Bourgain, M.; Villieras, J. *Bull. Soc. Chim. Fr.* ***1979***, II-309; Gendreau, Y.; Normant, J.F. *Tetrahedron* ***1979***, *35*, 1517; Calo, V.; Lopez, L.; Pesce, G. *J. Chem. Soc. Perkin Trans. 1* ***1988***, 1301. See also, Valverde, S.; Bernabé, M.; Garcia-Ochoa, S.; Gómez, A.M. *J. Org. Chem.* ***1990***, *55*, 2294.
[1531]Alexakis, A.; Marek, I.; Mangeney, P.; Normant, J.F. *Tetrahedron Lett.* ***1989***, *30*, 2387; *J. Am. Chem. Soc.* ***1990***, *112*, 8042.
[1532]Wenkert, E.; Michelotti, E.L.; Swindell, C.S.; Tingoli, M. *J. Org. Chem.* ***1984***, *49*, 4894; Kocieński, P.; Dixon, N.J.; Wadman, S. *Tetrahedron Lett.* ***1988***, *29*, 2353.
[1533]Hayashi, T.; Katsuro, Y.; Kumada, M. *Tetrahedron Lett.* ***1980***, *21*, 3915.
[1534]Lauens, M.; Renaud, J.-L.; Hiebert, S. *J. Am. Chem. Soc.* ***200***, *122*, 1804.

Certain acetals and ketals can be dimerized in a reaction similar to **10-56** by treatment with $TiCl_4$—$LiAlH_4$, for example,[1535]

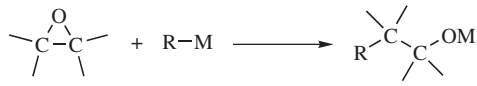


Also see, **10-65**.

OS **II**, 323; **III**, 701. Also see, OS **V**, 431.

10-65 The Reaction of Organometallic Reagents With Epoxides

3*(OC)-seco*-Alkyl-de-alkoxy-substitution



The reaction between Grignard reagents or organolithium reagents and epoxides is very valuable and is often used to increase the length of a carbon chain by two carbons.[1536] The Grignard reagent may be aromatic or aliphatic, although tertiary Grignard reagents give low yields. As expected for an S_N2 process, attack is at the less substituted carbon. With allylic Grignard reagents, the addition of a catalytic amount of $Yb(OTf)_3$ facilitated alkylation.[1537] Organolithium reagents,[1538] in the presence of chiral additives lead to the 2-substituted alcohol with good enantioselectivity. Similar reaction with a chiral Schiff base gave the same type of product, with excellent enantioselectivity.[1539]

Lithium dialkylcopper reagents also give the reaction,[1540] as do higher order cuprates,[1541] often producing higher yields. They have the additional advantage that they do not react with ester, ketone, or carboxyl groups so that the epoxide ring of epoxy esters, ketones, and carboxylic acids can be selectively attacked, often

[1535]Ishikawa, H.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* ***1978***, *51*, 2059.

[1536]For a review, see Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood Cliffs, NJ, ***1954***, pp. 961–1012. For a thorough discussion, see Schaap, A.; Arens, J.F. *Recl. Trav. Chim. Pays-Bas* ***1968***, *87*, 1249. For improved procedures, see Huynh, C.; Derguini-Boumechal, F.; Linstrumelle, G. *Tetrahedron Lett.* ***1979***, 1503; Schrumpf, G.; Grätz, W.; Meinecke, A.; Fellenberger, K. *J. Chem. Res. (S)* ***1982***, 162.

[1537]Likhar, P.R.; Kumar, M.P.; Bandyopadhyay, A.K. *Tetrahedron Lett.* ***2002***, *43*, 3333.

[1538]Harder, S.; van Lenthe, J.H.; van Eikkema Hommes, N.J.R.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1994***, *116*, 2508; Alexakis, A.; Vrancken, E.; Mangeney, P. *Synlett*, ***1998***, 1165.; Hodgson, D.M.; Stent, M.A.H.; Štefane, B.; Wilson, F.X. *Org. Biomol. Chem.* ***2003***, *1*, 1139; Hodgson, D.M.; Maxwell, C.R.; Miles, T.J.; Paruch, E.; Stent, M.A.H.; Matthews, I.R. Wilson, F.X.; Witherington, J. *Angew. Chem. Int. Ed.* ***2002***, *41*, 4313.

[1539]Oguni, N.; Miyagi, Y.; Itoh, K. *Tetrahedron Lett.* ***1998***, *39*, 9023.

[1540]For examples of the use of this reactions, see Posner, G.H. *An Introduction to Synthesis Using Organocopper Reagents*, Wiley, NY, ***1980***, pp. 103–113. See also, Lipshutz, B.H.; Kozlowski, J.; Wilhelm, R.S. *J. Am. Chem. Soc.* ***1982***, *104*, 2305; Blanchot-Courtois, V.; Hanna, I. *Tetrahedron Lett.* ***1992***, *33*, 8087.

[1541]Chauret, D.C.; Chong, J.M. *Tetrahedron Lett.* ***1993***, *34*, 3695.

in a regioselective manner.[1542] The use of BF_3 increases the reactivity of R_2CuLi, enabling it to be used with thermally unstable epoxides.[1543] Lithium diaminocyano cuprates have also been used.[1544]

The reaction has also been performed with other organometallic compounds.[1545] Trialkylaluminum reagents open epoxides with delivery of the alkyl group to carbon.[1546] In the presence of a Lewis acid catalyst, such as BF_3, alkylation can occur at the more substituted carbon.[1547] Friedel–Crafts type alkylation (see **11-11**) is possible when an aromatic compounds reacts with an epoxide and $AlCl_3$.[1548] Epoxides reaction with allyl bromide in the presence of indium metal, with the expected delivery of allyl to the less substituted carbon being the major product.[1549] Other organometallic reagents can be used.[1550] When a substituted epoxide was treated with CO, BF_3•$OEt_2$and a cobalt catalyst, carbonylation occurred and the final product was a β-lactone.[1551] Similar β-lactone forming reactions were reported using substituted epoxides, CO and a metal compound–BF_3 complex.[1552] Five-membered ring lactams were also formed from substituted epoxides using BF_3•OEt_2 followed by treatment with KHF_2.[1553] An interesting variation reacted an epoxy acetate (acetoxy at the 3-position relative to the first epoxy carbon) with Cp_2TiCl_2/Zn, and the product was an allylic alcohol where the epoxide ring was opened with loss of the acetoxy group.[1554]

[1542]Johnson, C.R.; Herr, R.W.; Wieland, D.M. *J. Org. Chem.* ***1973***, *38*, 4263; Hartman, B.C.; Livinghouse, T.; Rickborn, B. *J. Org. Chem.* ***1973***, *38*, 4346; Hudrlik, P.F.; Peterson, D.; Rona, R.J. *J. Org. Chem.* ***1975***, *40*, 2263; Chong, J.M.; Sharpless, K.B. *Tetrahedron Lett.* ***1985***, *26*, 4683; Chong, J.M.; Cyr, D.R.; Mar, E.K. *Tetrahedron Lett.* ***1987***, *28*, 5009; Larchevêque, M.; Petit, Y. *Tetrahedron Lett.* ***1987***, *28*, 1993.

[1543]See, for example, Alexakis, A.; Jachiet, D.; Normant, J.F. *Tetrahedron* ***1986***, *42*, 5607.

[1544]Yamamoto, Y.; Asao, N.; Meguro, M.; Tsukada, N.; Nemoto, H.; Sadayori, N.; Wilson, J.G.; Nakamura, H. *J. Chem. Soc., Chem. Commun.* ***1993***, 1201.

[1545]For lists of organometallic reagents that react with epoxides, see Wardell, J.L.; Paterson, E.S. in Hartley, F.R.; Patai, S. *The Chemistry of the Metal-Carbon Bond*, Vol. 2; Wiley, NY, ***1985***, pp. 307–310; Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1045–1063.

[1546]Schneider, C.; Brauner, J. *Eur. J. Org. Chem.* ***2001***, 4445; Sasaki, M.; Tanino, K.; Miyashita, M. *J. Org. Chem.* ***2001***, *66*, 5388; Sasaki, M.; Tanino, K.; Miyashita, M. *Org. Lett.* ***2001***, *3*, 1765; Shanmugam, P.; Miyashita, M. *Org. Lett.* ***2003***, *5*, 3265 (formation of *O*-silyl ether product). For the reaction in an ionic liquid see Zhou, H.; Campbell, E.J.; Nguyen, S.T. *Org. Lett.* ***2001***, *3*, 2229.

[1547]For an example, see Zhao, H.; Pagenkopf, B.L. *Chem. Commun.* ***2003***, 2592.

[1548]Lin, J.; Kanazaki, S.; Kashino, S.; Tsuboi, S. *Synlett* ***2002***, 899.

[1549]Yadav, J.S.; Anjaneyulu, S.; Ahmed, Md.M.; Subba Reddy, B.V. *Tetrahedron Lett.* ***2001***, *42*, 2557; Oh, B.K.; Cha, J.H.; Cho, Y.S.; Choi, K.I.; Koh, H.Y.; Chang, M.H.; Pae, A.N. *Tetrahedron Lett.* ***2003***, *44*, 2911; Hirashita, T.; Mitsui, K.; Hayashi, Y.; Araki, S. *Tetrahedron Lett.* ***2004***, *45*, 9189. For a reaction using palladium nanoparticles see Jiang, N.; Hu, Q.; Reid, C.S.; Ou, Y.; Li, C.J. *Chem. Commun.* ***2003***, 2318.

[1550]**Ba**: Yasue, K.; Yanagisawa, A.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* ***1997***, *70*, 493. **Mn**: Tang, J.; Yorimitsu, H.; Kakiya, H.; Inoue, R.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* ***1997***, *38*, 9019. **Sn**: Yadav, J.S.; Reddy, B.V.S.; Satheesh, G. *Tetahedron Lett.* ***2003***, *44*, 6501. **Zn**: Equey, O.; Vrancken, E.; Alexakis, A. *Eur. J. Org. Chem.* ***2004***, 2151.

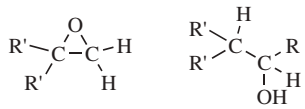
[1551]Lee, J.T.; Thomas, P.J.; Apler, H. *J. Org. Chem.* ***2001***, *66*, 5424.

[1552]Getzler, Y.D.Y.L.; Mahadevan V.; Lobkovsky, E.B.; Coates, G.W. *J. Am. Chem. Soc.* ***2002***, *124*, 1174; Schmidt, J.A.R.; Mahadevan, V.; Getzler, Y.D.Y.L.; Coates, G.W. *Org. Lett.* ***2004***, *6*, 373.

[1553]Movassaghi, M.; Jacobsen, E.N. *J. Am. Chem. Soc.* ***2002***, *124*, 2456.

[1554]Bermejo, F.; Sandoval, C. *J. Org. Chem.* ***2004***, *69*, 5275.

In the presence of a scandium catalyst, chiral allylic boranes open epoxides at the less substituted position to generate chiral, homoallylic alcohols.[1555]

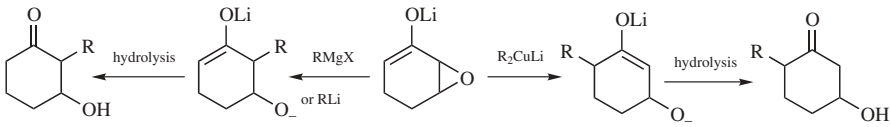


150 **151**

When *gem*-disubstituted epoxides (**150**) are treated with Grignard reagents (and sometimes other epoxides), the product may be **151**, that is, the new alkyl group may appear on the same carbon as the OH. In such cases, the epoxide is isomerized to an aldehyde or a ketone before reacting with the Grignard reagent. Halohydrins are often side products.

152

When the substrate is a vinylic epoxide,[1556] Grignard reagents generally give a mixture of the normal product and the product of allylic rearrangement (**152**).[1557] Butyllithium reacted with a difluoroalkylidene epoxide ($F_2C{=}CR{-}$epoxide) and S_N2' displacement gave alkylation at the difluoro carbon and opened the epoxide.[1558] The latter often predominates. In the case of R_2CuLi,[1559] acyclic substrates give mostly allylic rearrangement (S_N2').[1556] The double bond of the ''vinylic'' epoxide can be part of an enolate anion. In this case, R_2CuLi give exclusive allylic rearrangement (S_N2') to **153** after hydrolysis, while Grignard and organolithium reagents opened the epoxide directly (S_N2) to give **154** after hydrolysis.[1560]



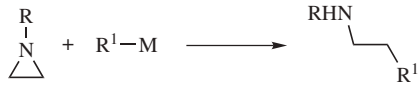
154 **153**

[1555]Lautens, M.; Maddess, M.L.; Sauer, E.L.O.; Oullet, S.G. *Org. Lett.* ***2002***, *4*, 83.
[1556]For a list of organometallic reagents that react with vinylic epoxides, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 244–250.
[1557]Anderson, R.J. *J. Am. Chem. Soc.* ***1970***, *92*, 4978; Johnson, C.R.; Herr, R.W.; Wieland, D.M. *J. Org. Chem.* ***1973***, *38*, 4263; Marshall, J.A.; Trometer, J.D.; Cleary, D.G. *Tetrahedron* ***1989***, *45*, 391.
[1558]Ueki, H.; Chiba, T.; Yamazaki, T.; Kitazume, T. *J. Org. Chem.* ***2004***, *69*, 7616.
[1559]For a review of the reactions of vinylic epoxides with organocopper reagents, see Marshall, J.A. *Chem. Rev.* ***1989***, *89*, 1503.
[1560]Wender, P.A.; Erhardt, J.M.; Letendre, L.J. *J. Am. Chem. Soc.* ***1981***, *103*, 2114.

An organometallic equivalent that opens epoxides is a hydrosilane, for example, Me_3SiH, and carbon monoxide, catalyzed by dicobalt octacarbonyl:[1561] See **10-55** for other coupling reactions with organosilanes. Silyl enol ethers react with epoxides in a related reaction, but a Lewis acid, such as $TiCl_4$, is required.[1562]

OS **I**, 306; **VII**, 501; **VIII**, 33, 516; **X**, 297.

10-66 Reaction of Organometallics With Aziridines



Aziridines have been opened by organometallic reagents to give amines.[1563] Although less reactive than epoxides, it is also possible to open aziridines[1564] with organometallic reagents particularly when there is a *N*-sulfonyl group such as tosyl (formally making it a sulfonamide). Grignard reagents react with *N*-tosyl 2-phenylaziridine to give the corresponding *N*-tosylamine.[1565] Organocuprates (**10-58**) reaction with *N*-alkylaziridines to give the corresponding amine.[1566] *N*-Tosyl aziridines have also been opened with enolate anions, which led to a pyrroline derivative,[1567] and with $Me_2S{=}CHCO_2Et$ (see **16-46**) to generate a *N*-tosyl azetidine.[1568] In a Friedel–Crafts type reaction (**11-11**), aziridines react with benzene, in the presence of $In(OTf)_3$, to give the β-aryl amine.[1569] Allylic alcohols open *N*-tosylaziridines with KSF–Montmorillonite clay.[1570]

Aziridines react with nucleophiles other than carbon nucleophiles. In the presence of TBAF, trimethylsilyl azide react with *N*-tosylaziridines to give the azido *N*-tosylamine.[1571] *N*-Benzylic aziridines are opened by trimethylsilyl azide in the presence of a chromium catalyst.[1572] Acetic anhydride reacts with *N*-tosylaziridines, in the presence of PBu_3, to give the *N*-tosylamino acetate.[1573] *N*-Tosylaziridines react with $InCl_3$ to give the chloro *N*-tosylamine.[1574]

[1561]Murai, T.; Kato, S.; Murai, T.; Toki, T.; Suzuki, S.; Sonoda, N. *J. Am. Chem. Soc.* ***1984***, *106*, 6093.
[1562]Lalić, G.; Petrovski, Ž.; Galonić, D.; Matović, R.; Saičić, R.N. *Tetrahedron* ***2001***, *57*, 583.
[1563]See, for example Eis, M.J.; Ganem, B. *Tetrahedron Lett.* ***1985***, *26*, 1153; Onistschenko, A.; Buchholz, B.; Stamm, H. *Tetrahedron* ***1987***, *43*, 565.
[1564]Crotti, P.; Favero, L.; Gardelli, C.; Macchia, F.; Pineschi, M. *J. Org. Chem.* ***1995***, *60*, 2514.
[1565]Toshimitsu, A.; Abe, H.; Hirosawa, C.; Tamao, K. *J. Chem. Soc. Perkin Trans. 1* ***1994***, 3465; Müller, P.; Nury, P. *Org. Lett.* ***1999***, *1*, 439; Müller, P.; Nury, P. *Helv. Chim. Acta* ***2001***, *84*, 662.
[1566]Penkett, C.S.; Simpson, I.D. *Tetrahedron Lett.* ***2001***, *42*, 1179.
[1567]Lygo, B. *Synlett*, ***1993***, 764.
[1568]Nadir, U.K.; Arora, A. *J. Chem. Soc. Perkin Trans. 1* ***1995***, 2605.
[1569]Saidi, M.R.; Azizi, N.; Naimi-Jamal, M.R. *Tetrahedron Lett.* ***2001***, *42*, 8111.
[1570]Yadav, J.S.; Reddy, B.V.S.; Balanarsaiah, E.; Raghavendra, S. *Tetrahedron Lett.* ***2002***, *43*, 5105.
[1571]Wu, J.; Hou, X.-L.; Dai, L.-X. *J. Org. Chem.* ***2000***, *65*, 1344.
[1572]Li, Z.; Fernández, M.; Jacobsen, E.N. *Org. Lett.* ***1999***, *1*, 1611.
[1573]Fan, R.-H.; Hou, X.-L. *Tetrahedron Lett.* ***2003***, *44*, 4411.
[1574]Yadav, J.S.; Subba Reddy, B.V.; Kumar, G.M. *Synlett* ***2001***, 1417.

10-67 Alkylation at a Carbon Bearing an Active Hydrogen

Bis(ethoxycarbonyl)methyl-de-halogenation, and so on.

The metal-catalyzed displacement of allylic acetates and carbonates (**10-60**) clearly falls in to this category. However, this section will focus on the more general reaction of active methylene compounds with substrates bearing a leaving group, not necessarily allylic substrates or metal catalyzed. When compounds contain two or three strong electron-withdrawing groups on a carbon atom bearing a proton (the so-called α-proton), that proton is more acidic than compounds without such groups (p. 252). Treatment with a suitable base (a base that has a conjugate acid with a pK_a greater than the α-proton) removes the α-proton and generates the corresponding enolate anion (**10-68**). These enolate anions react as carbon nucleophiles and attack alkyl halides, resulting in their alkylation.[1575] Both Z and Z′ may be COOR′, CHO, COR′,[1576] $CONR'_2$, COO^-, CN,[1577] NO_2, SOR′, SO_2R',[1578] SO_2OR', $SO_2NR'_2$ or similar groups.[1579] Some commonly used bases are sodium ethoxide and potassium *tert*-butoxide, each in its respective alcohol as solvent. With particularly acidic compounds (e.g., β-diketones–Z, Z′ = COR′), sodium hydroxide in water or aqueous alcohol or acetone, or even sodium carbonate,[1580] is a strong enough base for the reaction. If at least one Z group is COOR′, saponification is a possible side reaction. In addition to the groups listed above, Z may also be phenyl, but if two phenyl groups are on the same carbon, the acidity is less than in the other cases and a stronger base must be used. However, the reaction can be successfully carried out with diphenylmethane with $NaNH_2$ as the base.[1581] If the solvent used in the reaction is acidic enough to protonate either the enolate anion or the base, an equilibrium will be established leading to only small amounts of the enolate anion (thermodynamic conditions). Such aprotic solvents include

[1575]For dicussions of reactions **10-67** and **10-68**, see House, H.O. *Modern Synthetic Reactions*, 2nd ed., W. A. Benjamin, NY, ***1972***, pp. 492–570, 586–595; Carruthers, W. *Some Modern Methods of Organic Synthesis* 3rd ed., Cambridge University Press, Cambridge, ***1986***, pp. 1–26.

[1576]For a reaction using *n*-Bu_4NF as the base in aq. THF, see Christoffers, J. *Synth. Commun.* ***1999***, *29*, 117.

[1577]For reviews of the reactions of malononitrile $CH_2(CN)_2$, see Fatiadi, A.J. *Synthesis* ***1978***, 165, 241; Freeman, F. *Chem. Rev.* ***1969***, *69*, 591.

[1578]For a review of compounds with two SO_2R groups on the same carbon (*gem*-disulfones), see Neplyuev, V.M.; Bazarova, I.M.; Lozinskii, M.O. *Russ. Chem. Rev.* ***1986***, *55*, 883.

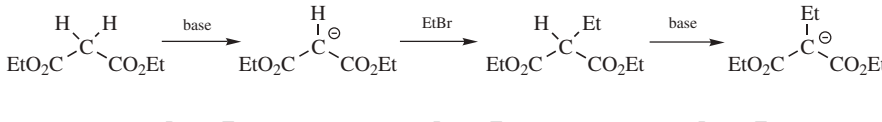
[1579]For lists of examples, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1522–1527 *ff*, 1765–1769.

[1580]See, for example, Fedoryński, M.; Wojciechowski, K.; Matacz, Z.; Makosza, M. *J. Org. Chem.* ***1978***, *43*, 4682.

[1581]Murphy, W.S.; Hamrick, Jr., P.J.; Hauser, C.R. *Org. Synth. V.* 523.

water, alcohols, or amines. In general, solvents that do not contain an acidic proton (aprotic solvents) are used, but protic solvents can be used in some cases. The use of polar aprotic solvents (e.g., DMF or DMSO) markedly increases the rate of alkylation,[1582] but also increases the extent of alkylation at the oxygen rather than the carbon with highly reactive species such as iodomethane (p. 513). In general, enolate anions such as those described here react with alkyl halides via *C*-alkylation, although trialkylsilyl halides and anhydrides tend to react via *O*-alkylation. Phase-transfer catalysis has also been used,[1583] and the use of chiral phase transfer catalysts led to enantioselectivity in the alkylated product.[1584] The reaction is successful for primary and secondary alkyl, allylic (with allylic rearrangement possible), and benzylic RX, but fails for tertiary halides, since these undergo elimination under the reaction conditions (see, however, p. 625). Various functional groups may be present in RX as long as they are not sensitive to base. Side reactions that may cause problems are the above-mentioned competing *O*-alkylation, elimination (if the enolate anion is a strong enough base), and dialkylation.

With substrates, such as ZCH_2Z', it is possible to alkylate twice. Initial removal of the proton with a base followed by alkylation of the resulting enolate anion with RX, can be followed by subsequent removal of the proton from $ZCHRZ'$ and then alkylation with the same or a different RX. An important example of this reaction is the *malonic ester synthesis*, in which both Z groups are COOEt. The product can be hydrolyzed and decarboxylated (**12-40**) to give a carboxylic acid. An illustration is the preparation of 2-ethylpentanoic acid (**155**) from malonic ester. A variation of this alkylation sequence employs 1,2-dibromoethane as the alkylating agent, and subsequent treatment with DBU leads to incorporation of a vinyl group on the α-carbon.[1585] Another variation involved coupling of a dimalonate with an allylic carbonate (see **10-60**), using a polymer-supported palladium catalyst.[1586]



155

It is obvious that many carboxylic acids of the formulas RCH_2COOH and $RR'CHCOOH$ can be synthesized by this method [for some other ways of preparing

[1582]Zaugg, H.E.; Dunnigan, D.A.; Michaels, R.J.; Swett, L.R.; Wang, T.S.; Sommers, A.H.; DeNet, R.W. *J. Org. Chem.* ***1961***, *26*, 644; Johnstone, R.A.W.; Tuli, D.; Rose, M.E. *J. Chem. Res. (S)* ***1980***, 283.

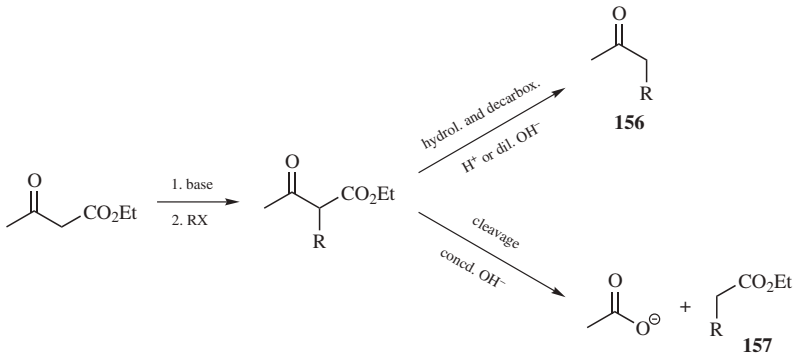
[1583]See Sukhanov, N.N.; Trappel', L.N.; Chetverikov, V.P.; Yanovskaya, L.A. *J. Org. Chem. USSR* ***1985***, *21*, 2288; Tundo, P.; Venturello, P.; Angeletti, E. *J. Chem. Soc. Perkin Trans. 1* ***1987***, 2159.

[1584]Park, E.J.; Kim, M.H.; Kim, D.Y. *J. Org. Chem.* ***2004***, *69*, 6897.

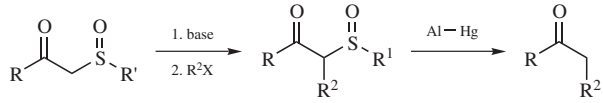
[1585]Bunce, R.A.; Burns, S.E. *Org. Prep. Proceed. Int.* ***1999***, *31*, 99.

[1586]Akiyama, R.; Kobayashi, S. *J. Am. Chem. Soc.* ***2003***, *125*, 3412.

such acids (see **10-70–10-73**)]. Another important example is the *acetoacetic ester synthesis*, in which Z is COOEt and Z′ is $COCH_3$. In this case, the product can be decarboxylated with acid or dilute base (**12-40**) to give a ketone (**156**) or cleaved with concentrated base (**12-43**) to give a carboxylic ester (**157**) and a salt of acetic acid. This reaction has been done in *tert*-butanol in the presence of alumina, *in vacuo*, to give the alkylated keto acid directly from the keto ester.[1587]



Another way of preparing ketones involves alkylation[1588] of β-keto sulfoxides[1589] or sulfones,[1590] to give **158**.



158

The sulfoxide group in the product (**158**) is easily reduced (desulfurized, see p. $$$) to give the ketone in high yields using aluminum amalgam or by electrolysis.[1591] β-Keto sulfoxides, such as **158** or sulfones (—SO_2—), are easily prepared (**16-86**). When one group attached to the sulfur atom is chiral, the alkylation proceeds to with reasonable enantioselectivity.[1592] Alkylation of α-nitrosulfones was reported, using photochemical conditions, $(Me_3Sn)_2$ and a secondary iodide.[1593]

Other examples of the reaction are the *cyanoacetic ester synthesis*, in which Z is COOEt and Z′ is CN (as in the malonic ester synthesis, the product here can be hydrolyzed and decarboxylated), and the *Sorensen* method of amino acid synthesis, in which

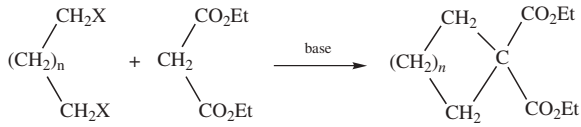
[1587]Bhar, S.; Chaudhuri, S.K.; Sahu, S.G.; Panja, C. *Tetrahedron* ***2001***, *57*, 9011.
[1588]For a review of the synthetic uses of β-keto sulfoxides, sulfones, and sulfides, see Trost, B.M. *Chem. Rev.* ***1978***, *78*, 363. For a review of asymmetric synthesis with chiral sulfoxides, see Solladié, G. *Synthesis* ***1981***, 185.
[1589]Gassman, P.G.; Richmond, G.D. *J. Org. Chem.* ***1966***, *31*, 2355. Such sulfoxides can be alkylated on the other side of the C=O group by the use of two moles of base: Kuwajima, I.; Iwasawa, H. *Tetrahedron Lett.* ***1974***, 107.
[1590]House, H.O.; Larson, J.K. *J. Org. Chem.* ***1968***, *33*, 61; Kurth, M.J.; O'Brien, M.J. *J. Org. Chem.* ***1985***, 3846.
[1591]Lamm, B.; Samuelsson, B. *Acta Chem. Scand.* ***1969***, *23*, 691.
[1592]Enders, D.; Harnying, W.; Vignola, N. *Eur. J. Org. Chem.* ***2003***, 3939.
[1593]Kim, S. Yoon, Y.-y.; Lim, C.J. *Synlett* ***2000***, 1151.

the reaction is applied to *N*-acetylaminomalonic ester $(EtOOC)_2CHNHCOCH_3$. Hydrolysis and decarboxylation of the product in this case gives an α-amino acid. The amino group is also frequently protected by conversion to a phthalimido group.

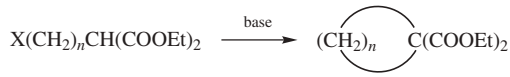
The reaction is not limited to $Z{-}CH_2{-}Z'$ compounds. Other compounds have acidic CH hydrogens. Some examples are the methyl hydrogens of α-aminopyridines, the methyl hydrogens of ynamines of the form $CH_3C{\equiv}CNR_2$[1594] (the product in this case can be hydrolyzed to an amide $RCH_2CH_2CONR_2$), the CH_2 hydrogens of cyclopentadiene and its derivatives (p. 63), hydrogens connected to a triple-bond carbon (**10-74**), and the hydrogen of HCN (**10-75**) can also be removed with a base and the resulting ion alkylated (see also, **10-68** to **10-72**). α-Imino esters have been used since treatment with a strong base with a titanium catalyst followed by an aldehyde leads to hydroxy-amino-esters.[1595]

Alkylation takes place at the most acidic position of a reagent molecule; for example, acetoacetic ester (CH_3COCH_2COOEt) is alkylated at the methylene and not at the methyl group, because the former is more acidic than the latter and hence gives up its proton to the base. However, if 2 equivalents of base are used, then not only is the most acidic proton removed, but also the second most acidic. Alkylation of this doubly charged anion (a dianion) occurs at the less acidic position, in this case the second most acidic position[1596] (see p. 513). The first and second ion pair acidities of β-diketones has been studied.[1597]

When ω,ω′-dihalides are used, ring closures can be effected:[1598]



This method has been used to close rings of from three ($n = 0$) to seven members, although five-membered ring closures proceed in highest yields. Another ring-closing method involves internal alkylation.[1599]



[1594]Corey, E.J.; Cane, D.E. *J. Org. Chem.* ***1970***, *35*, 3405.

[1595]Kanemasa, S.; Mori, T.; Wada, E.; Tatsukawa, A. *Tetrahedron Lett.* ***1993***, *34*, 677. See Kotha, S.; Kuki, A. *Tetrahedron Lett.* ***1992***, *33*, 1565 for a related reaction.

[1596]For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1540–1541. Also see, Lu, Y.-Q.; Li, C.-J. *Tetrahedron Lett.* ***1996***, *37*, 471.

[1597]Facchetti, A.; Streitwieser, A. *J. Org. Chem.* ***2004***, *69*, 8345.

[1598]Zefirov, N.S.; Kuznetsova, T.S.; Kozhushkov, S.I.; Surmina, L.S.; Rashchupkina, Z.A. *J. Org. Chem. USSR* ***1983***, *19*, 474.

[1599]For example, see Knipe, A.C.; Stirling, C.J.M. *J. Chem. Soc. B* ***1968***, 67; Gosselck, J.; Winkler, A. *Tetrahedron Lett.* ***1970***, 2437; Walborsky, H.M.; Murari, M.P. *Can. J. Chem.* ***1984***, *62*, 2464. For a review of this method as applied to the synthesis of β-lactams, see Bose, A.K.; Manhas, M.S.; Chatterjee, B.G.; Abdulla, R.F. *Synth. Commun.* ***1971***, *1*, 51. For a list of examples, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 156–157, 165–166.

This method has been shown to be applicable to medium rings (10–14 members) without the use of high-dilution techniques.[1600]

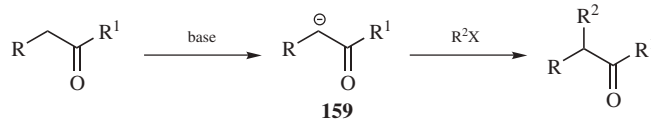
The mechanism of these reactions is usually S_N2 with inversion taking place at a chiral RX, although an SET[1601] mechanism may be involved in certain cases,[1602] especially where the nucleophile is an α-nitro carbanion[1603] and/or the substrate contains a nitro or cyano[1604] group. Tertiary alkyl groups can be introduced by an S_N1 mechanism if the ZCH_2Z' compound (not the enolate anion) is treated with a tertiary carbocation generated *in situ* from an alcohol or alkyl halide and BF_3 or $AlCl_3$,[1605] or with a tertiary alkyl perchlorate.[1606]

Alkylation α to a nitro group can be achieved with the Katritzky pyrylium–pyridinium reagents.[1607] This reaction probably has a free-radical mechanism.[1608]

OS **I**, 248, 250; **II**, 262, 279, 384, 474; **III**, 213, 219, 397, 405, 495, 705; **IV**, 10, 55, 288, 291, 623, 641, 962; **V**, 76, 187, 514, 523, 559, 743, 767, 785, 848, 1013; **VI**, 223, 320, 361, 482, 503, 587, 781, 991; **VII**, 339, 411; **VIII**, 5, 312, 381. See also, OS **VIII**, 235.

10-68 Alkylation of Ketones, Aldehydes, Nitriles, and Carboxylic Esters

α-Acylalkyl-de-halogenation, and so on



159

Ketones,[1609] nitriles,[1610] and carboxylic esters[1611] can be alkylated in the α position in a reaction similar to **10-67**.[1568] The pK_a of the proton α to the carbonyl or

[1600]Deslongchamps, P.; Lamothe, S.; Lin, H. *Can. J. Chem.* ***1984***, *62*, 2395; ***1987***, *65*, 1298; Brillon, D.; Deslongchamps, P. *Can. J. Chem.* ***1987***, *65*, 43, 56.

[1601]These SET mechanisms are often called $S_{RN}1$ mechanisms. See also, Ref. 96.

[1602]Kornblum, N.; Michel, R.E.; Kerber, R.C. *J. Am. Chem. Soc.* ***1966***, *88*, 5660, 5662; Russell, G.A.; Ros, F. *J. Am. Chem. Soc.* ***1985***, *107*, 2506; Ashby, E.C.; Argyropoulos, J.N. *J. Org. Chem.* ***1985***, *50*, 3274; Bordwell, F.G.; Harrelson, Jr., J.A. *J. Am. Chem. Soc.* ***1989***, *111*, 1052.

[1603]For a review of mechanisms with these nucleophiles, see Bowman, W.R. *Chem. Soc. Rev.* ***1988***, *17*, 283.

[1604]Kornblum, N.; Fifolt, M. *Tetrahedron* ***1989***, *45*, 1311.

[1605]For example, see Boldt, P.; Militzer, H. *Tetrahedron Lett.* ***1966***, 3599; Crimmins, T.F.; Hauser, C.R. *J. Org. Chem.* ***1967***, *32*, 2615; Boldt, P.; Militzer, H.; Thielecke, W.; Schulz, L. *Liebigs Ann. Chem.* ***1968***, *718*, 101.

[1606]Boldt, P.; Ludwieg, A.; Militzer, H. *Chem. Ber.* ***1970***, *103*, 1312.

[1607]Katritzky, A.R.; Kashmiri, M.A.; Wittmann, D.K. *Tetrahedron* ***1984***, *40*, 1501.

[1608]Katritzky, A.R.; Chen, J.; Marson, C.M.; Maia, A.; Kashmiri, M.A. *Tetrahedron* ***1986***, *42*, 101.

[1609]For a review of the alkylation and acylation of ketones and aldehydes, see Caine, D., in Augustine, R.L. *Carbon–Carbon Bond Formation*, Vol. 1, Marcel Dekker, NY, ***1979***, pp. 85–352.

[1610]For a review, see Arseniyadis, S.; Kyler, K.S.; Watt, D.S. *Org. React.* ***1984***, *31*, 1. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1801–1808. See Taber, D.F.; Kong, S. *J. Org. Chem.* ***1997***, *62*, 8575.

[1611]For a review, see Petragnani, N.; Yonashiro, M. *Synthesis* ***1982***, 521. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1724–1758*ff*.

CN is in the range of 19–25 (see p. 363), and a base that has a conjugate acid with a pK_a greater than that proton must be employed. Note that since only one activating group is present here, compared with two activating groups for the substrates in **10-67**, the pK_a of the α-proton is higher (a weaker acid) and a stronger base is required. Reaction of the α-proton with the base generates they key nucleophilic intermediate, an enolate anion (**159**). The most common bases[1612] are lithium diethylamide (Et_2NLi), lithium diisopropylamide[$(i\text{Pr})_2\text{NLi}$, LDA], *t*-BuOK, $NaNH_2$, and KH. A combination of lithium hexamethyldisilazide [$LiN(SiMe_3)_2$] followed by $MnBr_2$ is also effective for alkylation of ketones.[1613] The base lithium *N*-isopropyl-*N*-cyclohexylamide (LICA) is particularly successful for carboxylic esters[1614] and nitriles.[1615] Solid KOH in Me_2SO has been used to methylate ketones, in high yields.[1616] Some of these bases are strong enough to convert the ketone, nitrile, or ester completely to its enolate anion conjugate base; others (especially *t*-BuOK) convert a significant fraction of the molecules. In the latter case, the aldol reaction (**16-34**) or Claisen condensation (**16-85**) may be side reactions, since both the free molecule and its conjugate base are present at the same time. It is therefore important to use a base strong enough to convert the starting compound completely. Both lactones[1617] and lactams are similarly alkylated.[1618] Protic solvents are generally not suitable because they protonate the base (though of course this is not a problem with a conjugate pair, such as *t*-BuOK in *t*-BuOH). Some common solvents are 1,2-dimethoxyethane, THF, DMF, and liquid NH_3. Phase-transfer catalysis has been used to alkylate many nitriles, as well as some esters and ketones.[1619]

Direct alkylation of aldehydes is difficult when bases, such as KOH and NaOMe, are used due to rapid aldol reaction (**16-34**), but aldehydes bearing only one α hydrogen have been alkylated with allylic and benzylic halides in good yields by the use of the base KH to prepare the potassium enolate,[1620] or in moderate yields, by the use of a phase-transfer catalyst.[1621] Even the use of amide bases such as

[1612]For a list of some bases, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1476–1479.

[1613]Reetz, M.T.; Haning, H. *Tetrahedron Lett.* ***1993***, *34*, 7395.

[1614]Rathke, M.W.; Lindert, A. *J. Am. Chem. Soc.* ***1971***, *93*, 2319; Bos, W.; Pabon, H.J.J. *Recl. Trav. Chim. Pays-Bas* ***1980***, *99*, 141. See also, Cregge, R.J.; Herrmann, J.L.; Lee, C.S.; Richman, J.E.; Schlessinger, R.H. *Tetrahedron Lett.* ***1973***, 2425.

[1615]Watt, D.S. *Tetrahedron Lett.* ***1974***, 707.

[1616]Langhals, E.; Langhals, H. *Tetrahedron Lett.* ***1990***, *31*, 859.

[1617]For a discusson of the stereochemistry of lactone alkylation see Ibrahim-Ouali, M.; Parrain, J.-L.; Santelli, M. *Org. Prep. Proceed. Int.* ***1999***, *31*, 467. Enolate anions of β-lactones are subject to ring opening: see Mori, S.; Shindo, M. *Org. Lett.* ***2004***, *6*, 3945.

[1618]Matsuo, J.-i.; Kobayashi, S.; Koga, K. *Tetrahedron Lett.* ***1998***, *39*, 9723.

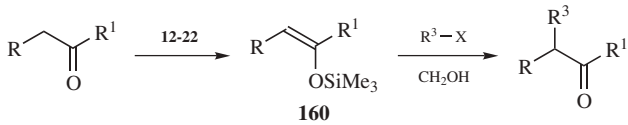
[1619]For reviews, see Makosza, M. *Russ. Chem. Rev.* ***1977***, *46*, 1151; *Pure Appl. Chem.* ***1975***, *43*, 439; Starks, C.M.; Liotta, C. *Phase Transfer Catalysis*, Acaemic Press, NY, ***1978***, pp. 170–217; Weber, W.P.; Gokel, G.W. *Phase Transfer Catalysis in Organic Synthesis*, Springer, NY, ***1977***, pp. 136–204.

[1620]Groenewegen, F.; Kallenberg, H.; van der Gen, A. *Tetrahedron Lett.* ***1978***, 491; Artaud, I.; Torossian, G.; Viout, P. *Tetrahedron* ***1985***, *41*, 5031.

[1621]Dietl, H.K.; Brannock, K.C. *Tetrahedron Lett.* ***1973***, 1273; Purohit, V.G.; Subramanian, R. *Chem. Ind. (London)* ***1978***, 731; Buschmann, E.; Zeeh, B. *Liebigs Ann. Chem.* ***1979***, 1585.

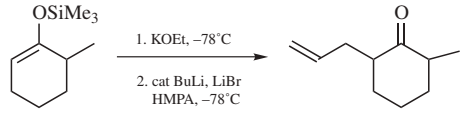
lithium diisopropylamide (LDA), lithium hexamethyldisilazide (LHMDS), or lithium tetramethylpiperidide (LTMP) to generate the enolate anion in an aprotic solvent, such as ether or THF, cannot preclude rapid aldol side reactions.

As in **10-67**, the alkyl halide that reacts with the enolate anion may be primary or secondary. Tertiary halides give elimination. Even primary and secondary halides give predominant elimination if the enolate anion is a strong enough base (e.g., the enolate anion from Me_3CCOMe).[1622] Tertiary alkyl groups, as well as other groups that normally give S_N1 reactions, can be introduced if the reaction is performed on a silyl enol ether[1623] of a ketone, aldehyde, or ester (see **160**) with a Lewis acid catalyst.[1624] Tertiary alkyl fluorides were coupled to silyl enol ethers with BF_3•etherate.[1625] An interesting reaction reacted a methyl ketone, such as acetophenone (1-phenyl-1-ethanone) with tributylamine, in the presence of a ruthenium catalyst at 180°C, and the product resulted from *C*-alkylation (1-phenyl-1-hexanone).[1626] Note that tin enolates ($C{=}C{-}OSnR_3$) react with halides in the presence of a zinc catalyst.[1627] A chiral variation of this latter reaction was reported involving generation of the enolate anion in the presence of Me_3SnCl, a palladium catalyst and a chiral ligand.[1628]



160

Silyl enol ethers can be converted to the enolate anion, which can then be alkylated in the usual manner. The reaction of silyl enol ether **161** using KOEt followed by LiBr at a catalytic amount of *n*-butyllithium with allyl iodide gave **162**.[1629] Initial conversion of the silyl enol ether to the enolate anion allows the alkylation process to take place.



161 **162**

[1622]Zook, H.D.; Kelly, W.L.; Posey, I.Y. *J. Org. Chem.* ***1968***, *33*, 3477.
[1623]For a list of alkylations of silyl enol ethers, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1494–1505.
[1624]Reetz, M.T.; Sauerwald, M. *J. Organomet. Chem.* ***1990***, *382*, 121; Kad, G.L.; Singh, V.; Khurana, A.; Chaudhary, S.; Singh, J. *Synth. Commun.* ***1999***, *29* , 3439; Kang, S.-K.; Ryu, H.-C.; Hong, Y.-T. *J. Chem. Soc., Perkin Trans. 1* ***2000***, 3350. For a review, see Reetz, M.T. *Angew. Chem. Int. Ed.* ***1982***, *21*, 96.
[1625]Hirano, K.; Fujita, K.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* ***2004***, *45*, 2555.
[1626]Cho, C.S.; Kim, B.T.; Lee, M.J.; Kim, T.-J.; Shim, S.C. *Angew. Chem. Int. Ed.* ***2001***, *40*, 958.
[1627]Yasuda, M.; Tsuji, S.; Shigeyoshi, Y.; Baba, A. *J. Am. Chem Soc.* ***2002***, *124*, 7440.
[1628]Trost, B.M.; Schroeder, G.M. *J. Am. Chem. Soc.* ***1999***, *121*, 6759.
[1629]Yu, W.; Jin, Z. *Tetrahedron Lett.* ***2001***, *42*, 369.

Enol carbonates react with alkylating agents in the presence of a palladium catalyst. The decarboxylative alkylation of allyl enol carbonates to the corresponding allylcyclohexanone derivatives is known as the *Tsuji alkylation.*[1630] An asymmetric version of this reaction has been reported.[1631] The same reaction can be done using enolate anion and allylic acetates with a palladium catalyst.[1632]

Vinylic and aryl halides can be used to vinylate or arylate carboxylic esters (but not ketones) by the use of $NiBr_2$ as a catalyst.[1633] Ketones have been vinylated by treating their enol acetates with vinylic bromides in the presence of a Pd compound catalyst,[1634] but direct reaction of a ketone, a vinyl halide, sodium *tert*-butoxide and a palladium catalyst also give the α-vinyl ketone.[1635] Also as in **10-67**, this reaction can be used to close rings.[1636] Rings have been closed by treating a dianion of a dialkyl succinate with a 1,ω-dihalide or ditosylate.[1637] This was applied to the synthesis of three-, four-, five-, and six-membered rings. When the attached groups were chiral (e.g., menthyl) the product was formed with >90% ee.[1636]

Efficient enantioselective alkylations are known.[1638] In another method enantioselective alkylation can be achieved by using a chiral base to form the enolate.[1639] Alternatively, a chiral auxiliary can be attached. Many auxiliaries are based on the use of chiral amides[1640] or esters.[1641] Subsequent formation of the enolate anion allows alkylation to proceed with high enantioselectivity. A subsequent step is

[1630]Tsuji, J.; Minami, I. *Acc. Chem. Res.* ***1987***, *20*, 140; Tsuji, J.; Minami, I.; Shimizu, I. *Tetrahedron Lett.* ***1983***, *24*, 1793; Tsuji, J.; Shimizu, I.; Minami, I.; Ohashi, Y.; Sugiura, T.; Takahashi, K. *J. Org. Chem.* ***1985***, *50*, 1523; Tsuji, J.; Minami, I.; Shimizu, I. *Chem. Lett.* ***1983***, *12*, 1325. See also, Nicolaou, K.C.; Vassilikogiannakis, G.; Mägerlein, W.; Kranich, R. *Angew. Chem. Int. Ed.* ***2001***, *40*, 2482; Herrinton, P.M.; Klotz, K.L.; Hartley, W.M. *J. Org. Chem.* ***1993***, *58*, 678.

[1631]Behenna, D.C.; Stoltz, B.M. *J. Am. Chem. Soc.* ***2004***, *126*, 15044.

[1632]Trost, B.M.; Schroeder, G.M.; Kristensen, J. *Angew. Chem. Int. Ed.* ***2002***, *41*, 3492.

[1633]Millard, A.A.; Rathke, M.W. *J. Am. Chem. Soc.* ***1977***, *99*, 4833.

[1634]Kosugi, M.; Hagiwara, I.; Migita, T. *Chem. Lett.* ***1983***, 839. For other methods, see Negishi, E.; Akiyoshi, K. *Chem. Lett.* ***1987***, 1007; Chang, T.C.T.; Rosenblum, M.; Simms, N. *Org. Synth. 66*, 95.

[1635]Chieffi, A.; Kamikawa, K.; Åhman, J.; Fox, J.M.; Buchwald, S.L *Org. Lett.* ***2001***, *3*, 1897.

[1636]For example, see Etheredge, S.J. *J. Org. Chem.* ***1966***, *31*, 1990; Wilcox, C.F.; Whitney, G.C. *J. Org. Chem.* ***1967***, *32*, 2933; Bird, R.; Stirling, C.J.M. *J. Chem. Soc. B* ***1968***, 111; Stork, G.; Boeckman, Jr., R.K. *J. Am. Chem. Soc.* ***1973***, *95*, 2016; Stork, G.; Cohen, J.F. *J. Am. Chem. Soc.* ***1974***, *96*, 5270. In the last case, the substrate moiety is an epoxide function.

[1637]Misumi, A.; Iwanaga, K.; Furuta, K.; Yamamoto, H. *J. Am. Chem. Soc.* ***1985***, *107*, 3343; Furuta, K.; Iwanaga, K.; Yamamoto, H. *Org. Synth. 67*, 76.

[1638]For reviews of stereoselective alkylation of enolates, see Nógrádi, M. *Stereoselective Synthesis*, VCH, NY, ***1986***, pp. 236–245; Evans, D.A. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 3, Academic Press, NY, ***1984***, pp. 1–110.

[1639]For example, see Murakata, M.; Nakajima, N.; Koga, K. *J. Chem. Soc., Chem. Commun.* ***1990***, 1657. For a review, see Cox. P.J.; Simpkins, N.S. *Tetrahedron: Asymmetry* ***1991***, *2*, 1, pp. 6–13.

[1640]Chiral oxazolidinones such as the Evan's auxiliaries derived from chiral amino alcohols: Lafontaine, J.A.; Provencal, D.P.; Gardelli, C.; Leahy, J.W. *J. Org. Chem.* ***2003***, *68*, 4215; Bull, S.D.; Davies, S.G.; Nicholson, R.L.; Sanganee, H.J.; Smith, A.D. *Tetrahedron Asymmetry* ***2000***, *11*, 3475. See Evans, D.A.; Chapman, K.T.; Bisaha, J. *Tetrahedron Lett.* ***1984***, *25*, 4071; Evans, D.A. Chapman, K.T.; Bisaha, J. *J. Am. Chem. Soc.* ***1984***, *106*, 4261. Oppolzer's sultam: Oppolzer, W.; Chapuis, C.; Dupuis, D.; Guo, M. *Helv. Chim. Acta* ***1985***, *68*, 2100. Chiral sulfonamides: Schmierer, R.; Grotemeier, G.; Helmchen, G.; Selim, A. *Angew. Chem. Int. Ed.* ***1981***, *20*, 207.

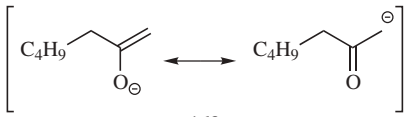
[1641]Oppolzer, W.; Dudfield, P.; Stevenson, T.; Godel, T. *Helv. Chim. Acta* ***1985***, *68*, 212.

required to convert the chiral amide or ester to the corresponding carboxylic acid. Chiral additives can also be used.[1642]

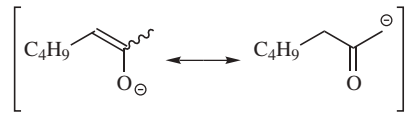
When the compound to be alkylated is an unsymmetrical ketone, the question arises as to which side will be alkylated. If a phenyl or a vinylic group is present on one side, alkylation goes predominantly on that side. When only alkyl groups are present, the reaction is generally not regioselective; mixtures are obtained in which sometimes the more alkylated and sometimes the less alkylated side is predominantly alkylated. Which product is found in higher yield depends on the nature of the substrate, the base,[1643] the cation, and the solvent. In any case, di- and trisubstitution are frequent[1644] and it is often difficult to stop with the introduction of just one alkyl group.[1645]

Several methods have been developed for ensuring that alkylation takes place regioselectively on the *desired* side of a ketone.[1646] Among these are

1. Block one side of the ketone by introducing a removable group. Alkylation takes place on the other side; the blocking group is then removed. A common reaction for this purpose is formylation with ethyl formate (**16-86**); this generally blocks the less hindered side. The formyl group is easily removed by alkaline hydrolysis (**12-43**).
2. Introduce an activating group on one side; alkylation then takes place on that side (**10-67**); the activating group is then removed.
3. Prepare the desired one of the two possible enolate anions.[1647] The two ions, for example, **163** and **164** for 2-heptanone, interconvert rapidly only in



163



164

the presence of the parent ketone or any stronger acid.[1648] In the absence of such acids, it is possible to prepare either **163** or **164** and thus achieve

[1642]Denmark, S.E.; Stavenger, R.A. *Acc. Chem. Res.* ***2000***, *33*, 432; Machajewski, T.D.; Wong, C.-H. *Angew. Chem. Int. Ed.* ***2000***, *39*, 1352.

[1643]Sterically hindered bases may greatly favor one enolate over the other. See, for example, Prieto, J.A.; Suarez, J.; Larson, G.L. *Synth. Commun.* ***1988***, *18*, 253; Gaudemar, M.; Bellassoued, M. *Tetrahedron Lett.* ***1989***, *30*, 2779.

[1644]For a procedure for completely methylating the apositions of a ketone, see Lissel, M.; Neumann, B.; Schmidt, S. *Liebigs Ann. Chem.* ***1987***, 263.

[1645]For some methods of reducing dialkylation, see Hooz, J.; Oudenes, J. *Synth. Commun.* ***1980***, *10*, 139; Morita, J.; Suzuki, M.; Noyori, R. *J. Org. Chem.* ***1989***, *54*, 1785.

[1646]For a review, see House, H.O. *Rec. Chem. Prog.* ***1968***, *28*, 99. For a review with respect to cyclohexenones, see Podraza, K.F. *Org. Prep. Proced. Int.* ***1991***, *23*, 217.

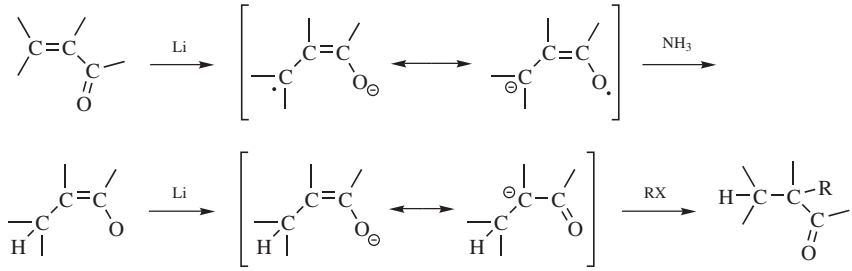
[1647]For reviews, see d'Angelo, J. *Tetrahedron* ***1976***, *32*, 2979; Stork, G. *Pure Appl. Chem.* ***1975***, *43*, 553.

[1648]House, H.O.; Trost, B.M. *J. Org. Chem.* ***1965***, *30*, 1341.

selective alkylation on either side of the ketone.[1649] The desired enolate anion can be obtained by treatment of the corresponding enol acetate with two equivalents of methyllithium in 1,2-dimethoxyethane. Each enol acetate gives the corresponding enolate, for example,

The enol acetates, in turn, can be prepared by treatment of the parent ketone with an appropriate reagent.[1241] Such treatment generally gives a mixture of the two enol acetates in which one or the other predominates, depending on the reagent. The mixtures are easily separable.[1648] An alternate procedure involves conversion of a silyl enol ether[1650] (see **12-17**) or a dialkylboron enol ether[1651] (an enol borinate, see p. 645) to the corresponding enolate anion. If the less hindered enolate anion is desired (e.g., **126**), it can be prepared directly from the ketone by treatment with LDA in THF or 1,2-dimethoxyethane (DME) at −78°C.[1652]

4. Begin not with the ketone itself, but with an α,β-unsaturated ketone in which the double bond is present on the side where alkylation is desired. Upon treatment with lithium in liquid NH_3, such a ketone is reduced to an enolate anion. When the alkyl halide is added, it must react with the enolate anion on



the side where the double bond was.[1653] Of course, this method is not actually an alkylation of the ketone, but of the α,β-unsaturated ketone, although the

[1649]Whitlock Jr., H.W.; Overman, L.E. *J. Org. Chem.* ***1969***, *34*, 1962; House, H.O.; Gall, M.; Olmstead, H.D. *J. Org. Chem.* ***1971***, *36*, 2361. For an improved procedure, see Liotta, C.L.; Caruso, T.C. *Tetrahedron Lett.* ***1985***, *26*, 1599.

[1650]Stork, G.; Hudrlik, P.F. *J. Am. Chem. Soc.* ***1968***, *90*, 4462, 4464. For reviews, see Kuwajima, I.; Nakamura, E. *Acc. Chem. Res.* ***1985***, *18*, 181; Fleming, I. *Chimia*, ***1980***, *34*, 265; Rasmussen, J.K. *Synthesis* ***1977***, 91.

[1651]Pasto, D.J.; Wojtkowski, P.W. *J. Org. Chem.* ***1971***, *36*, 1790.

[1652]House, H.O.; Gall, M.; Olmstead, H.D. *J. Org. Chem.* ***1971***, *36*, 2361. See also, Corey, E.J.; Gross, A.W. *Tetrahedron Lett.* ***1984***, *25*, 495.

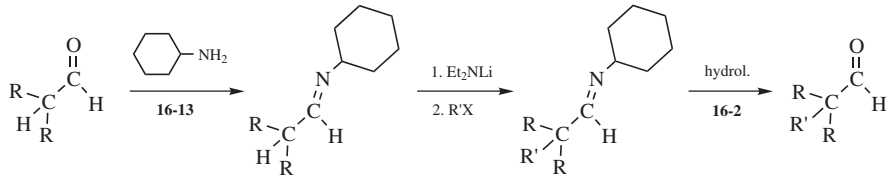
[1653]Stork, G.; Rosen, P.; Goldman, N.; Coombs, R.V.; Tsuji, J. *J. Am. Chem. Soc.* ***1965***, *87*, 275. For a review, see Caine, D. *Org. React.* ***1976***, *23*, 1. For similar approaches, see Coates, R.M.; Sowerby, R.L. *J. Am. Chem. Soc.* ***1971***, *93*, 1027; Näf, F.; Decorzant, R. *Helv. Chim. Acta* ***1974***, *57*, 1317; Wender, P.A.; Eissenstat, M.A. *J. Am. Chem. Soc.* ***1978***, *100*, 292.

product is the same as if the saturated ketone had been alkylated on the desired side.

Both sides of acetone have been alkylated with different alkyl groups, in one operation, by treatment of the *N,N*-dimethylhydrazone of acetone with *n*-BuLi, followed by a primary alkyl, benzylic, or allylic bromide or iodide; then another mole of *n*-BuLi, a second halide, and finally hydrolysis of the hydrazone.[1654] Alkylation of an unsymmetrical ketone at the more substituted position was reported using an alkyl bromide, NaOH, and a calix[*n*]arene catalyst (see p. 122 for calixarenes).[1655]

Among other methods for the preparation of alkylated ketones are (*1*) Alkylation of silyl enol ethers using various reagents as noted above, (*2*) the Stork enamine reaction (**10-69**), (*3*) the acetoacetic ester synthesis (**10-67**), (*4*) alkylation of β-keto sulfones or sulfoxides (**10-67**), (*5*) acylation of $CH_3SOCH_2^-$ followed by reductive cleavage (**16-86**), (*6*) treatment of α-halo ketones with lithium dialkylcopper reagents (**10-57**), and (*7*) treatment of α-halo ketones with trialkylboranes (**10-73**).

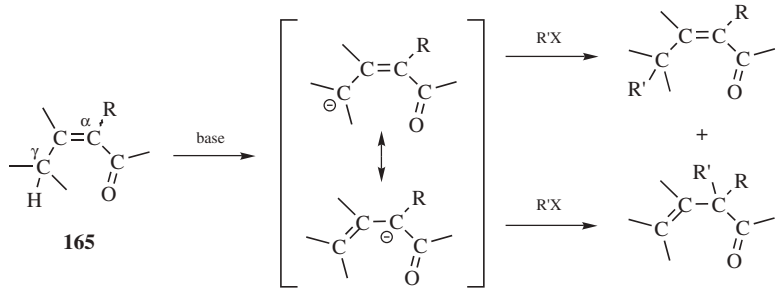
Aldehydes can be indirectly alkylated via an imine derivative of the aldehyde.[1656] The derivative is easily prepared (**16-13**) and the product easily hydrolyzed to the aldehyde (**16-2**). Either or both R groups may be hydrogen, so that



mono-, di-, and trisubstituted acetaldehydes can be prepared by this method. R′ may be primary alkyl, allylic, or benzylic. Imine alkylation can also be applied to the preparation of substituted amine derivatives. An amino acid surrogate, such as $Ph_2C{=}NCH_2CO_2R$, when treated with KOH and an alkyl halide gives the *C*-alkylated product.[1657] When a chiral additive is used, good enantioselectivity was observed. This reaction has also been done in the ionic liquid bmim tetrafluoroborate (see p. 415).[1658] It is possible to alkylate α-amino amides directly.[1659]

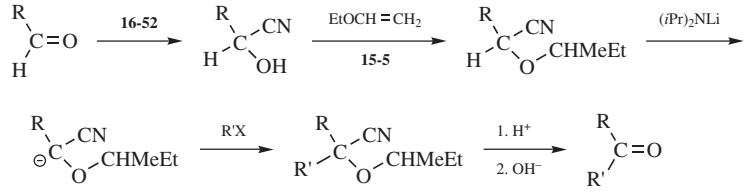
[1654]Yamashita, M.; Matsuyama, K.; Tanabe, M.; Suemitsu, R. *Bull. Chem. Soc. Jpn.* ***1985***, *58*, 407.
[1655]Shimizu, S.; Suzuki, T.; Sasaki, Y.; Hirai, C. *Synlett* ***2000***, 1664.
[1656]Cuvigny, T.; Normant, H. *Bull. Soc. Chim. Fr.* ***1970***, 3976. For reviews, see Fraser, R.R., in Buncel, E.; Durst, T. *Comprehensive Carbanion Chemistry*, Vol. 5, pt. B, Elsevier, NY, ***1984***, pp. 65–105; Whitesell, J.K.; Whitesell, M.A. *Synthesis* ***1983***, 517. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1513–1518. For a method in which the metalated imine is prepared from a nitrile, see Goering, H.L.; Tseng, C.C. *J. Org. Chem.* ***1981***, *46*, 5250.
[1657]Park, H.-g.; Jeong, B.-s.; Yoo, M.-s.; Park, M.-k.; Huh, H.; Jew, S.-s. *Tetrahedron Lett.* ***2001***, *42*, 4645; Jew, S.-s.; Jeong, B.-s.; Yoo, M.-s.; Huh, H.; Park, H.-g. *Chem. Commun.* ***2001***, 1244.
[1658]Pellissier, H.; Santelli, M. *Tetrahedron* ***2003***, *59*, 701.
[1659]Myers, A.G.; Schnider, P.; Kwon, S.; Kung, D.W. *J. Org. Chem.* ***1999***, *64*, 3322.

Hydrazones and other compounds with C=N bonds can be similarly alkylated.[1639] The use of chiral amines or hydrazines[1660] (followed by hydrolysis **16-2** of the alkylated imine) can lead to chiral alkylated ketones in high optical yields[1661] (for an example, see p. 170).



165

In α,β-unsaturated ketones, nitriles, and esters (e.g., **165**), the γ hydrogen assumes the acidity normally held by the position α to the carbonyl group, especially when R is not hydrogen and so cannot compete. This principle, called *vinylogy*, operates because the resonance effect is transmitted through the double bond. However, because of the resonance, alkylation at the α position (with allylic rearrangement) competes with alkylation at the γ position and usually predominates.



166

α-Hydroxynitriles (cyanohydrins), protected by conversion to acetals with ethyl vinyl ether (**15-5**), can be easily alkylated with primary or secondary alkyl or allylic halides.[1662] The R group can be aryl or a saturated or unsaturated alkyl. Since the cyanohydrins[1663] are easily formed from aldehydes (**16-52**) and the product is easily hydrolyzed to a ketone, this is a method for converting an aldehyde

[1660]For a review of the alkylation of chiral hydrazones, see Enders, D., in Morrison, J.D. *Asymmetric Synthesis*, Vol. 3, Academic Press, NY, ***1984***, pp. 275–339.

[1661]Meyers, A.I.; Williams, D.R.; Erickson, G.W.; White, S.; Druelinger, M. *J. Am. Chem. Soc.* ***1981***, *103*, 3081; Meyers, A.I.; Williams, D.R.; White, S.; Erickson, G.W. *J. Am. Chem. Soc.* ***1981***, *103*, 3088; Enders, D.; Bockstiegel, B. *Synthesis* ***1989***, 493; Enders, D.; Kipphardt, H.; Fey, P. *Org. Synth. 65*, 183.

[1662]Stork, G.; Maldonado, L. *J. Am. Chem. Soc.* ***1971***, *93*, 5286; Stork, G.; Depezay, J.C.; D'Angelo, J. *Tetrahedron Lett.* ***1975***, 389. See also, Rasmussen, J.K.; Heilmann, S.M. *Synthesis* ***1978***, 219; Ahlbrecht, H.; Raab, W.; Vonderheid, C. *Synthesis* ***1979***, 127; Hünig, S.; Marschner, C.; Peters, K.; von Schnering, H.G. *Chem. Ber.* ***1989***, *122*, 2131, and other papers in this series.

[1663]For a review of **166**, see Albright, J.D. *Tetrahedron* ***1983***, *39*, 3207.

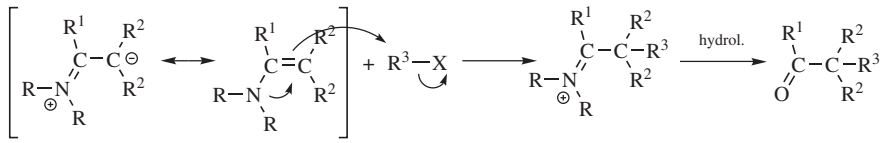
RCHO to a ketone RCOR′[1664] (for other methods, see **10-71**, **16-82**, and **18-9**).[1665] In this procedure the normal mode of reaction of a carbonyl carbon is reversed. The C atom of an aldehyde molecule is normally electrophilic and is attacked by nucleophiles (Chapter 16), but by conversion to the protected cyanohydrin this carbon atom has been induced to perform as a nucleophile.[1666] The German word *Umpolung*[1667] is used to describe this kind of reversal (another example is found in **10-71**). Since the ion **166** serves as a substitute for the unavailable $R-^{\ominus}C{=}O$ anion, it is often called a ''masked'' $R(^{\ominus}C{=}O)$ ion. This method fails for formaldehyde (R = H), but other masked formaldehydes have proved successful.[1668] In an interesting variation of nitrile alkylation, a quaternary bromide [PhC(Br)(Me)CN] reacted with allyl bromide, in the presence of a Grignard reagent, to give the alkylated product $[PhC(CN)(Me)CH_2CH{=}CH_2]$.[1669]

A coupling react of two ketones to form a 1,4-diketone has been reported, using $ZnCl_2/Et_2NH$.[1670]

OS **III**, 44, 219, 221, 223, 397; **IV**, 278, 597, 641, 962; **V**, 187, 514, 559, 848; **VI**, 51, 115, 121, 401, 818, 897, 958, 991; **VII**, 153, 208, 241, 424; **VIII**, 141, 173, 241, 403, 460, 479, 486; **X**, 59, 460; **80**, 31.

10-69 The Stork Enamine Reaction

α-Acylalkyl-de-halogenation[1671]



[1664]For similar methods, see Stetter, H.; Schmitz, P.H.; Schreckenberg, M. *Chem. Ber.* ***1977***, *110*, 1971; Hünig, S. *Chimia*, ***1982***, *36*, 1.

[1665]For a review of methods of synthesis of aldehydes, ketones and carboxylic acids by coupling reactions, see Martin, S.F. *Synthesis* ***1979***, 633.

[1666]For reviews of such reversals of carbonyl group reactivity, see Block, E. *Reactions of Organosulfur Compounds*, Academic Press, NY, ***1978***, pp. 56–67; Gröbel, B.; Seebach, D. *Synthesis* ***1977***, 357; Lever, Jr., O.W. *Tetrahedron* ***1976***, *32*, 1943; Seebach, D.; Kolb, M. *Chem. Ind. (London)* ***1974***, 687; Seebach, D. *Angew. Chem. Int. Ed.* ***1969***, *8*, 639. For a compilation of references to masked acyl and formyl anions, see Hase, T.A.; Koskimies, J.K. *Aldrichimica Acta* ***1981***, *14*, 73. For tables of masked reagents, see Hase, T.A. Umpoled Synthons, Wiley, NY, ***1987***, pp. xiii-xiv, 7–18, 219–317. For lists of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1435–1438.

[1667]For a monograph, see Hase, T.A. *Umpoled Synthons*, Wiley, NY, ***1987***. For a review, see Seebach, D. *Angew. Chem. Int. Ed.* ***1979***, *18*, 239.

[1668]Possel, O.; van Leusen, A.M. *Tetrahedron Lett.* ***1977***, 4229; Stork, G.; Ozorio, A.A.; Leong, A.Y.W. *Tetrahedron Lett.* ***1978***, 5175.

[1669]Fleming, F.F.; Zhang, Z.; Knochel, P. *Org. Lett.* ***2004***, *6*, 501.

[1670]Nevar, N.M.; Kel'in, A.V.; Kulinkovich, O.G. *Synthesis* ***2000***, 1259.

[1671]This is the IUPAC name with respect to the halide as substrate.

When enamines are treated with alkyl halides, an alkylation occurs to give an iminium salt via electron transfer from the electron pair on nitrogen, through the C=C to the electrophilic carbon of the alkyl halide.[1672] In effect, an enamine behaves as a ''nitrogen enolate'' and generally react as carbon nucleophiles.[1673] Hydrolysis of the iminium salt gives a ketone. Since the enamine is normally formed from a ketone (**16-13**), the net result is alkylation of the ketone at the α position. The method, known as the *Stork enamine reaction*,[1674] is an alternative to the ketone alkylation considered in **10-68**, generally giving monoalkylation of the ketone. Alkylation usually takes place on the less substituted side of the original ketone. The most commonly used amines are the cyclic amines piperidine, morpholine, and pyrrolidine.

The method is quite useful for particularly active alkyl halides, such as allylic, benzylic, and propargylic halides, and for α-halo ethers and esters. Other primary and secondary halides can show sluggish reactivity. The react of enamines with benzotriazole derivatives has been reported.[1675] Tertiary halides do not give the reaction at all since, with respect to the halide, this is nucleophilic substitution and elimination predominates. The reaction can also be applied to activated aryl halides (e.g., 2,4-dinitrochlorobenzene; see Chapter 13), to epoxides,[1676] and to activated alkenes, such as acrylonitrile. The latter is a Michael-type reaction (**15–24**) with respect to the alkene.

Acylation[1677] can be accomplished with acyl halides or with anhydrides. Hydrolysis of the resulting iminium salt leads to a 1,3-diketone. A COOEt group can be introduced by treatment of the enamine with ethyl chloroformate ClCOOEt,[1678] a CN group with cyanogen chloride[1679] (not cyanogen bromide or iodide, which leads to halogenation of the enamine), a CHO group with the mixed anhydride of formic and acetic acids[1678] or with DMF and phosgene,[1680] and a $C(R)=NR'$ group with a nitrilium salt $RC\equiv N^{+}R'$.[1681] The acylation of the enamine can take

[1672]See Adams, J.P. *J. Chem. Soc., Perkin Trans. 1* ***2000***, 125.

[1673]For a discussion of structure–nucleophilicity relationships, see Kempf, B.; Hampel, N.; Ofial, A.R.; Mayr, H. *Chem. Eur. J.* ***2003***, *9*, 2209.

[1674]Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc*., ***1963***, *85*, 207. For general reviews of enamines, see Hickmott, P.W. *Tetrahedron*, ***1984***, *40*, 2989; ***1982***, *38*, 1975, 3363; Granik, V.G. *Russ. Chem. Rev.*, ***1984***, *53*, 383. For reviews of this reaction, see, in Cook, A.G. *Enamines*, 2nd ed.; Marcel Dekker, NY, ***1988***, the articles by Alt, G.H.; Cook, A.G. pp. 181–246, and Gadamasetti, G.; Kuehne, M.E. pp. 531–689; Whitesell, J.K.; Whitesell, M.A. *Synthesis*, ***1983***, 517; Kuehne, M.E. *Synthesis*, ***1970***, 510; House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 570–582, 766–772; Bláha, K.; Červinka, O. *Adv. Heterocycl. Chem.*, ***1966***, *6*, 147, pp. 186.

[1675]Katritzky, A.R.; Fang, Y.; Silina, A. *J. Org. Chem.* ***1999***, *64*, 7622; Katritzky, A.R.; Huang, Z.; Fang, Y. *J. Org. Chem.* ***1999***, *64*, 7625.

[1676]Britten, A.Z.; Owen, W.S.; Went, C.W. *Tetrahedron* ***1969***, *25*, 3157.

[1677]For reviews, see Hickmott, P.W. *Chem. Ind. (London)* ***1974***, 731; Hünig, S.; Hoch, H. *Fortschr. Chem. Forsch.* ***1970***, *14*, 235.

[1678]Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc*. ***1963***, *85*, 207.

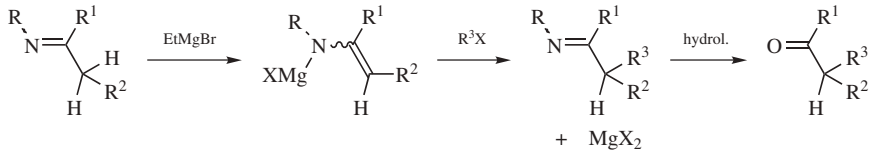
[1679]Kuehne, M.E. *J. Am. Chem. Soc*., ***1959***, *81*, 5400.

[1680]Ziegenbein, W. *Angew. Chem. Int. Ed. Engl.*, ***1965***, *4*, 358.

[1681]Baudoux, D.; Fuks, R. *Bull. Soc. Chim. Belg.*, ***1984***, *93*, 1009.

place by the same mechanism as alkylation, but another mechanism is also possible, if the acyl halide has an a hydrogen and if a tertiary amine is present, as it often is (it is added to neutralize the HX given off). In this mechanism, the acyl halide is dehydrohalogenated by the tertiary amine, producing a ketene (**17-14**), which adds to the enamine to give a cyclobutanone (**15-63**). This compound can be cleaved in the solution to form the same acylated imine salt (that would form by the more direct mechanism, or it can be isolated (in the case of enamines derived from aldehydes), or it may cleave in other ways.[1682]

N-Alkylation can be a problem, particularly with enamines derived from aldehydes. An alternative method, which gives good yields of alkylation with primary and secondary halides, is alkylation of enamine *salts*, which are prepared by treating an imine with ethylmagnesium bromide in THF:[1683]



The imines are prepared by the reaction of secondary amines with aldehydes or ketones, mainly ketones (**16-13**). The enamine salt method has also been used to give good yields of mono α alkylation of α,β-unsaturated ketones.[1684] Enamines prepared from aldehydes and butylisobutylamine can be alkylated by simple primary alkyl halides in good yields.[1685] *N*-Alkylation in this case is presumably prevented by steric hindrance.

When the nitrogen of the substrate contains a chiral R group, both the Stork enamine synthesis and the enamine salt method can be used to perform enantioselective syntheses.[1686] The use of *S*-proline can generate a chiral enamine *in situ*, thus allowing alkylation to occur, giving alkylated product with good enantioselectivity,. The reaction has been done intramolecularly.[1687]

Conjugate addition (Michael addition) occurs when enamines react with conjugated ketones. This reaction is discussed in Section **15-24**.

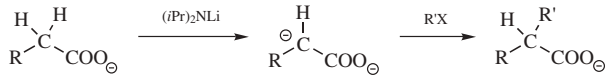
Although not formally the enamine synthesis, reaction of an enamine with methyl bromoacetate in the presence of indium metal leads to α-alkylation: $R_2N{-}CH{=}CHR \rightarrow R_2N{-}CH(R')CHR$.[1688]

OS **V**, 533, 869; **VI**, 242, 496, 526; **VII**, 473.

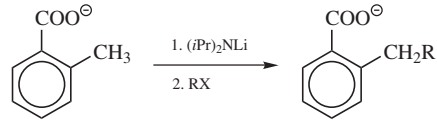
[1682]See Alt, G.H.; Cook, A.G., in Cook, A.G. *Enamines*, 2nd ed., Marcel Dekker, NY, ***1988***, pp. 204–215.
[1683]Stork, G.; Dowd, S.R. *J. Am. Chem. Soc*., ***1963***, *85*, 2178.
[1684]Stork, G.; Benaim, J. *J. Am. Chem. Soc*., ***1971***, *93*, 5938.
[1685]Curphey, T.J.; Hung, J.C.; Chu, C.C.C. *J. Org. Chem*., ***1975***, *40*, 607. See also, Ho, T.; Wong, C.M. *Synth. Commun.*, ***1974***, *4*, 147.
[1686]For reviews, see Nógrádi, M. *Stereoselective Synthesis*, VCH, NY, ***1986***, pp. 248–255; Whitesell, J.K. *Acc. Chem. Res.*, ***1985***, *18*, 280; Bergbreiter, D.E.; Newcomb, M., in Morrison, J.D. *Asymmetric Synthesis*, Vol. 2, Academic Press, NY, ***1983***, pp. 243–273.
[1687]Vignola, N.; List, B. *J. Am. Chem. Soc*. ***2004***, *126*, 450.
[1688]Bossard, F.; Dambrin, V.; Lintanf, V.; Beuchet, P.; Mosset, P. *Tetrahedron Lett.*, ***1995***, *36*, 6055.

10-70 Alkylation of Carboxylic Acid Salts

α-Carboxyalkyl-de-halogenation



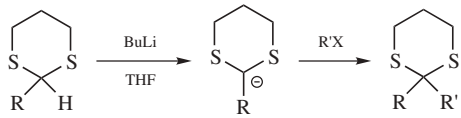
Carboxylic acids can be alkylated in the a position by conversion of their salts to dianions [which have resonance contributors $RCH{=}C(O^-)_2$[1689]] by treatment with a strong base, such as LDA.[1690] The use of Li^+ as the counterion increases the solubility of the dianionic salt. The reaction has been applied[1691] to primary alkyl, allylic, and benzylic halides, and to carboxylic acids of the form RCH_2COOH and $RR^2CHCOOH$.[1610] Allkylation occurs at carbon, the more nucleophilic site relative to the carboxylate oxygen anion (see p. 513). this procedure is an alternative to the malonic ester synthesis (**10-67**) as a means of preparing carboxylic acids and has the advantage that acids of the form $RR'R^2CCOOH$ can also be prepared. In a related reaction, methylated aromatic acids can be alkylated at the methyl group by a similar procedure.[1692]



OS **V**, 526; **VI**, 517; **VII**, 249. See also, OS **VII**, 164.

10-71 Alkylation at a Position α to a Heteroatom.

2-(2-Alkyl-thio)de-halogenation

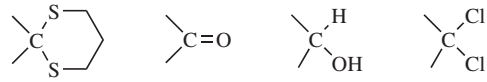


The presence of a sulfur atom on a carbon enhances the acidity of a proton on that carbon, and in dithioacetals and dithioketals that proton ($RSCH_2SR$) is even more acidic. 1,3-Dithianes can be alkylated[1693] if a proton is first removed by

[1689]Mladenova, M.; Blagoev, B.; Gaudemar, M.; Dardoize, F.; Lallemand, J.Y. *Tetrahedron* ***1981***, *37*, 2153.
[1690]Cregar, P.L. *J. Am. Chem. Soc.* ***1967***, *89*, 2500; ***1970***, *92*, 1397; Pfeffer, P.E.; Silbert, L.S.; Chirinko, Jr., J.M. *J. Org. Chem.* ***1972***, *37*, 451.
[1691]For lists of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1717–1720*ff*.
[1692]Cregar, P.L. *J. Am. Chem. Soc.* ***1970***, *92*, 1396.
[1693]Seebach, D.; Corey, E.J. *J. Org. Chem.* ***1975***, *40*, 231. For reviews, see Page, P.C.B.; van Niel, M.B.; Prodger, J.C. *Tetrahedron* ***1989***, *45*, 7643; Ager, D.J., in Hase, T.A. *Umpoled Synthons*, Wiley, NY, ***1987***, pp. 19–37; Seebach, D. *Synthesis* ***1969***, 17, especially pp. 24–27; Olsen, R.K.; Curriev, Jr., Y.O., in Patai, S. *The Chemistry of the Thiol Group*, pt. 2, Wiley, NY, ***1974***, pp. 536–547.

treatment with butyllithium in THF.[1694] Since 1,3-dithianes can be prepared by treatment of an aldehyde or its acetal (see OS **VI**, 556) with 1,3-propanedithiol (**16-11**) and can be hydrolyzed (**10-7**), this is a method for the conversion of an aldehyde to a ketone[1695] (see also, **10-68** and **18-9**):

This is another example of Umpolung (see **10-68**);[1664] the normally electrophilic carbon of the aldehyde is made to behave as a nucleophile. The reaction can be applied to the unsubstituted dithiane (R = H) and one or two alkyl groups can be introduced, so a wide variety of aldehydes and ketones can be made starting with formaldehyde.[1696] The R′ group may be primary or secondary alkyl or benzylic. Iodides give the best results. The reaction has been used to close rings.[1697] A similar synthesis of aldehydes can be performed starting with ethyl ethylthiomethyl sulfoxide ($EtSOCH_2SEt$).[1698]



A **B** **C** **D**

The group **A** may be regarded as a structural equivalent for the carbonyl group **B**, since introduction of **A** into a molecule is actually an indirect means of introducing **B**. It is convenient to have a word for units within molecules; such a word is *synthon*, introduced by Corey,[1699] which is defined as a structural unit within a molecule that can be formed and/or assembled by known or conceivable synthetic operations. There are many other synthons equivalent to **A** and **B**, for example, **C** (by reactions **19-36** and **19-3**) and **D** (by reactions **10-2** and **16-23**).[1700]

Carbanions generated from 1,3-dithianes also react with epoxides[1701] to give the expected products.

[1694]For an improved method of removing the proton, see Lipshutz, B.H.; Garcia, E. *Tetrahedron Lett.* ***1990***, *31*, 7261.

[1695]For examples of the use of this reaction, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1451–1454.

[1696]For a direct conversion of RX to RCHO, see **10-76**.

[1697]For example, see Seebach, D.; Jones, N.R.; Corey, E.J. *J. Org. Chem.* ***1968***, *33*, 300; Hylton, T.; Boekelheide, V. *J. Am. Chem. Soc.* ***1968***, *90*, 6887; Ogura, K.; Yamashita, M.; Suzuki, M.; Tsuchihashi, G. *Tetrahedron Lett.* ***1974***, 3653.

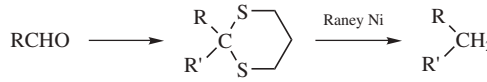
[1698]Richman, J.E.; Herrmann, J.L.; Schlessinger, R.H. *Tetrahedron Lett.* ***1973***, 3267. See also, Ogura, K.; Tsuchihashi, G. *Tetrahedron Lett.* ***1971***, 3151; Schill, G.; Jones, P.R. *Synthesis* ***1974***, 117; Hori, I.; Hayashi, T.; Midorikawa, H. *Synthesis* ***1974***, 705.

[1699]Corey, E.J. *Pure Appl. Chem.* ***1967***, *14*, 19, pp. 20–23.

[1700]For a long list of synthons for RCO, with references, see Hase, T.A.; Koskimies, J.K. *Aldrichimica Acta* ***1982***, *15*, 35.

[1701]For example, see Corey, E.J.; Seebach, D. *J. Org. Chem.* ***1975***, *40*, 231; Jones, J.B.; Grayshan, R. *Chem. Commun.* ***1970***, 141, 741.

Another useful application of this reaction stems from the fact that dithianes can be desulfurated with Raney nickel (**14-27**). Aldehydes can therefore be converted to chain-extended hydrocarbons:[1702]



Similar reactions have been carried out with other thioacetals, as well as with compounds containing three thioether groups on a carbon.[1703]

If a stabilizing group other than sulfur is attached to the S-CH_2 unit of a thioether ($RSCH_2X$, where X is a stabilizing group), formation of the anion and alkylation can be facile. For example, benzylic and allylic thioethers ($RSCH_2Ar$ and $RSCH_2CH{=}CH_2$)[1704] and thioethers of the form $RSCH_3$ (R = tetrahydrofuranyl or 2-tetrahydropyranyl)[1705] have been successfully alkylated at the carbon adjacent to the sulfur atom.[1706] Stabilization by one thioether group has also been used in a method for the homologation of primary halides.[1707] Thioanisole is treated with BuLi to give the corresponding anion,[1708] which reacts with the halide to give the thioether, which is then refluxed with a mixture of methyl iodide and sodium iodide in DMF to give the alkyl iodide as the final product (via an intermediate sulfonium salt). By this sequence an alkyl halide RX is converted to its homolog RCH_2X by a pathway involving two laboratory steps (see also, **10-64**).

Vinylic sulfides containing an a hydrogen can also be alkylated[1709] by alkyl halides or epoxides. This is a method for converting an alkyl halide RX to an α,β-unsaturated aldehyde, which is the synthetic equivalent of the unknown $H^{\ominus}C{=}CH{-}CHO$ ion.[1710] Even simple alkyl aryl sulfides (RCH_2SAr and $RR'CHSAr$) have been alkylated to the sulfur.[1711]

[1702]For examples, see Hylton, T.; Boekelheide, V. *J. Am. Chem. Soc.* ***1968***, *90*, 6887; Jones, J.B.; Grayshan, R.*Chem. Commun.* ***1970***, 141, 741.

[1703]For example, see Seebach, D. *Angew. Chem. Int. Ed.* ***1967***, *6*, 442; Olsson, K. *Acta Chem. Scand.* ***1968***, *22*, 2390; Mori, K.; Hashimoto, H.; Takenaka, Y.; Takigawa, T. *Synthesis* ***1975***, 720; Lissel, M. *Liebigs Ann. Chem.* ***1982***, 1589.

[1704]Uemoto, K.; Kawahito, A.; Matsushita, N.; Skamoto, I.; Kaku, H.; Tsunoda, T. *Tetrahedron Lett.* ***2001***, *42*, 905.

[1705]Block, E.; Aslam, M. *J. Am. Chem. Soc.* ***1985***, *107*, 6729.

[1706]Biellmann, J.F.; Ducep, J.B. *Tetrahedron Lett.* ***1968***, 5629; ***1969***, 3707; *Tetrahedron* ***1971***, *27*, 5861. See also, Narasaka, K.; Hayashi, M.; Mukaiyama, T. *Chem. Lett.* ***1972***, 259.

[1707]Corey, E.J.; Jautelat, M. *Tetrahedron Lett.* ***1968***, 5787.

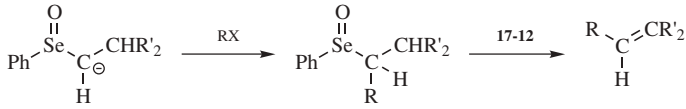
[1708]Corey, E.J.; Seebach, D. *J. Org. Chem.* ***1966***, *31*, 4097.

[1709]Oshima, K.; Shimoji, K.; Takahashi, H.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* ***1973***, *95*, 2694.

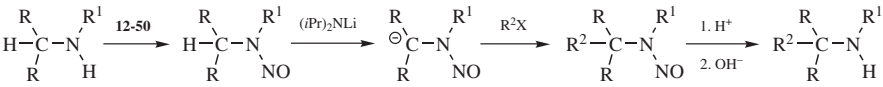
[1710]For references to other synthetic equivalents of this ion, see Funk, R.L.; Bolton, G.L. *J. Am. Chem. Soc.* ***1988***, *110*, 1290.

[1711]Dolak, T.M.; Bryson, T.A. *Tetrahedron Lett.* ***1977***, 1961.

Sulfones[1712] and sulfonic esters can also be alkylated in the a position if strong enough bases are used.[1713] Alkylation at the α position of selenoxides allows the formation of alkenes, since selenoxides easily undergo elimination (**17-12**).[1714]



Alkylation can also be carried out, in certain compounds, at positions α to other heteroatoms,[1715] for example, at a position α to the nitrogen of tertiary amines.[1716] Alkylation α to the nitrogen of primary or secondary amines is not generally feasible because an NH hydrogen is usually more acidic than a CH



hydrogen. α-Lithiation of *N*-Boc amines has been accomplished and these react with halides in the presence of a palladium catalyst.[1717] Alkylation α to the nitrogen atom of a carbamate occurs when the carbamate is treated with a Grignard reagent under electrolysis conditions.[1718] α-Methoxy amides also react with allyl halides and zinc metal to give alkylation via replacement of the OMe unit.[1719] It has been accomplished, however, by replacing the NH hydrogens with other (removable) groups.[1720] In one example, a secondary amine is converted to its *N*-nitroso derivative (**12-50**).[1721] The *N*-nitroso product is easily hydrolyzed to the product

[1712]For a review, see Magnus, P.D. *Tetrahedron* ***1977***, *33*, 2019, 2022–2025. For alkylation of sulfones containing the F_3CSO_2 group, see Hendrickson, J.B.; Sternbach, D.D.; Bair, K.W. *Acc. Chem. Res.* ***1977***, *10*, 306.

[1713]For examples, see Truce, W.E.; Hollister, K.R.; Lindy, L.B.; Parr, J.E. *J. Org. Chem.* ***1968***, *33*, 43; Julia, M.; Arnould, D. *Bull. Soc. Chim. Fr.* ***1973***, 743, 746; Bird, R.; Stirling, C.J.M. *J. Chem. Soc. B* ***1968***, 111.

[1714]Reich, H.J.; Shah, S.K. *J. Am. Chem. Soc.* ***1975***, *97*, 3250.

[1715]For a review of anions α to a selenium atom on small rings, see Krief, A. *Top. Curr. Chem.* ***1987***, *135*, 1. For alkylation α to boron see Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, ***1988***, pp. 336–341.

[1716]Lepley, A.R.; Khan, W.A. *J. Org. Chem.* ***1966***, *31*, 2061, 2064; *Chem. Commun.* ***1967***, 1198; Lepley, A.R.; Giumanini, A.G. *J. Org. Chem.* ***1966***, *31*, 2055; Ahlbrecht, H.; Dollinger, H. *Tetrahedron Lett.* ***1984***, *25*, 1353.

[1717]Dieter, R.K.; Li, S. *Tetrahedron Lett.* ***1995***, *36*, 3613.

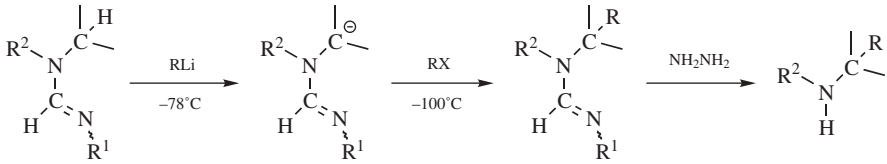
[1718]Suga, S.; Okajima, M.; Yoshida, J.-i. *Tetrahedron Lett.* ***2001***, *42*, 2173.

[1719]Kise, N.; Yamazaki, H.; Mabuchi, T.; Shono, T. *Tetrahedron Lett.* ***1994***, *35*, 1561.

[1720]For a review, see Beak, P.; Zajdel, W.J.; Reitz, D.B. *Chem. Rev.* ***1984***, *84*, 471.

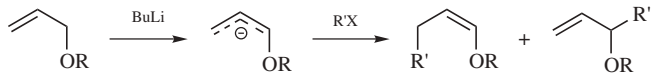
[1721]Seebach, D.; Enders, D.; Renger, B. *Chem. Ber.* ***1977***, *110*, 1852; Renger, B.; Kalinowski, H.; Seebach, D. *Chem. Ber.* ***1977***, *110*, 1866. For a review, see Seebach, D.; Enders, D. *Angew. Chem. Int. Ed.* ***1975***, *14*, 15.

amine (**19-51**).[1722] Alkylation of secondary and primary amines has also been accomplished with >10 other protecting groups, involving conversion of amines to amides, carbamates,[1723] formamidines,[1724] and phosphoramides.[1719] In the case of formamidines (**167**), use of a chiral R′ leads to a chiral amine, in high ee, even when R is not chiral.[1725]



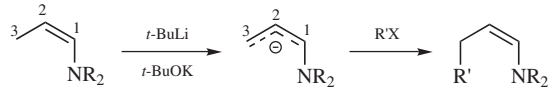
167

A proton can be removed from an allylic ether by treatment with an alkyllithium at about −70°C (at higher temperatures the Wittig rearrangement, **18-22**, takes place) to give the ion **168**, which reacts with alkyl halides to give the two products



168

shown.[1726] Similar reactions[1727] have been reported for allylic[1728] and vinylic tertiary amines. In the latter case, enamines **169**, treated with a strong base, are converted to anions that are then alkylated, generally at C-3.[1729] (For direct alkylation of enamines at C-2, see **10-69**.)



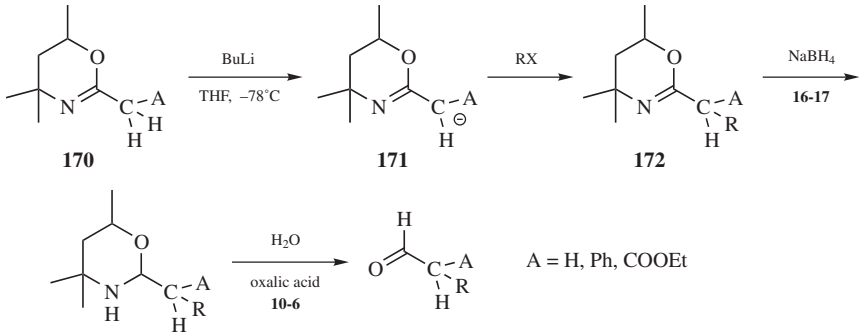
169

[1722]Fridman, A.L.; Mukhametshin, F.M.; Novikov, S.S. *Russ. Chem. Rev.* ***1971***, *40*, 34, pp. 41–42.
[1723]For the use of *tert*-butyl carbamates, see Beak, P.; Lee, W. *Tetrahedron Lett.* ***1989***, *30*, 1197.
[1724]For a review, see Meyers, A.I. *Aldrichimica Acta* ***1985***, *18*, 59.
[1725]Gawley, R.E.; Hart, G.; Goicoechea-Pappas, M.; Smith, A.L. *J. Org. Chem.* ***1986***, *51*, 3076; Gawley, R.E. *J. Am. Chem. Soc.* ***1987***, *109*, 1265; Meyers, A.I.; Miller, D.B.; White, F. *J. Am. Chem. Soc.* ***1988***, *110*, 4778; Gonzalez, M.A.; Meyers, A.I. *Tetrahedron Lett.* ***1989***, *30*, 43, 47, and references cited therein.
[1726]Evans, D.A.; Andrews, G.C.; Buckwalter, B. *J. Am. Chem. Soc.* ***1974***, *96*, 5560; Still, W.C.; Macdonald, T.L. *J. Am. Chem. Soc.* ***1974***, *96*, 5561; Funk, R.L.; Bolton, G.L. *J. Am. Chem. Soc.* ***1988***, *110*, 1290. For a similar reaction with triple-bond compounds, see Hommes, H.; Verkruijsse, H.D.; Brandsma, L. *Recl. Trav. Chim. Pays-Bas* ***1980***, *99*, 113, and references cited therein.
[1727]For a review of allylic and benzylic carbanions substituted by heteroatoms, see Biellmann, J.F.; Ducep, J. *Org. React.* ***1982***, *27*, 1.
[1728]Martin, S.F.; DuPriest, M.T. *Tetrahedron Lett.* ***1977***, 3925, and references cited therein.
[1729]For a review, see Ahlbrecht, H. *Chimia* ***1977***, *31*, 391.

It is also possible to alkylate a methyl, ethyl, or other primary group of an aryl ester ArCOOR, where Ar is a 2,4,6-trialkylphenyl group.[1730] Since esters can be hydrolyzed to alcohols, this constitutes an indirect alkylation of primary alcohols. Methanol has also been alkylated by converting it to $^{\ominus}CH_2O^{\ominus}$.[1731]

OS **VI**, 316, 364, 542, 704, 869; **VIII**, 573.

10-72 Alkylation of Dihydro-1,3-Oxazine: The Meyers Synthesis of Aldehydes, Ketones, and Carboxylic Acids



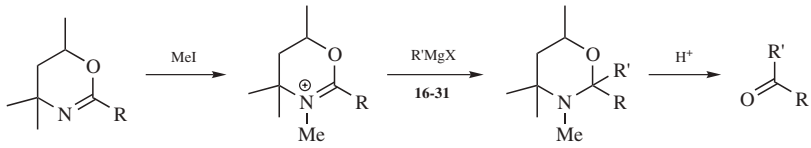
A synthesis of aldehydes[1732] developed by Meyers[1733] begins with the commercially available dihydro-1,3-oxazine derivatives **170** (A = H, Ph, or COOEt).[1734] Removal of a proton from the indicated carbon in **170** leads to the resonance stabilized and bidentate anion **172**. Alkylation occurs regioselectively at carbon by a many alkyl bromides and iodides. The R group of RX can be primary or secondary alkyl, allylic, or benzylic and can carry another halogen or a CN group.[1735] The alkylated oxazine **173** is then reduced and hydrolyzed to give an aldehyde containing two more carbons than the starting RX. This method thus complements **10-71**, which converts RX to an aldehyde containing one more carbon. Since A can be H, mono- or disubstituted acetaldehydes can be produced by this method.

The ion **171** also reacts with epoxides, to form γ-hydroxy aldehydes after reduction and hydrolysis,[1736] and with aldehydes and ketones (**16-38**). Similar aldehyde

[1730]Beak, P.; Carter. L.G. *J. Org. Chem.* ***1981***, *46*, 2363.
[1731]Seebach, D.; Meyer, N. *Angew. Chem. Int. Ed.* ***1976***, *15*, 438.
[1732]For examples of the preparation of aldehydes and ketones by the reactions in this section, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1461–1465.
[1733]Meyers, A.I.; Nabeya, A.; Adickes, H.W.; Politzer, I.R.; Malone, G.R.; Kovelesky, A.C.; Nolen, R.L.; Portnoy, R.C. *J. Org. Chem.* ***1973***, *38*, 36.
[1734]For reviews of the preparation and reactions of **169**, see Schmidt, R.R. *Synthesis* ***1972***, 333; Collington, E.W. *Chem. Ind. (London)* ***1973***, 987.
[1735]Meyers, A.I.; Malone, G.R.; Adickes, H.W. *Tetrahedron Lett.* ***1970***, 3715.
[1736]Adickes, H.W.; Politzer, I.R.; Meyers, A.I. *J. Am. Chem. Soc.* ***1969***, *91*, 2155.

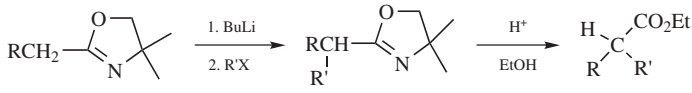
synthesis has also been carried out with thiazoles[1737] and thiazolines[1738] (five-membered rings containing N and S in the 1 and 3 positions).

The reaction has been extended to the preparation of ketones:[1739] Treatment of a dihydro-1,3-oxazine (**172**) with iodomethane forms the iminium salt **173** (**10-31**) which, when treated with a Grignard reagent or organolithium compound (**16-31**)



173 **174**

produces **174**, which can be hydrolyzed to a ketone. The R group can be alkyl, cycloalkyl, aryl, benzylic, and so on, and R′ of the Grignard reagent can be alkyl, aryl, benzylic, or allylic. Note that the hetereocycles **170**, **172**, or **173** do not react directly with Grignard reagents. In another procedure, 2-oxazolines (**175**)[1740] can be alkylated to give **176**,[1741] which are easily converted directly to the esters **177** by heating in 5–7% ethanolic sulfuric acid.



175 **176** **177**

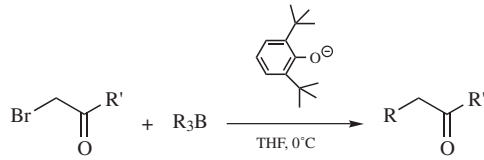
2-Oxazolines **175** and **176** are thus synthons for carboxylic acids; this is another indirect method for the α alkylation of a carboxylic acid,[1742] representing an alternative to the malonic ester synthesis (**10-67**) and to **10-70** and **10-73**. The method can be adapted to the preparation of optically active carboxylic acids by the use of a chiral reagent.[1743] Note that, unlike **170**, **175** can be alkylated even if R is alkyl. However, the C=N bond of **175** and **176** cannot be effectively reduced, so that aldehyde synthesis is not feasible here.[1744]

OS **VI**, 905.

[1737]Altman, L.J.; Richheimer, S.L. *Tetrahedron Lett.* ***1971***, 4709.
[1738]Meyers, A.I.; Durandetta, J.L. *J. Org. Chem.* ***1975***, *40*, 2021.
[1739]Meyers, A.I.; Smith, E.M. *J. Am. Chem. Soc.* ***1970***, *92*, 1084; *J. Org. Chem.* ***1972***, *37*, 4289.
[1740]For a review, see Meyers, A.I.; Mihelich, E.D. *Angew. Chem. Int. Ed.* ***1976***, *15*, 270.
[1741]Meyers, A.I.; Temple, Jr., D.L.; Nolen, R.L.; Mihelich, E.D. *J. Org. Chem.* ***1974***, *39*, 2778; Meyers, A.I.; Mihelich, E.D.; Nolen, R.L. *J. Org. Chem.* ***1974***, *39*, 2783; Meyers, A.I.; Mihelich, E.D.; Kamata, K. *J. Chem. Soc., Chem. Commun.* ***1974***, 768.
[1742]For reviews, see Meyers, A.I. *Pure Appl. Chem.* ***1979***, *51*, 1255; *Acc. Chem. Res.* ***1978***, *11*, 375. See also, Hoobler, M.A.; Bergbreiter, D.E.; Newcomb, M. *J. Am. Chem. Soc.* ***1978***, *100*, 8182; Meyers, A.I.; Snyder, E.S.; Ackerman, J.J.H. *J. Am. Chem. Soc.* ***1978***, *100*, 8186.
[1743]For a review of asymmetric synthesis via chiral oxazolines, see Lutomski, K.A.; Meyers, A.I., in Morrison, J.D. *Asymmetric Synthesis*, Vol. 3, Academic Press, NY, ***1984***, pp. 213–274.
[1744]Meyers, A.I.; Temple Jr., D.L. *J. Am. Chem. Soc.* ***1970***, *92*, 6644, 6646.

10-73 Alkylation with Trialkylboranes

Alkyl-de-halogenation



Trialkylboranes react rapidly and in high yields with α-halo ketones,[1745] α-halo esters,[1746] α-halo nitriles,[1747] and α-halo sulfonyl derivatives (sulfones, sulfonic esters, sulfonamides)[1748] in the presence of a base to give, respectively, alkylated ketones, esters, nitriles, and sulfonyl derivatives.[1749] Potassium *tert*-butoxide is often a suitable base, but potassium 2,6-di-*tert*-butylphenoxide at 0°C in THF gives better results in most cases, possibly because the large bulk of the two *tert*-butyl groups prevents the base from coordinating with the R_3B.[1750] The trialkylboranes are prepared by treatment of 3 equivalents of an alkene with 1 equivalent of BH_3 (**15-16**).[1751] With appropriate boranes, the R group transferred to α-halo ketones, nitriles, and esters can be vinylic,[1752] or (for α-halo ketones and esters) aryl.[1753]

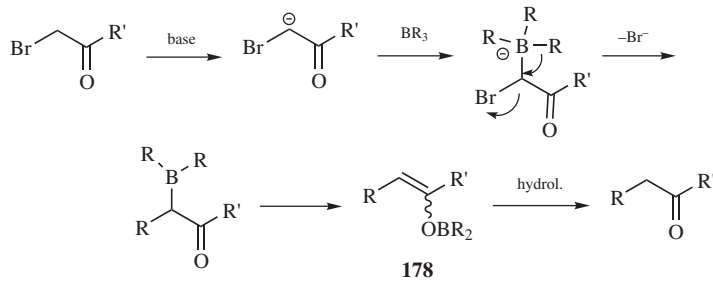
The reaction can be extended to α,α-dihalo esters[1754] and α,α-dihalo nitriles.[1755] It is possible to replace just one halogen or both. In the latter case the two alkyl groups can be the same or different. When dialkylation is applied to dihalo nitriles, the two alkyl groups can be primary or secondary, but with dihalo esters, dialkylation is limited to primary R. Another extension is the reaction of boranes (BR_3) with γ-halo-α,β-unsaturated esters.[1756] Alkylation takes place in the γ position, but the double bond migrates out of conjugation with the COOEt unit [$BrCH_2CH{=}CHCOOEt \rightarrow RCH{=}CHCH_2COOEt$]. In this case, however, double-bond

[1745]Brown, H.C.; Rogić, M.M.; Rathke, M.W. *J. Am. Chem. Soc.* ***1968***, *90*, 6218.
[1746]Brown, H.C.; Rogić, M.M.; Rathke, M.W.; Kabalka, G.W. *J. Am. Chem. Soc.* ***1968***, *90*, 818.
[1747]Brown, H.C.; Nambu, H.; Rogić, M.M. *J. Am. Chem. Soc.* ***1969***, *91*, 6854.
[1748]Truce, W.E.; Mura, L.A.; Smith, P.J.; Young, F. *J. Org. Chem.* ***1974***, *39*, 1449.
[1749]For reviews, see Negishi, E.; Idacavage, M.J. *Org. React.* ***1985***, *33*, 1, 42–43, 143–150; Weill-Raynal, J. *Synthesis* ***1976***, 633; Brown, H.C.; Rogić, M.M. *Organomet. Chem. Synth.* ***1972***, *1*, 305; Rogić, M.M. *Intra-Sci. Chem. Rep.* ***1973***, *7(2)*, 155; Brown, H.C. *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, NY, ***1972***, pp. 372–391, 404–409; Cragg, G.M.L. *Organoboranes in Organic Synthesis*, Marcel Dekker, NY, ***1973***, pp. 275–278, 283–287.
[1750]Brown, H.C.; Nambu, H.; Rogić, M.M. *J. Am. Chem. Soc.* ***1969***, *91*, 6852, 6854, 6855.
[1751]For an improved procedure, with B-9-BBN (see p. $$$), see Brown, H.C.; Rogić, M.M. *J. Am. Chem. Soc.* ***1969***, *91*, 2146; Brown, H.C.; Rogić, M.M.; Nambu, H.; Rathke, M.W. *J. Am. Chem. Soc.* ***1969***, *91*, 2147; Katz, J.; Dubois, J.E.; Lion, C. *Bull. Soc. Chim. Fr.* ***1977***, 683.
[1752]Brown, H.C.; Bhat, N.G.; Campbell, Jr., J.B. *J. Org. Chem.* ***1986***, *51*, 3398.
[1753]Brown, H.C.; Rogić, M.M. *J. Am. Chem. Soc.* ***1969***, *91*, 4304.
[1754]Brown, H.C.; Rogić, M.M.; Rathke, M.W.; Kabalka, G.W. *J. Am. Chem. Soc.* ***1968***, *90*, 1911.
[1755]Nambu, H.; Brown, H.C. *J. Am. Chem. Soc.* ***1970***, *92*, 5790.
[1756]Brown, H.C.; Nambu, H. *J. Am. Chem. Soc.* ***1970***, *92*, 1761.

migration is an advantage, because nonconjugated β,γ-unsaturated esters are usually much more difficult to prepare than their α,β-unsaturated isomers.

The alkylation of activated halogen compounds is one of several reactions of trialkylboranes developed by H.C. Brown[1757] (see also, **15-16**, **15-27**, **18-31-18-40**, and so on). These compounds are extremely versatile and can be used for the preparation of many types of compounds. In this reaction, for example, an alkene (through the BR_3 prepared from it) can be coupled to a ketone, a nitrile, a carboxylic ester, or a sulfonyl derivative. Note that this is still another indirect way to alkylate a ketone (see **10-68**) or a carboxylic acid (see **10-70**), and provides an additional alternative to the malonic ester and acetoacetic ester syntheses (**10-67**).

Although superficially this reaction resembles **10-57** it is likely that the mechanism is quite different, involving migration of an R group from boron to carbon (see also, **18-23**–**18-26**). The mechanism is not known with certainty,[1758] but it may be tentatively shown as (illustrated for an α-halo ketone):



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The first step is removal of the acidic proton by the base to give an enolate anion that combines with the borane (Lewis acid–base reaction). An R group then migrates, displacing the halogen leaving group.[1759] Another migration follows, this time of BR_2 from carbon to oxygen to give the enol borinate **178**,[1760] which is hydrolyzed. Configuration at R is retained.[1761]

[1757]Brown, H.C. *Organic Syntheses via Boranes*, Wiley, NY, ***1975***; *Hydroboration*, W.A. Benjamin, NY, ***1962***; *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, NY, ***1972***; Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, ***1988***.

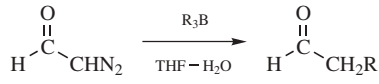
[1758]See Prager, R.H.; Reece, P.A. *Aust. J. Chem.* ***1975***, *28*, 1775.

[1759]It has been shown that this migration occurs stereospecifically with inversion in the absence of a solvent, but nonstereospecifically in the presence of a solvent, such as THF or dimethyl sulfide: Midland, M.M.; Zolopa, A.R.; Halterman, R.I. *J. Am. Chem. Soc.* ***1979***, *101*, 248. See also, Midland, M.M.; Preston, S.B. *J. Org. Chem.* ***1980***, *45*, 747.

[1760]Pasto, D.J.; Wojtkowski, P.W. *Tetrahedron Lett.* ***1970***, 215, Pasto, D.J.; Wojtkowski, P.W. *J. Org. Chem.* ***1971***, *36*, 1790.

[1761]Brown, H.C.; Rogić, M.M.; Rathke, M.W.; Kabalka, G.W. *J. Am. Chem. Soc.* ***1969***, *91*, 2150.

The reaction has also been applied to compounds with other leaving groups. Diazo ketones, diazo esters, diazo nitriles, and diazo aldehydes (**179**)[1762] react with trialkylboranes in a similar manner.



179

The mechanism is probably also similar. In this case a base is not needed, since the carbon already has an available pair of electrons. The reaction with diazo aldehydes[1763] is especially notable, since successful reactions cannot be obtained with α-halo aldehydes.[1764]

OS **VI**, 919; **IX**, 107.

10-74 Alkylation at an Alkynyl Carbon

Alkynyl-de-halogenation

$$RX + R'C{\equiv}C^- \longrightarrow RC{\equiv}CR'$$

The reaction between alkyl halides and acetylide ions is useful but of limited scope.[1765] Only primary halides unbranched in the β-position give good yields, although allylic halides can be used if CuI is present.[1766] If acetylene is the reagent, two different groups can be successively attached. Sulfates, sulfonates, and epoxides[1767] are sometimes used as substrates. The acetylide ion is often prepared by treatment of an alkyne with a strong base such as $NaNH_2$. Magnesium acetylides (ethynyl Grignard reagents; prepared as in **12-22**) are also frequently used, although they react only with active substrates, such as allylic, benzylic, and propargylic halides, and not with primary alkyl halides. Alternatively, the alkyl halide can be treated with a lithium acetylide–ethylenediamine complex.[1768] If 2 equivalents of a very

[1762]Hooz, J.; Gunn, D.M.; Kono, H. *Can. J. Chem.* ***1971***, *49*, 2371; Mikhailov, B.M.; Gurskii, M.E. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1973***, *22*, 2588.

[1763]Hooz, J.; Morrison, G.F. *Can J. Chem.* ***1970***, *48*, 868.

[1764]For an improved procedure, see Hooz, J.; Bridson, J.N.; Calzada, J.G.; Brown, H.C.; Midland, M.M.; Levy, A.B. *J. Org. Chem.* ***1973***, *38*, 2574.

[1765]For reviews, see Ben-Efraim, D.A., in Patai, S. *The Chemistry of the Carbon–Carbon Triple Bond*, Wiley, NY, ***1978***, pp. 790–800; Ziegenbein, W., in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 185–206, 241–244. For a discussion of the best ways of preparing various types of alkyne, see Bernadou, F.; Mesnard, D.; Miginiac, L. *J. Chem. Res. (S)* ***1978***, 106; ***1979***, 190.

[1766]Bourgain, M.; Normant, J.F. *Bull. Soc. Chim. Fr.* ***1973***, 1777; Jeffery, T. *Tetrahedron Lett.* ***1989***, *30*, 2225.

[1767]For example, see Fried, J.; Lin, C.; Ford, S.H. *Tetrahedron Lett.* ***1969***, 1379; Krause, N.; Seebach, D. *Chem. Ber.* ***1988***, *121*, 1315.

[1768]Smith, W.N.; Beumel Jr., O.F. *Synthesis* ***1974***, 441.

strong base are used, alkylation can be effected at a carbon α to a terminal triple bond: $RCH_2C{\equiv}CH + 2BuLi \rightarrow RCHC{\equiv}C^- + R'Br \rightarrow RR'CHC{\equiv}C^-$.[1769] For another method of alkylating at an alkynyl carbon, see **18-26**. An alternative method for generating an alkyne anion treated a trialkylsilyl alkyne with potassium carbonate in methanol, and then methyllithium/LiBr.[1770] In the presence of an alkyl iodide, alkylation at the alkynyl carbon occurred.

Alkynes couple with alkyl halides in the presence of SmI_2/Sm.[1771] Alkynes react with hypervalent iodine compounds[1772] and with reactive alkanes such as adamantane in the presence of AIBN.[1773] The reaction of benzylic amines with terminal alkynes, in the presence of copper triflate and *tert*-butylhydroperoxide leads to incorporation of the alkyne group α to the nitrogen.[1774] A similar reaction occurs at a methyl group of *N,N*-dimethylaniline.[1775] α-Methoxycarbamates ($MeO{-}CHR{-}NR^1{-}CO_2R^2$) react with terminal alkynes and CuBr to give the alkynylamine.[1776] In the presence of $GaCl_3$, $ClC{\equiv}CSiMe_3$ reacts with silyl enol ethers to give, after treatment with methanolic acid, an α-ethynyl ketone.[1777]

1-Haloalkynes ($R{-}C{\equiv}C{-}X$) react with $ArSnBu_3$ and CuI to give $R{-}C{\equiv}C{-}Ar$.[1778] Organozirconium compounds react in a similar manner.[1779] Acetylene reacts with 2 equivalents of iodobenzene, in the presence of a palladium catalyst and CuI, to give 1,2-diphenylethyne.[1780] 1-Trialkylsilyl alkynes react with 1-haloalkynes, in the presence of a CuCl catalyst, to give diynes[1781] and with aryl triflates to give 1-aryl alkynes.[1782]

In a related reaction, terminal alkynes react with silanes (R_3SiH) in the presence of an iridium catalyst to give the 1-trialkylsilyl alkyne.[1783] similar products are obtained when terminal alkynes react with *N*-trialkylsilylamines and $ZnCl_2$.[1784]

[1769]Bhanu, S.; Scheinmann, F. *J. Chem. Soc. Perkin Trans.1*, ***1979***, 1218; Quillinan, A.J.; Scheinmann, F. *Org. Synth.* ***VI***, 595.
[1770]Fiandanese, V.; Bottalico, D.; Marchese, G.; Punzi, A. *Tetrahedron Lett.* ***2003***, *44*, 9087.
[1771]Murakami, M.; Hayashi, M.; Ito, Y. *Synlett*, ***1994***, 179.
[1772]Kang, S.-K.; Lim, K.-H.; Ho, P.-S.; Kim, W.-Y. *Synthesis* ***1997***, 874.
[1773]Xiang, J.; Jiang, W.; Fuchs, P.L. *Tetrahedron Lett.* ***1997***, *38*, 6635.
[1774]Li, Z.; Li, C.-J. *Org. Lett.* ***2004***, *6*, 4997.
[1775]Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* ***2004***, *126*, 11810.
[1776]Zhang, J.; Wei, C.; Lei, C.-J. *Tetrahedron Lett.* ***2002***, *43*, 5731.
[1777]Arisawa, M.; Amemiya, R.; Yamaguchi, M. *Org. Lett.* ***2002***, *4*, 2209.
[1778]Kang, S.-K.; Kim, W.-Y.; Jiao, X. *Synthesis* ***1998***, 1252.
[1779]Liu, Y.; Xi, C.; Hara, R.; Nakajima, K.; Yamazaki, A.; Kotora, M.; Takahashi, T. *J. Org. Chem.* ***2000***, *65*, 6951.
[1780]Pal, M.; Kundu, N.G. *J. Chem. Soc. Perkin Trans 1*, ***1996***, 449. Also see, Nguefack, J.-F.; Bolitt, V.; Sinou, D. *Tetrahedron Lett*, ***1996***, *37*, 5527.
[1781]Nishihara, Y.; Ikegashira, K.; Mori, A.; Hiyama, T. *Tetrahedron Lett.* ***1998***, *39*, 4075.
[1782]Bumagin, N.A.; Sukhmolinova, L.I.; Luzikova, E.V.; Tolstaya, T.P.; Beletskaya, I.P. *Tetrahedron Lett.* ***1996***, *37*, 897; Powell, N.A.; Rychnovsky, S.D. *Tetrahedron Lett.* ***1996***, *37*, 7901; Nishihara, Y.; Ikegashira, K.; Mori, A.; Hiyama, T. *Chem. Lett.* ***1997***, 1233.
[1783]Shimizu, R; Fuchikami, T. *Tetrahedron Lett.* ***2000***, *41*, 907.
[1784]Andreev, A.A.; Konshin, V.V.; Komarov, N.V.; Rubin, M.; Brouwer, C.; Gevorgyan, V. *Org. Lett.* ***2004***, *6*, 421.

OS **IV**, 117; **VI**, 273, 564, 595; **VIII**, 415; **IX**, 117, 477, 688; **76**, 263. Also see, OS **IV**, 801; **VI**, 925.

10-75 Preparation of Nitriles

Cyano-de-halogenation

$$RX + {}^{-}CN \longrightarrow RCN$$

The reaction between cyanide ion and alkyl halides is a convenient method for the preparation of nitriles.[1785] Primary, benzylic, and allylic halides give good yields of nitriles; secondary halides give moderate yields. The reaction fails for tertiary halides, which give elimination under these conditions. Many other groups on the molecule do not interfere. A number of solvents have been used, but the high yields and short reaction times observed with DMSO make it a very good solvent for this reaction.[1786] Other ways to obtain high yields under mild conditions are to use a phase-transfer catalyst,[1787] in alternative solvents, such as PEG 400 (a polyethylene glycol),[1788] or with ultrasound.[1789] This is an important way of increasing the length of a carbon chain by one carbon, since nitriles are easily hydrolyzed to carboxylic acids (**16-4**).

The cyanide ion is an ambident nucleophile (it can react via N or via C) and isocyanides (also called isonitriles, R—N≡C) may be side products.[1790] If the preparation of isocyanides is desired, they can be made the main products by the use of reagents with more covalent metal–carbon bonds, such as silver or copper(I) cyanide[1791] (p. 515). However, the use on an excess of LiCN in acetone/THF gave the nitrile as the major product.[1792] Tosyl cyanide ($TolSO_2CN$) has been used in some cases.[1793]

Vinylic bromides can be converted to vinylic cyanides with CuCN,[1794] with KCN, a crown ether, and a Pd(0) complex,[1795] or with KCN and a Ni(0)

[1785]For reviews, see, in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C*, pt. 1, Wiley, NY, ***1983***, the articles by Fatiadi, A.J. pt. 2, pp. 1057–1303, and Friedrich, K. pt. 2, pp. 1343–1390; Friedrich, K.; Wallenfels, K., in Rappoport, Z. *The Chemistry of the Cyano Group*, Wiley, NY, ***1970***, pp. 77–86.

[1786]Smiley, R.A.; Arnold, C. *J. Org. Chem.* ***1960***, *25*, 257; Friedman, L.; Shechter, H. *J. Org. Chem.* ***1960***, *25*, 877.

[1787]For reviews, see Starks, C.M.; Liotta, C. *Phase Transfer Catalysis*, Acaemic Press, NY, ***1978***, pp. 94–112; Weber, W.P.; Gokel, G.W. *Phase Transfer Catalysis in Organic Synthesis*, Springer, NY, ***1977***, pp. 96–108. See also, Bram, G.; Loupy, A.; Pedoussaut, M. *Tetrahedron Lett.* ***1986***, *27*, 4171; *Bull. Soc. Chim. Fr.* ***1986***, 124.

[1788]Cao, Y.-Q.; Che, B.-H.; Pei, B.-G. *Synth. Commun.* ***2001***, *31*, 2203.

[1789]Ando, T.; Kawate, T.; Ichihara, J.; Hanafusa, T. *Chem. Lett.* ***1984***, 725.

[1790]For a solid-phase synthesis of isonitriles see Luanay, D.; Booth, S.; Clemens, I.; Merritt, A.; Bradley, M. *Tetrahedron Lett.* ***2002***, *43*, 7201.

[1791]For an example, see Jackson, H.L.; McKusick, B.C. *Org. Synth.* ***IV***, 438.

[1792]Ciaccio, J.A.; Smrtka, M.; Maio, W.A.; Rucando, D. *Tetrahedron Lett.* ***2004***, *45*, 7201.

[1793]Kim, S.; Song, H.-J. *Synlett* ***2002***, 2110.

[1794]For example, see Koelsch, C.F. *J. Am. Chem. Soc.* ***1936***, *58*, 1328; Newman, M.S.; Boden, H. *J. Org. Chem.* ***1961***, *26*, 2525; Lapouyade, R.; Daney, M.; Lapenue, M.; Bouas-Laurent, H. *Bull. Soc. Chim. Fr.* ***1973***, 720.

[1795]Yamamura, K.; Murahashi, S. *Tetrahedron Lett.* ***1977***, 4429.

catalyst.[1796] Halides can be converted to the corresponding nitriles by treatment with trimethylsilyl cyanide in the presence of catalytic amounts of $SnCl_4$: $R_3CCl + Me_3\ SiCN \rightarrow R_3CCN$.[1797] Primary, secondary, and tertiary alcohols are converted to nitriles in good yields by treatment with NaCN, Me_3SiCl, and a catalytic amount of NaI in DMF–MeCN.[1798] Lewis acids have been used in conjunction with NaCN or KCN.[1799] α,β-Epxoy amides were opened to the β-cyano-α-hydroxyamide with Et_2AlCN.[1800] Cyanohydrins react with alkyl halides in some cases to give the nitrile.[1801]

Substrates that react with cyanide may contain leaving groups other than halides, such as esters of sulfuric and sulfonic acids (sulfates and sulfonates, respectively). Vinylic triflates give vinylic cyanides when treated with LiCN, a crown ether, and a palladium catalyst.[1802] Epoxides give β-hydroxy nitriles. The C-2-selectivity was observed when NaCN and $B(OMe)_3$ were reacted with a disubstituted epoxide.[1803] The use of trimethylsilyl cyanide (Me_3SiCN) and a Lewis acid generates the *O*-TMS β-hydroxy nitrile, and the use of $YbCl_3$ and a salen complex gave good enantioselectivity.[1804] One alkoxy group of acetals is replaced by CN [$R_2C(OR')_2 \rightarrow R_2C(OR')CN$] with Me_3SiCN and a catalyst[1805] or with *t*-BuNC and $TiCl_4$.[1806] Tetrabutylammonium cyanide converted a primary alcohol to the corresponding nitrile in the presence of PPh_3/DDQ.[1807]

Sodium cyanide in HMPA selectively cleaves methyl esters in the presence of ethyl esters:

$$RCOOMe + CN^- \longrightarrow MeCN + RCOO^-.\ ^{1808}$$

[1796]Sakakibara, Y.; Yadani, N.; Ibuki, I.; Sakai, M.; Uchino, N. *Chem. Lett.* ***1982***, 1565; Procházka, M.; Siroky, M. *Collect. Czech. Chem. Commun.* ***1983***, *48*, 1765.

[1797]Reetz, M.T.; Chatziiosifidis, I. *Angew. Chem. Int. Ed.* ***1981***, *20*, 1017; Zieger, H.E.; Wo, S. *J. Org. Chem.* ***1994***, *59*, 3838. See Tsuji, Y.; Yamada, N.; Tanaka, S. *J. Org. Chem.* ***1993***, *58*, 16 for a similar reaction with allylic acetates. See Hayashi, M.; Tamura, M.; Oguni, N. *Synlett*, ***1992***, 663 for a similar reaction with epoxides using a titanium catalyst.

[1798]Davis, R.; Untch, K.G. *J. Org. Chem.* ***1981***, *46*, 2985. See also, Mizuno, A.; Hamada, Y.; Shioiri, T. *Synthesis* ***1980***, 1007; Manna, S.; Falck, J.R.; Mioskowski, C. *Synth. Commun.* ***1985***, *15*, 663; Camps, F.; Gasol, V.; Guerrero, A. *Synth. Commun.* ***1988***, *18*, 445.

[1799]$Ce(OTf)_4$: Iranpoor, N.; Shekarriz, M. *Synth. Commun.* ***1999***, *29*, 2249.

[1800]Ruano, J.L.G.; Fernández-Ibáñez, M.Á.; Castro, A.M.M.; Ramos, J.H.R.; Flamarique, A.C.R. *Tetrahedron Asymmetry* ***2002***, *13*, 1321.

[1801]Dowd, P.; Wilk, B.K.; Wlostowski, M. *Synth. Commun.* ***1993***, *23*, 2323; Wilk, B.K. *Synth. Commun.* ***1993***, *23*, 2481 and see Ohno, H.; Mori, A.; Inoue, S. *Chem. Lett.* ***1993***, 975 and Mitchell, D.; Koenig, T.M. *Tetrahedron Lett.* ***1992***, *33*, 3281 for similar reactions with epoxides.

[1802]Piers, E.; Fleming, F.F. *J. Chem. Soc., Chem. Commun.* ***1989***, 756.

[1803]Sasaki, M.; Tanino, K.; Hirai, A.; Miyashita, M. *Org. Lett.* ***2003***, *5*, 1789.

[1804]Schaus, S.E.; Jacobsen, E.N. *Org. Lett.* ***2000***, *2*, 1001.

[1805]Torii, S.; Inokuchi, T.; Kobayashi, T. *Chem. Lett.* ***1984***, 897; Soga, T.; Takenoshita, H.; Yamada, M.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* ***1990***, *63*, 3122.

[1806]Ito, Y.; Imai, H.; Segoe, K.; Saegusa, T. *Chem. Lett.* ***1984***, 937.

[1807]Iranpoor, N.; Firouzabadi, H.; Akhlaghinia, B.; Nowrouzi, N. *J. Org. Chem.* ***2004***, *69*, 2562.

[1808]Müller, P.; Siegfried, B. *Helv. Chim. Acta* ***1974***, *57*, 987.

OS **I**, 46, 107, 156, 181, 254, 256, 536; **II**, 292, 376; **III**, 174, 372, 557; **IV**, 438, 496, 576; **V**, 578, 614.

10-76 Direct Conversion of Alkyl Halides to Aldehydes and Ketones

Formyl-de-halogenation

$$RX + Na_2Fe(CO)_4 \xrightarrow{PPh_3} \underset{\mathbf{180}}{RCOFe(CO)_3PPh_3^-} \xrightarrow{HOAc} RCHO$$

The direct conversion of alkyl bromides to aldehydes, with an increase in the chain length by one carbon, can be accomplished[1809] by treatment with sodium tetracarbonylferrate(-2)[1810] (*Collman's reagent*) in the presence of triphenylphosphine and subsequent quenching of **180** with acetic acid. The reagent $Na_2Fe(CO)_4$ can be prepared by treatment of iron pentacarbonyl $Fe(CO)_5$ with sodium amalgam in THF. Good yields are obtained from primary alkyl bromides; secondary bromides give lower yields. The reaction is generally not satisfactory for benzylic bromides, but a good yield of the ketone was obtained using benzyl chloride and aryl iodides.[1811] The initial species produced from RX and $Na_2Fe(CO)_4$ is the ion $RFe(CO)_4^-$ (which can be isolated[1812]); it then reacts with Ph_3P to give **180**.[1813]

The synthesis can be extended to the preparation of ketones in six distinct ways.[1814] These include quenching **180** with a second alkyl halide (R′X) rather than acetic acid; omitting PPh_3 with first RX and then adding the second, R′X; treatment with RX in the presence of CO,[1810] followed by treatment with R′X'; treatment with an acyl halide followed by treatment with an alkyl halide or an epoxide, gives an α,β-unsaturated ketone.[1815] The final variations involve reaction of alkyl halides or tosylates with $Na_2Fe(CO)_4$ in the presence of ethylene to give alkyl ethyl ketones;[1816] when 1,4-dihalides are used, five-membered cyclic ketones are prepared.[1817]

[1809]Cooke, Jr., M.P. *J. Am. Chem. Soc.* ***1970***, *92*, 6080.

[1810]For a review of this reagent, see Collman, J.P. *Acc. Chem. Res.* ***1975***, *8*, 342. For a review of the related tetracarbonylhydridoferrates $MHFe(CO)_4$, see Brunet, J. *Chem. Rev.* ***1990***, *90*, 1041.

[1811]Dolhem, E.; Barhdadi, R.; Folest, J.C.; Nédélec, J.Y.; Troupel, M. *Tetrahedron* ***2001***, *57*, 525.

[1812]Siegl, W.O.; Collman, J.P. *J. Am. Chem. Soc.* ***1972***, *94*, 2516.

[1813]For the mechanism of the conversion $RFe(CO)_4^- \rightarrow$ **180**, see Collman, J.P.; Finke, R.G.; Cawse, J.N.; Brauman, J.I. *J. Am. Chem. Soc.* ***1977***, *99*, 2515; ***1978***, *100*, 4766.

[1814]For the first four of these methods, see Collman, J.P.; Winter, S.R.; Clark, D.R. *J. Am. Chem. Soc.* ***1972***, *94*, 1788; Collman, J.P.; Hoffman, N.W. *J. Am. Chem. Soc.* ***1973***, *95*, 2689.

[1815]Yamashita, M.; Yamamura, S.; Kurimoto, M.; Suemitsu, R. *Chem. Lett.* ***1979***, 1067.

[1816]Cooke, Jr., M.P.; Parlman, R.M. *J. Am. Chem. Soc.* ***1975***, *97*, 6863. The reaction was not successful for higher alkenes, except that where the double bond and the tosylate group are in the same molecule, five- and six-membered rings can be closed: see McMurry, J.E.; Andrus, A. *Tetrahedron Lett.* ***1980***, *21*, 4687, and references cited therein.

[1817]Yamashita, M.; Uchida, M.; Tashika, H.; Suemitsu, R. *Bull. Chem. Soc. Jpn.* ***1989***, *62*, 2728.

Yet another approach uses electrolysis conditions with the alkyl chloride, $Fe(CO)_5$ and a nickel catalyst and gives the ketone directly, in one step.[1818] In the first stage of methods 1, 2, and 3, primary bromides, iodides, and tosylates and secondary tosylates can be used. The second stage of the first four methods requires more active substrates, such as primary iodides or tosylates or benzylic halides. Method 5 has been applied to primary and secondary substrates.

Other acyl organometallic reagents are known. An acyl zirconium reagent, such as $RCOZr(Cl)Cp_2$, reacted with allylic bromide in the presence of CuI to give the corresponding ketone, but with allylic rearrangement.[1819]

Symmetrical ketones R_2CO can be prepared by treatment of a primary alkyl or benzylic halide with $Fe(CO)_5$ and a phase transfer catalyst,[1820] or from a halide RX (R = primary alkyl, aryl, allylic, or benzylic) and CO by an electrochemical method involving a nickel complex.[1821] Aryl, benzylic, vinylic, and allylic halides have been converted to aldehydes by treatment with CO and Bu_3SnH, with a Pd(0) catalyst.[1822] Various other groups do not interfere. Several procedures for the preparation of ketones are catalyzed by palladium complexes. Alkyl aryl ketones are formed in good yields by treatment of a mixture of an aryl iodide, an alkyl iodide, and a Zn–Cu couple with CO ($ArI + RI + CO \rightarrow RCOAr$).[1823] Vinylic halides react with vinylic tin reagents in the presence of CO to give unsymmetrical divinyl ketones.[1824] Aryl, vinylic, and benzylic halides can be converted to methyl ketones ($RX \rightarrow RCOMe$) by reaction with (α-ethoxyvinyl)tributyltin Bu_3Sn-$C(OEt)=CH_2$.[1825] In addition, SmI_2 can be used to convert alkyl chloride to ketones, in the presence of 50 atm of CO.[1826] Carbonylation can also be done with Zn/CuI,[1827] Zn, and then $CoBr_2$,[1828] or with AIBN and $(Me_3Si)_3SiH$.[1829]

[1818]Dolhem, E.; Oçafrain, M.; Nédélec, J.Y.; Troupel, M. *Tetrahedron* ***1997***, *53*, 17089; Yoshida, K.; Kobayashi, M.; Amano, S. *J. Chem. Soc. Perkin Trans. 1* ***1992***, 1127.

[1819]Hanzawa, Y.; Narita, K.; Taguchi, T. *Tetrahedron Lett.* ***2000***, *41*, 109.

[1820]Kimura, Y.; Tomita, Y.; Nakanishi, S.; Otsuji, Y. *Chem. Lett.* ***1979***, 321; des Abbayes, H.; Clément, J.; Laurent, P.; Tanguy, G.; Thilmont, N. *Organometallics* ***1988***, *7*, 2293.

[1821]Garnier, L.; Rollin, Y.; Périchon, J. *J. Organomet. Chem.* ***1989***, *367*, 347.

[1822]Baillargeon, V.P.; Stille, J.K. *J. Am. Chem. Soc.* ***1986***, *108*, 452. See also, Kasahara, A.; Izumi, T.; Yanai, H. *Chem. Ind. (London)* ***1983***, 898; Pri-Bar, I.; Buchman, O. *J. Org. Chem.* ***1984***, *49*, 4009; Takeuchi, R.; Tsuji, Y.; Watanabe, Y. *J. Chem. Soc., Chem. Commun.* ***1986***, 351; Ben-David, Y.; Portnoy, M.; Milstein, D. *J. Chem. Soc., Chem. Commun.* ***1989***, 1816.

[1823]Tamaru, Y.; Ochiai, H.; Yamada, Y.; Yoshida, Z. *Tetrahedron Lett.* ***1983***, *24*, 3869.

[1824]Goure, W.F.; Wright, M.E.; Davis, P.D.; Labadie, S.S.; Stille, J.K. *J. Am. Chem. Soc.* ***1984***, *106*, 6417. For a similar preparation of diallyl ketones, see Merrifield, J.H.; Godschalx, J.P.; Stille, J.K. *Organometallics* ***1984***, *3*, 1108.

[1825]Kosugi, M.; Sumiya, T.; Obara, Y.; Suzuki, M.; Sano, H.; Migita, T. *Bull. Chem. Soc. Jpn.* ***1987***, *60*, 767.

[1826]Ogawa, A.; Sumino, Y.; Nanke, T.; Ohya, S.; Sonoda, N.; Hirao, T. *J. Am. Chem. Soc.*, ***1997***, *119*, 2745.

[1827]Tsunoi, S.; Ryu, I.; Fukushima, H.; Tanaka, M.; Komatsu, M.; Sonoda, N. *Synlett*, ***1995***, 1249.

[1828]Devasagayaraj, A.; Knochel, P. *Tetrahedron Lett.* ***1995***, *36*, 8411.

[1829]Ryu, I.; Hasegawa, M.; Kurihara, A.; Ogawa, A.; Tsunoi, S.; Sonoda, N. *Synlett*, ***1993***, 143.

The conversion of alkyl halides to aldehydes and ketones can also be accomplished indirectly (**10-71**). See also, **12-33**.

OS **VI**, 807.

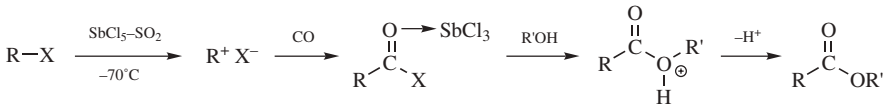
10-77 Carbonylation of Alkyl Halides, Alcohols, or Alkanes

Alkoxycarbonyl-de-halogenation

$$RX + CO + R'OH \xrightarrow[-70^\circ C]{SbCl_5–SO_2} RCOOR'$$

A direct method for preparing a carboxylic acid treats an alkyl halide with $NaNO_2$ in acetic acid and DMSO.[1830] Reaction of an alkyl halide with $ClCO-CO_2Me$ and $(Bu_3Sn)_2$ under photochemical conditions leads to the corresponding methyl ester.[1831]

Several methods, all based on carbon monoxide or metal carbonyls, have been developed for converting an alkyl halide to a carboxylic acid or an acid derivative with the chain extended by one carbon.[1832] When an alkyl halide is treated with $SbCl_5—SO_2$ at $-70^\circ C$, it dissociates into the corresponding carbocation (p. 236). If carbon monoxide and an alcohol are present, a carboxylic ester is formed by the following route:[1833]



This has also been accomplished with concentrated H_2SO_4 saturated with CO.[1834] Not surprisingly, only tertiary halides perform satisfactorily; secondary halides give mostly rearrangement products. An analogous reaction takes place with alkanes possessing a tertiary hydrogen, using $HF—SbF_5—CO$.[1835]

Carboxylic acids or esters are the products, depending on whether the reaction mixture is solvolyzed with water or an alcohol. Alcohols with more than seven

[1830]Matt, C.; Wagner, A.; Mioskowski, C. *J. Org. Chem.* ***1997***, *62*, 234.

[1831]Kim, S.; Jon, S.Y. *Tetrahedron Lett.* ***1998***, *39*, 7317.

[1832]For discussions of most of the reactions in this section, see Colquhoun, H.M.; Holton, J.; Thompson, D.J.; Twigg, M.V. *New Pathways for Organic Synthesis*; Plenum, NY, ***1984***, pp. 199–204, 212–220, 234–235. For lists of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1684–1685, 1694–1698, 1702–1704.

[1833]Yoshimura, M.; Nojima, M.; Tokura, N. *Bull. Chem. Soc. Jpn.* ***1973***, *46*, 2164; Puzitskii, K.V.; Pirozhkov, S.D.; Ryabova, K.G.; Myshenkova, T.N.; Éidus, Ya.T. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1974***, *23*, 192.

[1834]Takahashi, Y.; Yoneda, N. *Synth. Commun.* ***1989***, *19*, 1945.

[1835]Paatz, R.; Weisgerber, G. *Chem. Ber.* ***1967***, *100*, 984. For a related reaction using $AlBr_3$ see Akhrem, I.; Afanas'eva, L.; Petrovskii, P.; Vitt, S.; Orlinkov, A. *Tetrahedron Lett.* ***2000***, *41*, 9903.

carbons are cleaved into smaller fragments by this procedure.[1836] Similarly, tertiary alcohols[1837] react with H_2SO_4 and CO (which is often generated from HCOOH and the H_2SO_4 in the solution) to give trisubstituted acetic acids in a process called the *Koch–Haaf reaction* (see also, **15-35**).[1838] If a primary or secondary alcohol is the substrate, the carbocation initially formed rearranges to a tertiary ion before reacting with the CO. Better results are obtained if trifluoromethanesulfonic acid F_3CSO_2OH is used instead of H_2SO_4.[1839] Iodo alcohols were transformed into lactones under radical conditions (AIBN, allyl$SnBu_3$) and 45 atm of CO.[1840]

Another method[1841] for the conversion of alkyl halides to carboxylic esters is treatment of a halide with nickel carbonyl $Ni(CO)_4$ in the presence of an alcohol and its conjugate base.[1842] When R′ is primary, RX may only be a vinylic or an aryl halide; retention of configuration is observed at a vinylic R. Consequently, a carbocation intermediate is not involved here. When R′ is tertiary, R may be primary alkyl as well as vinylic or aryl. This is thus one of the few methods for preparing esters of tertiary alcohols. Alkyl iodides give the best results, then bromides. In the presence of an amine, an amide can be isolated directly, at least in some instances.

$$\text{RX} + \text{Ni(CO)}_4 \xrightarrow[\text{R'OH}]{\text{R'O}^-} \text{RCOOR'}$$

Still another method for the conversion of halides to acid derivatives makes use of $Na_2Fe(CO)_4$. As described in **10-76**, primary and secondary alkyl halides and tosylates react with this reagent to give the ion $RFe(CO)_4^-$ or, if CO is present, the ion $RCOFe(CO)_4^-$. Treatment of $RFe(CO)_4^-$ or $RCOFe(CO)_4^-$ with oxygen or sodium hypochlorite gives, after hydrolysis, a carboxylic acid.[1843] Alternatively, $RFe(CO)_4^-$ or $RCOFe(CO)_4^-$ reacts with a halogen (e.g., I_2) in the presence of an

[1836]Yoneda, N.; Takahashi, Y.; Fukuhara, T.; Suzuki, A. *Bull. Chem. Soc. Jpn.* ***1986***, *59*, 2819.

[1837]For reviews of other carbonylation reactions of alcohols and other saturated oxygenated compounds, see Bahrmann, H.; Cornils, B., in Falbe, J. *New Syntheses with Carbon Monoxide*, Springer, NY, ***1980***, pp. 226–241; Piacenti, F.; Bianchi, M. in Wender, I.; Pino, P. *Organic Syntheses via Metal Carbonyls*, Vol. 2, Wiley, NY, ***1977***, pp. 1–42.

[1838]For a review, see Bahrmann, H., in Falbe, J. *New Syntheses with Carbon Monoxide*, Springer, NY, ***1980***, pp. 372–413.

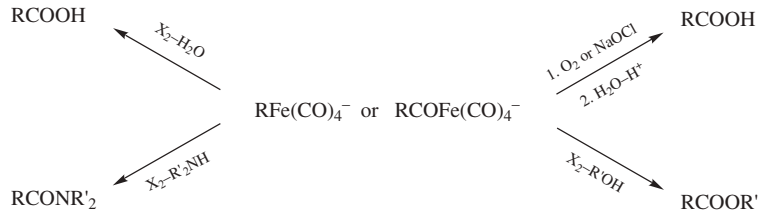
[1839]Booth, B.L.; El-Fekky, T.A. *J. Chem. Soc. Perkin Trans. 1* ***1979***, 2441.

[1840]Kreimerman, S.; Ryu, I.; Minakata, S.; Komatsu, M. *Org. Lett.* ***2000***, *2*, 389.

[1841]For reviews of methods involving transition metals, see Collman, J.P.; Hegedus, L.S.; Norton, J.R.; Finke, R.G. *Principles and Applications of Organotransition Metal Chemistry*, 2nd ed., University Science Books, Mill Valley, CA, ***1987***, pp. 749–768; Anderson, G.K.; Davies, J.A., in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 3, Wiley, NY, pp. 335–359, pp. 348–356; Heck, R.F. *Adv. Catal.*, ***1977***, *26*, 323, see pp. 323; Cassar, L.; Chiusoli, G.P.; Guerrieri, F. *Synthesis* ***1973***, 509.

[1842]Corey, E.J.; Hegedus, L.S. *J. Am. Chem. Soc.* ***1969***, *91*, 1233. See also, Crandall, J.K.; Michaely, W.J. *J. Organomet. Chem.* ***1973***, *51*, 375.

[1843]Collman, J.P.; Winter, S.R.; Komoto, R.G. *J. Am. Chem. Soc.* ***1973***, *95*, 249.



alcohol to give a carboxylic ester,[1844] or in the presence of a secondary amine or water to give, respectively, the corresponding amide or free acid. The compound $RFe(CO)_4^-$ and $RCOFe(CO)_4^-$, what are prepared from primary R, give high yields. With secondary R, the best results are obtained in the solvent THF by the use of $RCOFe(CO)_4^-$ prepared from secondary tosylates. Ester and keto groups may be present in R without being affected. Carboxylic esters RCO_2R' have also been prepared by treating primary alkyl halides RX with alkoxides $R'O^-$ in the presence of $Fe(CO)_5$.[1845] $RCOFe(CO)_4^-$ is presumably an intermediate.

Palladium complexes also catalyze the carbonylation of halides.[1846] Aryl (see **13-15**),[1847] vinylic,[1848] benzylic, and allylic halides (especially iodides) can be converted to carboxylic esters with CO, an alcohol or alkoxide, and a palladium complex.[1849] Similar reactivity was reported with vinyl triflates.[1850] α-Halo ketones are converted to β-keto esters with CO, an alcohol, NBu_3 and a palladium catalyst at 110°C.[1851] Use of an amine instead of the alcohol or alkoxide leads to an amide.[1852]

[1844]Collman, J.P.; Winter, S.R.; Komoto, R.G. *J. Am. Chem. Soc.* ***1973***, *95*, 249; Masada, H.; Mizuno, M.; Suga, S.; Watanabe, Y.; Takegami, Y. *Bull. Chem. Soc. Jpn.* ***1970***, *43*, 3824.

[1845]Yamashita, M.; Mizushima, K.; Watanabe, Y.; Mitsudo, T.; Takegami,Y. *Chem. Lett.* ***1977***, 1355. See also, Tanguy, G.; Weinberger, B.; des Abbayes, H. *Tetrahedron Lett.* ***1983***, *24*, 4005.

[1846]For reviews, see Gulevich, Yu.V.; Bumagin, N.A.; Beletskaya, I.P. *Russ. Chem. Rev.* ***1988***, *57*, 299, 303–309; Heck, R.F. *Palladium Reagents in Organic Synthesis*, Academic Press, NY, ***1985***, pp. 348–356, 366–370.

[1847]For an example, see Bessard, Y; Crettaz, R. *Heterocycles* ***1999***, *51*, 2589.

[1848]For conversion of vinylic triflates to carboxylic esters and amides, see Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* ***1985***, *26*, 1109.

[1849]Tsuji, J.; Kishi, J.; Imamura, S.; Morikawa, M. *J. Am. Chem. Soc.* ***1964***, *86*, 4350; Schoenberg, A.; Bartoletti, I.; Heck, R.F. *J. Org. Chem.* ***1974***, *39*, 3318; Adapa, S.R.; Prasad, C.S.N. *J. Chem. Soc. Perkin Trans. 1* ***1989***, 1706; Kiji, J.; Okano, T.; Higashimae, Y.; Kukui, Y. *Bull. Chem. Soc. Jpn.* ***1996***, *69*, 1029; Okano, T.; Okabe, N.; Kiji, J. *Bull. Chem. Soc. Jpn.* ***1992***, *65*, 2589.

[1850]Jutand, A.; Négri, S. *Synlett*, ***1997***, 719.

[1851]Lapidus, A.L.; Eliseev, O.L.; Bondarenko, T.N.; Sizan, O.E.; Ostapenko, A.G.; Beletskaya, I.P. *Synthesis* ***2002***, 317.

[1852]Schoenberg, A.; Heck, R.F. *J. Org. Chem.* ***1974***, *39*, 3327. See also, Lindsay, L.M.; Widdowson, D.A. *J. Chem. Soc. Perkin Trans. 1* ***1988***, 569; Cai, M.-Z.; Song, C.-S.; Huang, X. *Synth. Commun.* ***1997***, *27*, 361. For a review of some methods of amide formation that involve transition metals, see Screttas, C.G.; Steele, B.R. *Org. Prep. Proceed. Int.* ***1990***, *22*, 271, 288–314. See Satoh, T.; Ikeda, M.; Kushino, Y.; Miura, M.; Nomura, M. *J. Org. Chem.* ***1997***, *62*, 2662 for the carbonylation of an alcohol to give the corresponding ester by a similar method.

Reaction with an amine, AIBN, CO and a tetraalkyltin catalyst also leads to an amide.[1853] Benzylic and allylic halides were converted to carboxylic acids electrocatalytically, with CO and a cobalt imine complex.[1854] Vinylic halides were similarly converted with CO and nickel cyanide, under phase-transfer conditions.[1855] Allylic *O*-phosphates were converted to allylic amides with CO and ClTi=NTMS, in the presence of a palladium catalyst.[1856] Terminal alkynes were converted to the alkynyl ester using CO, $PdBr_2$, $CuBr_2$ in methanol and sodium bicarbonate.[1857]

Other organometallic reagents can be used to convert alkyl halides to carboxylic acid derivatives. Benzylic halides were converted to carboxylic esters with CO in the presence of a rhodium complex.[1858] Variations introduce the R′ group via an ether R'_2O,[1859] a borate ester $B(OR')_3$,[1860] or an Al, Ti, or Zr alkoxide.[1861] The reaction of an alkene, a primary alcohol and CO, in the presence of a rhodium catalyst, led to carbonylation of the alkene and formation of the corresponding ester.[1862] Vinyl triflates were converted to the conjugated carboxylic acid with CO_2 and a nickel catalyst.[1863] Hydrogen peroxide with a catalytic amount of Na_2WO_4•2 H_2O converted benzylic chlorides to the corresponding benzoic acid.[1864] Reaction with an α,ω-diiodide, Bu_4NF and $Mo(CO)_6$ gave the corresponding lactone.[1865]

Reaction of an alkyl halide with $(MeS)_3C{-}Li$ followed by aqueous HBF_4 leads to a thioester.[1866]

A number of double carbonylations have been reported. In these reactions, two molecules of CO are incorporated in the product, leading to α-keto acids or their derivatives.[1867] When the catalyst is a palladium complex, best results are obtained in the formation of α-keto amides.[1868] R is usually aryl or vinylic.[1869] The formation

[1853]Ryu, I.; Nagahara, K.; Kambe, N.; Sonoda, N.; Kreimerman, S.; Komatsu, M. *Chem. Commun.* ***1998***, 1953.

[1854]Folest, J.; Duprilot, J.; Perichon, J.; Robin, Y.; Devynck, J. *Tetrahedron Lett.* ***1985***, *26*, 2633. See also, Miura, M.; Okuro, K.; Hattori, A.; Nomura, M. *J. Chem. Soc. Perkin Trans. 1* ***1989***, 73; Urata, H.; Goto, D.; Fuchikami, T. *Tetrahedron Lett.* ***1991***, *32*, 3091; Isse, A.A.; Gennaro, A. *Chem. Commun.* ***2002***, 2798.

[1855]Alper, H.; Amer, I.; Vasapollo, G. *Tetrahedron Lett.* ***1989***, *30*, 2615. See also, Amer, I.; Alper, H. *J. Am. Chem. Soc.* ***1989***, *111*, 927.

[1856]Ueda, K.; Mori, M. *Tetrahedron Lett.* ***2004***, *45*, 2907. For an intramolecular carbonylation to generate a cyclic amide, see Trost, B.M.; Ameriks, M.K. *Org. Lett.* ***2004***, *6*, 1745.

[1857]Li, J.; Jiang, H.; Chen, M. *Synth. Commun.* ***2001***, *31*, 199.

[1858]For an example, see Giroux, A.; Nadeau, C.; Han, Y. *Tetrahedron Lett.* ***2000***, *41*, 7601.

[1859]Buchan, C.; Hamel, N.; Woell, J.B.; Alper, H. *Tetrahedron Lett.* ***1985***, *26*, 5743.

[1860]Alper, H.; Hamel, N.; Smith, D.J.H.; Woell, J.B. *Tetrahedron Lett.* ***1985***, *26*, 2273.

[1861]Woell, J.B.; Fergusson, S.B.; Alper, H. *J. Org. Chem.* ***1985***, *50*, 2134.

[1862]Yokoa, K.; Tatamidani, H.; Fukumoto, Y.; Chatani, N. *Org. Lett.* ***2003***, *5*, 4329.

[1863]Senboku, H.; Kanaya, H.; Tokuda, M. *Synlett* ***2002***, 140.

[1864]Shi, M.; Feng, Y.-S. *J. Org. Chem.* ***2001***, *66*, 3235.

[1865]Imbeaux, M.; Mestdagh, H.; Moughamir, K.; Rolando, C. *J. Chem. Soc., Chem. Commun.* ***1992***, 1678.

[1866]Barbero, M.; Cadamuro, S.; Degani, I.; Dughera, S.; Fochi, R. *J. Chem. Soc. Perkin Trans. 1* ***1993***, 2075.

[1867]For a review, see Collin, J. *Bull. Soc. Chim. Fr.* ***1988***, 976.

[1868]Kobayashi, T.; Tanaka, M. *J. Organomet. Chem.* ***1982***, *233*, C64; Ozawa, F.; Sugimoto, T.; Yuasa, Y.; Santra, M.; Yamamoto, T.; Yamamoto, A. *Organometallics* ***1984***, *3*, 683.

[1869]Son, T.; Yanagihara, H.; Ozawa, F.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* ***1988***, *61*, 1251.

of α-keto acids[1870] or esters[1871] requires more severe conditions. α-Hydroxy acids were obtained from aryl iodides when the reaction was carried out in the presence of an alcohol, which functioned as a reducing agent.[1872] Cobalt catalysts have also been used and require lower CO pressures.[1867]

OS **V**, 20, 739.

[1870]Tanaka, M.; Kobayashi, T.; Sakakura, T. *J. Chem. Soc., Chem. Commun.* ***1985***, 837.
[1871]See Ozawa, F.; Kawasaki, N.; Okamoto, H.; Yamamoto, T.; Yamamoto, A. *Organometallics* ***1987***, *6*, 1640.
[1872]Kobayashi, T.; Sakakura, T.; Tanaka, M. *Tetrahedron Lett.* ***1987***, *28*, 2721.

CHAPTER 11

Aromatic Substitution, Electrophilic

Most substitutions at an aliphatic carbon are by nucleophiles. In aromatic systems the situation is reversed, because the high electron density at the aromatic ring leads to its reactivity as a Lewis base or a Brønsted–Lowry base, depending on the positive species. In electrophilic substitutions, a positive ion or the positive end of a dipole or induced dipole is attacked by the aromatic ring. The leaving group (the electrofuge) must necessarily depart without its electron pair. In nucleophilic substitutions, the chief leaving groups are those best able to carry the unshared pair: Br^-, H_2O, OTs^-, and so on., that is, the weakest bases. In electrophilic substitutions the most important leaving groups are those that can best exist without the pair of electrons necessary to fill the outer shell, that is, the weakest Lewis acids.

MECHANISMS

Electrophilic aromatic substitutions are unlike nucleophilic substitutions in that the large majority proceed by just one mechanism with respect to the substrate.[1] In this mechanism, which we call the *arenium ion mechanism*, the electrophile (which can be viewed as a Lewis acid) is attacked by the π-electrons of the aromatic ring (behaving as a Lewis base in most cases) in the first step. This reaction leads to formation of a new C—X bond and a new sp^3 carbon in a positively charged intermediate called an arenium ion, where X is the electrophile. The positively charged intermediate (the arenium ion) is resonance stabilized, but not aromatic. Loss of a proton from the sp^3 carbon that is ''adjacent'' to the positive carbon in the arenium ion, in what is effectively an E1 process (see p. 1487), is driven by rearomatization of the ring from the arenium ion to give the aromatic substitution product. A proton

[1]For monographs, see Taylor, R. *Electrophilic Aromatic Substitution*, Wiley, NY, ***1990***; Katritzky, A.R.; Taylor, R. *Electrophilic Substitution of Heterocycles: Quantitative Aspects* (Vol. 47 of *Adv. Heterocycl. Chem.*), Academic Press, NY, ***1990***. For a review, see Taylor, R., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, ***1972***, pp. 1–406.

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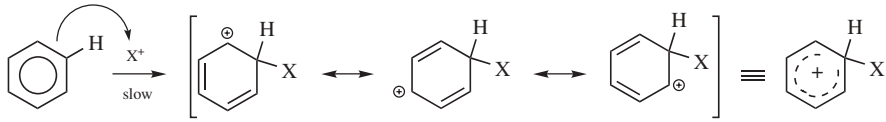
therefore becomes the leaving group in this overall transformation, where X replaces H. The IUPAC designation for this mechanism is $A_E + D_E$. Another mechanism, much less common, consists of the opposite behavior: a leaving group departs *before* the electrophile arrives. In this case, a substituent (*not* H) is attached to the aromatic ring, and the substituent is lost prior to incorporation of the electrophile. This mechanism, the S_E1 mechanism, corresponds to the S_N1 mechanism of nucleophilic substitution. Simultaneous attack and departure mechanisms (corresponding to S_N2) are not found at all. An addition–elimination mechanism has been postulated in one case (see **11-6**).

The Arenium Ion Mechanism[2]

In the arenium ion mechanism the electrophilic species may be produced in various ways, but when H is replaced by X conversion of the aromatic ring to an arenium ion is basically the same in all cases. For this reason, most attention in the study of this mechanism centers around the identity of the electrophilic entity and how it is produced.



1 **2**

The electrophile may be a positive ion or be a molecule that has a positive dipole. If it is a positive ion, it is attacked by the ring (a pair of electrons from the aromatic sextet is donated to the electrophile) to give a carbocation. This intermediate is a resonance hybrid as shown in **1**, but is often represented as in **2**. For convenience, the H atom to be replaced by X is shown in **1**. Ions of this type are called[3] *Wheland intermediates*, σ *complexes*, or *arenium ions*.[4] The inherent stability associated with aromaticity is no longer present in **1**, but the ion is stabilized by resonance. For this reason, the arenium ion is generally a highly reactive intermediate, although there are cases in which it has been isolated (see p. 661).

Carbocations can react in various ways (see p. 247), but for this type of ion the most likely pathway[5] is loss of either X^+ or H^+. In the second step of the

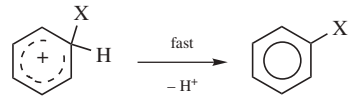
[2]This mechanism is sometimes called the S_E2 mechanism because it is bimolecular, but in this book we reserve that name for aliphatic substrates (see Chapter 12).

[3]General agreement on what to call these ions has not yet been reached. The term σ complex is a holdover from the time when much less was known about the structure of carbocations and it was thought they might be complexes of the type discussed in Chapter 3. Other names have also been used. We will call them arenium ions, following the suggestion of Olah, G.A. *J. Am. Chem. Soc.* ***1971***, *94*, 808.

[4]For reviews of arenium ions formed by addition of a proton to an aromatic ring, see Brouwer, D.M.; Mackor, E.L.; MacLean, C. in Olah, G.A.; Schleyer, P.V.R. *Carbonium Ions*, vol. 2, Wiley, NY, ***1970***, pp. 837–897; Perkampus, H. *Adv. Phys. Org. Chem.* ***1966***, *4*, 195.

[5]For a discussion of cases in which **1** stabilizes itself in other ways, see de la Mare, P.B.D. *Acc. Chem. Res.* ***1974***, *7*, 361.

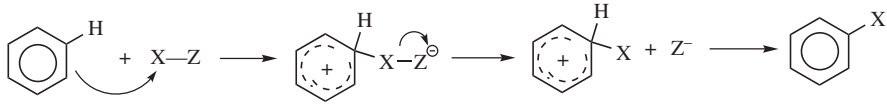
mechanism, the reaction proceeds with loss of the proton and the aromatic sextet is restored in the final product **3**.



3

The second step is nearly always faster than the first, making the first rate determining, and the reaction is second order. If formation of the attacking species is slower still, the aromatic compound does not take part in the rate expression at all. If X^+ is lost, there is no net reaction, but if H^+ is lost, an aromatic substitution has taken place and a base (generally the counterion of the electrophilic species although solvents can also serve this purpose) is necessary to help remove it.

If the attacking species is not an ion, but a dipole, the product must have a negative charge unless part of the dipole, with its pair of electrons, is broken off somewhere in the process, as in the conversion of **4** to **5**. Note that when the aromatic ring attacks X, Z may be lost directly to give **5**.



4 **5**

The electrophilic entities and how they are formed are discussed for each reaction in the reactions section of this chapter.

The evidence for the arenium ion mechanism is mainly of two kinds:

1. *Isotope Effects*. If the hydrogen ion departs before the arrival of the electrophile (S_E1 mechanism) or if the arrival and departure are simultaneous, there should be a substantial isotope effect (i.e., deuterated substrates should undergo substitution more slowly than non-deuterated compounds) because, in each case, the C—H bond is broken in the rate-determining step. However, in the arenium ion mechanism, the C—H bond is not broken in the rate-determining step, so no isotope effect should be found. Many such studies have been carried out and, in most cases, especially in the case of nitrations, there is no isotope effect.[6] This result is incompatible with either the S_E1 or the simultaneous mechanism.

However, in many instances, isotope effects have been found. Since the values are generally much lower than expected for either the S_E1 or the simultaneous mechanisms (e.g., 1–3 for k_H/k_D instead of 6–7), we must look elsewhere for

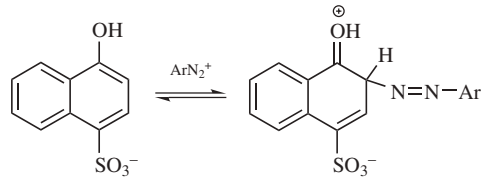
[6]The pioneering studies were by Melander, L. *Ark. Kemi* ***1950***, *2*, 213; Berglund-Larsson, U.; Melander, L. *Ark. Kemi* ***1953***, *6*, 219. See also, Zollinger, H. *Adv. Phys. Org. Chem.* ***1964***, *2*, 163.

the explanation. For the case where hydrogen is the leaving group, the arenium ion mechanism can be summarized:

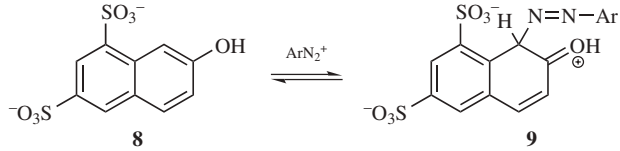
Step 1 $\mathrm{ArH + Y^+} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{Ar(H)(Y)^+}$

Step 2 $\mathrm{Ar(H)(Y)^+} \xrightarrow{k_2} \mathrm{ArY + H^+}$

The small isotope effects found most likely arise from the reversibility of step 1 by a *partitioning effect*.[7] The rate at which $ArHY^+$ reverts to ArH should be essentially the same as that at which $ArDY^+$ (or $ArTY^+$) reverts to ArD (or ArT), since the Ar—H bond is not cleaving. However, $ArHY^+$ should go to ArY faster than either $ArDY^+$ or $ArTY^+$, since the Ar—H bond is broken in this step. If $k_2 \gg k_{-1}$, this does not matter; since a large majority of the intermediates go to product, the rate is determined only by the slow step ($k_1[ArH][Y^+]$) and no isotope effect is predicted. However, if $k_2 \leq k_{-1}$, reversion to starting materials is important. If k_2 for $ArDY^+$ (or $ArTY^+$) is $<$ k_2 for $ArHY^+$, but k_{-1} is the same, then a larger proportion of $ArDY^+$ reverts to starting compounds. That is, k_2/k_{-1} (the *partition factor)* for $ArDY^+$ is less than that for $ArHY^+$. Consequently, the reaction is slower for ArD than for ArH and an isotope effect is observed.



6 **7**



8 **9**

One circumstance that could affect the k_2/k_{-1} ratio is steric hindrance. Thus, diazonium coupling of **6** gave no isotope effect, while coupling of **8** gave a k_H/k_D ratio of 6.55.[8] For steric reasons, it is much more difficult for **9** to lose a proton (it is harder for a base to approach) than it is for **7**, so k_2 is greater for the latter. Since no base is necessary to remove ArN_2^+, k_{-1} does not depend on steric factors[9] and is about the same for each. Thus the partition factor k_2/k_{-1}

[7]For a discussion, see Hammett, L.P. *Physical Organic Chemistry*, 2nd ed., McGraw-Hill, NY, ***1970***, pp. 172–182.
[8]Zollinger, H. *Helv. Chim. Acta* ***1955***, *38*, 1597, 1617, 1623.
[9]Snyckers, F.; Zollinger, H. *Helv. Chim. Acta* ***1970***, *53*, 1294.

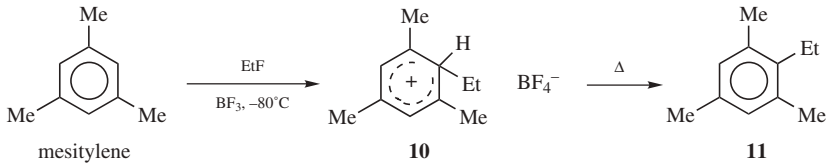
is sufficiently different for **7** and **9** that **8** exhibits a large isotope effect and **6** exhibits none.[10] Base catalysis can also affect the partition factor, since an increase in base concentration increases the rate at which the intermediate goes to product without affecting the rate at which it reverts to starting materials. In some cases, isotope effects can be diminished or eliminated by a sufficiently high concentration of base.

Evidence for the arenium ion mechanism has also been obtained from other kinds of isotope-effect experiments, involving substitutions of the type

$$ArMR_3 + H_3O^+ \longrightarrow ArH + R_3MOH_2^+$$

where M is Si, Ge, Sn, or Pb, and R is methyl or ethyl. In these reactions, the proton is the electrophile. If the arenium ion mechanism is operating, then the use of D_3O^+ should give rise to an isotope effect, since the D–O bond would be broken in the rate-determining step. Isotope effects of 1.55–3.05 were obtained,[11] in accord with the arenium ion mechanism.

2. *Isolation of Arenium Ion Intermediates*. Very strong evidence for the arenium ion mechanism comes from the isolation of arenium ions in a number of instances.[12] For example, **7** was isolated as a solid with a



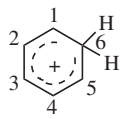
melting point of −15°C from treatment of mesitylene with ethyl fluoride and the catalyst BF_3 at −80°C. When **10** was heated, the normal substitution product **11** was obtained.[13] Even the simplest such ion, the benzenonium ion (**12**), has been prepared in HF–SbF_5–SO_2ClF–SO_2F_2 at −134°C, where it could be studied

[10]For some other examples of isotope effects caused by steric factors, see Helgstrand, E. *Acta Chem. Scand.* ***1965***, *19*, 1583; Nilsson, A. *Acta Chem. Scand.* ***1967***, *21*, 2423; Baciocchi, E.; Illuminati, G.; Sleiter, G.; Stegel, F. *J. Am. Chem. Soc.* ***1967***, *89*, 125; Myhre, P.C.; Beug, M.; James, L.L. *J. Am. Chem. Soc.* ***1968***, *90*, 2105; Dubois, J.E.; Uzan, R. *Bull. Soc. Chim. Fr.* ***1968***, 3534; Márton, J. *Acta Chem. Scand.* ***1969***, *23*, 3321, 3329.

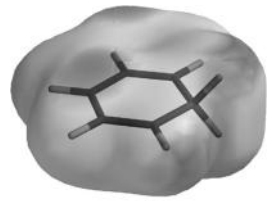
[11]Bott, R.W.; Eaborn, C.; Greasley. P.M. *J. Chem. Soc.* ***1964***, 4803.

[12]For reviews, see Koptyug, V.A. *Top. Curr. Chem.* ***1984***, *122*, 1; *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1974***, *23*, 1031. For a review of polyfluorinated arenium ions, see Shteingarts, V.D. *Russ. Chem. Rev.* ***1981***, *50*, 735. For a review of the protonation of benzene and simple alkylbenzenes, see Fărcaşiu, D. *Acc. Chem. Res.* ***1982***, *15*, 46.

[13]Olah, G.A.; Kuhn, S.J. *J. Am. Chem. Soc.* ***1958***, *80*, 6541. For some other examples, see Ershov, V.V.; Volod'kin, A.A. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1962***, 680; Farrell, P.G.; Newton, J.; White, R.F.M. *J. Chem. Soc. B* ***1967***, 637; Kamshii, L.P.; Koptyug, V.A. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1974***, *23*, 232; Olah, G.A.; Spear, R.J.; Messina, G.; Westerman, P.W. *J. Am. Chem. Soc.* ***1975***, *97*, 4051; Nambu, N.; Hiraoka, N.; Shigemura, K.; Hamanaka, S.; Ogawa, M. *Bull. Chem. Soc. Jpn.* ***1976***, *49*, 3637; Chikinev, A.V.; Bushmelev, V.A.; Shakirov, M.; Shubin, V.G. *J. Org. Chem. USSR* ***1986***, *22*, 1311; Knoche, W.; Schoeller, W.W.; Schomäcker, R.; Vogel, S. *J. Am. Chem. Soc.* ***1988***, *110*, 7484; Effenberger, F. *Acc. Chem. Res.* ***1989***, *22*, 27.



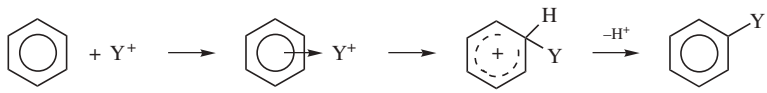
12



13

spectrally.[14] The ^{13}C NMR spectra of the benzenonium ion[15] and the pentamethylbenzenonium ion[16] give graphic evidence for the charge distribution shown in **1** (see the electron density map for the arenium ion, **13**). According to this, the 1, 3, and 5 carbons, each of which bears a positive charge of $+\frac{1}{3}$ [note that C-1,-3,-5 (numbering from **12**) are lighter,indicating less electron density in **13**, whereas C-2,-4 are darker for higher electron density], should have a greater chemical shift in the NMR than the 2 and 4 carbons, which are uncharged. The spectra bear this out. For example, ^{13}C NMR chemical shifts for **12** are C-3: 178.1; C-1 and C-5: 186.6; C-2 and C-4: 136.9, and C-6: 52.2.[15]

In Chapter 3, it was mentioned that positive ions can form addition complexes with π systems. Since the initial step of electrophilic substitution involves attack of a positive ion by an aromatic ring, it has been suggested[17] that such a complex, called a π *complex* (represented as **14**), is formed first, and then is converted to the arenium ion **15**.[18] Stable solutions of arenium ions or π complexes (e.g., with Br_2, I_2,



14 15

picric acid, Ag^+, or HCl) can be formed.[19] For example, π complexes are formed when aromatic hydrocarbons are treated with HCl alone, but the use of HCl plus a

[14]Olah, G.A.; Schlosberg, R.H.; Porter, R.D.; Mo, Y.K.; Kelly, D.P.; Mateescu, G.D. *J. Am. Chem. Soc.* ***1972***, *94*, 2034.

[15]Olah, G.A.; Staral, J.S.; Asencio, G.; Liang, G.; Forsyth, D.A.; Mateescu, G.D. *J. Am. Chem. Soc.* ***1978***, *100*, 6299.

[16]Lyerla, J.R.; Yannoni, C.S.; Bruck, D.; Fyfe, C.A. *J. Am. Chem. Soc.* ***1979***, *101*, 4770.

[17]Dewar, M.J.S. *Electronic Theory of Organic Chemistry;* Clarendon Press: Oxford, ***1949***.

[18]For a discussion of both σ- and π-complexes in electrophilic aromatic substitution, see Hubig, S. M.; Kochi, J. K. *J. Org. Chem.* ***2000***, *65*, 6807.

[19]For an *ab initio* study involving the interaction of water and hexafluorobenzene, to determine the efficacy of lone-pair binding to a π-system, see Gallivan, J.P.; Dougherty, D.A. *Org. Lett.* ***1999***, *1*, 103. For a study concerning preorganization and charge-transfer complexes, see Rosokha, S.V.; Kochi, J.K. *J. Org. Chem.* ***2002***, *67*, 1727.

TABLE 11.1. Relative Stabilities of Arenium Ions and π Complexes and Relative Rates of Chlorination and Nitration[a]

Substituents	Relative Arenium Ion Stability[20]	Relative π-Complex Stability[20]	Rate of Chlorination[21]	Rate of Nitration[26]
None (benzene)	0.09	0.61	0.0005	0.51
Me	0.63	0.92	0.157	0.85
p-Me_2	1.00	1.00	1.00	1.00
o-Me_2	1.1	1.13	2.1	0.89
m-Me_2	26	1.26	200	0.84
1,2,4-Me_3	63	1.36	340	
1,2,3-Me_3	69	1.46	400	
1,2,3,4-Me_4	400	1.63	2,000	
1,2,3,5-Me_4	16,000	1.67	240,000	
Me_5	29,900		360,000	

[a]In each case, p-xylene = 1.00.

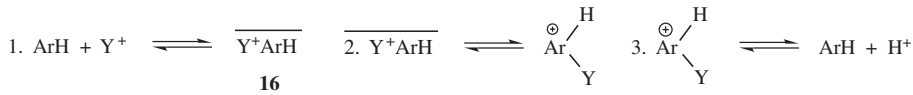
Lewis acid (e.g., $AlCl_3$) gives arenium ions. The two types of solution have very different properties. For example, a solution of an arenium ion is colored and conducts electricity (showing positive and negative ions are present), while a π complex formed from HCl and benzene is colorless and does not conduct a current. Furthermore, when DCl is used to form a π complex, no deuterium exchange takes place (because there is no covalent bond between the electrophile and the ring), while formation of an arenium ion with DCl and $AlCl_3$ gives deuterium exchange. The relative stabilities of some methylated arenium ions and π complexes are shown in Table 11.1. The arenium ion stabilities listed were determined by the relative basicity of the substrate toward HF.[20] The π complex stabilities are relative equilibrium constants for the reaction[21] between the aromatic hydrocarbon and HCl. As shown in Table 11.1, the relative stabilities of the two types of species are very different: the π complex stability changes very little with methyl substitution, but the arenium ion stability changes a great deal. It is noted that stable arenium ions have been obtained from large methylene-bridged polycyclic aromatic hydrocarbons.[22]

How can we tell if **14** is present on the reaction path? If it is present, there are two possibilities: (*1*) The formation of **14** is rate determining (the conversion of **14** to **15** is much faster), or (*2*) the formation of **14** is rapid, and the conversion **14** to **15** is rate determining. One way to ascertain which species is formed in the rate-determining step in a given reaction is to use the stability information given in Table 11.1. We measure the relative rates of reaction of a given electrophile with the series of compounds listed in Table 11.1. If the relative rates resemble the arenium ion stabilities, we conclude that the arenium ion is formed in the slow step; but if they

[20]Kilpatrick, M.; Luborsky, F.E. *J. Am. Chem. Soc.* ***1953***, *75*, 577.
[21]Brown, H.C.; Brady, J.D. *J. Am. Chem. Soc.* ***1952***, *74*, 3570.
[22]Laali, K.K.; Okazaki, T.; Harvey, R.G. *J. Org. Chem.* ***2001***, *66*, 3977.

resemble the stabilities of the π complexes, the latter are formed in the slow step.[23] When such experiments are carried out, it is found in most cases that the relative rates are similar to the arenium ion and not to the π complex stabilities. For example, Table 11.1 lists chlorination rates.[21] Similar results were obtained in room-temperature bromination with Br_2 in acetic acid[24] and in acetylation with CH_3CO^+ SbF_6^-.[25] It is clear that in these cases the π complex either does not form at all, or if it does, its formation is not rate determining (unfortunately, it is very difficult to distinguish between these two possibilities).

On the other hand, in nitration with the powerful electrophile NO_2^+ (in the form of NO_2^+ BF_4^-), the relative rates resembled π complex stabilities much more than arenium ion stabilities (Table 11.1).[26] Similar results were obtained for bromination with Br_2 and $FeCl_3$ in nitromethane. These results were taken to mean[27] that in these cases π complex formation is rate determining. However, graphical analysis of the NO_2^+ data showed that a straight line could not be drawn when the nitration rate was plotted against π complex stability,[28] which casts doubt on the rate-determining formation of a π complex in this case.[29] There is other evidence, from positional selectivities (discussed on p. 682), that *some* intermediate is present before the arenium ion is formed, whose formation can be rate determining with powerful electrophiles. Not much is known about this intermediate, which is given the nondescriptive name *encounter complex* and generally depicted as **16**. The arenium complex mechanism is therefore written as[30]



[23]Condon, F.E. *J. Am. Chem. Soc.* ***1952***, *74*, 2528.

[24]Brown, H.C.; Stock, L.M. *J. Am. Chem. Soc.* ***1957***, *79*, 1421.

[25]Olah, G.A.; Kuhn, S.J.; Flood, S.H.; Hardie, B.A. *J. Am. Chem. Soc.* ***1964***, *86*, 2203.

[26]Olah, G.A.; Kuhn, S.J.; Flood, S.H. *J. Am. Chem. Soc.* ***1961***, *83*, 4571, 4581.

[27]Olah, G.A.; Kuhn, S.J.; Flood, S.H.; Hardie, B.A. *J. Am. Chem. Soc.* ***1964***, *86*, 1039, 1044; Olah, G.A.; Kuhn, S.J.; Flood, S.H. *J. Am. Chem. Soc.* ***1961***, *83*, 4571, 4581.

[28]Rys, P.; Skrabal, P.; Zollinger, H. *Angew. Chem. Int. Ed.* ***1972***, *11*, 874. See also, DeHaan, F.P.; Covey, W.D.; Delker, G.L.; Baker, N.J.; Feigon, J.F.; Miller, K.D.; Stelter, E.D. *J. Am. Chem. Soc.* ***1979***, *101*, 1336; Santiago, C.; Houk, K.N.; Perrin, C.L. *J. Am. Chem. Soc.* ***1979***, *101*, 1337.

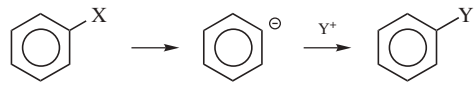
[29]For other evidence against π complexes, see Tolgyesi, W.S. *Can. J. Chem.* ***1965***, *43*, 343; Caille, S.Y.; Corriu, R.J.P. *Tetrahedron* ***1969***, *25*, 2005; Coombes, R.G.; Moodie, R.B.; Schofield, K. *J. Chem. Soc. B* ***1968***, 800; Hoggett, J.G.; Moodie, R.B.; Schofield, K. *J. Chem. Soc. B* ***1969***, 1; Christy, P.F.; Ridd, J.H.; Stears, N.D. *J. Chem. Soc. B* ***1970***, 797; Ridd, J.H. *Acc. Chem. Res.* ***1971***, *4*, 248; Taylor, R.; Tewson, T.J. *J. Chem. Soc., Chem. Commun.* ***1973***, 836; Naidenov, S.V.; Guk, Yu.V.; Golod, E.L. *J. Org. Chem. USSR* ***1982***, *18*, 1731. For further support for π complexes, see Olah, G.A. *Acc. Chem. Res.* ***1971***, *4*, 240; Olah, G.A.; Lin, H.C. *J. Am. Chem. Soc.* ***1974***, *96*, 2892; Koptyug, V.A.; Rogozhnikova, O.Yu.; Detsina, A.N. *J. Org. Chem. USSR* ***1983***, *19*, 1007; El-Dusouqui, O.M.E.; Mahmud, K.A.M.; Sulfab, Y. *Tetrahedron Lett.* ***1987***, *28*, 2417; Sedaghat-Herati, M.R.; Sharifi, T. *J. Organomet. Chem.* ***1989***, *363*, 39. For an excellent discussion of the whole question, see Banthorpe, D.V. *Chem. Rev.* ***1970***, *70*, 295, especially Sections VI and IX.

[30]For discussions, see Stock, L.M. *Prog. Phys. Org. Chem.* ***1976***, *12*, 21; Ridd, J.H. *Adv. Phys. Org. Chem.* ***1978***, *16*, 1.

For the reason given above and for other reasons, it is unlikely that the encounter complex is a π complex, but just what kind of attraction exists between Y^+ and ArH is not known, other than the presumption that they are together within a solvent cage (see also p. 682). There is evidence (from isomerizations occurring in the alkyl group, as well as other observations) that π complexes are present on the pathway from substrate to arenium ion in the gas-phase protonation of alkylbenzenes.[31]

The S_E1 Mechanism

The S_E1 mechanism (*substitution electrophilic unimolecular*) is rare, being found only in certain cases in which carbon is the leaving atom (see **11-33**, **11-35**) or when a very strong base is present (see **11-1**, **11-10**, and **11-39**).[32] It consists of two steps with an intermediate carbanion. The IUPAC designation is $D_E + A_E$.



Reactions **12-41**, **12-45**, and **12-46** also take place by this mechanism when applied to aryl substrates.

ORIENTATION AND REACTIVITY

Orientation and Reactivity in Monosubstituted Benzene Rings[33]

When an electrophilic substitution reaction is performed on a monosubstituted benzene, the new group may be directed primarily to the ortho, meta, or para position and the substitution may be slower or faster than with benzene itself. The group already on the ring determines which position the new group will take and whether the reaction will be slower or faster than with benzene. Groups that increase the reaction rate are called *activating* and those that slow it *deactivating*. Some groups are predominantly meta directing; all of these are deactivating. Others are mostly ortho-para directing; some of these are deactivating too, but most are activating. Groups direct *predominantly*, but usually not *exclusively*. For example, nitration of nitrobenzene gave 93% *m*-dinitrobenzene, 6% of the ortho, and 1% of the para isomer.

The orientation and reactivity effects are explained on the basis of resonance and field effects of each group on the stability of the intermediate arenium ion. To understand why we can use this approach, it is necessary to know that in these reactions

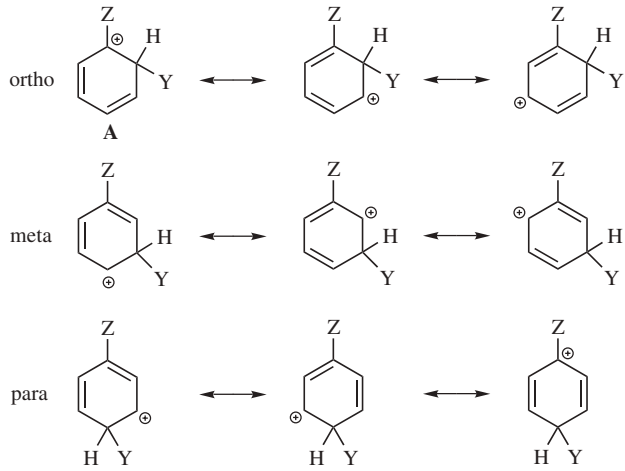
[31]Holman, R.W.; Gross, M.L. *J. Am. Chem. Soc.* ***1989***, *111*, 3560.

[32]It has also been found with a metal ($SnMe_3$) as electrofuge: Eaborn, C.; Hornfeld, H.L.; Walton, D.R.M. *J. Chem. Soc. B* ***1967***, 1036.

[33]For a review of orientation and reactivity in benzene and other aromatic rings, see Hoggett, J.G.; Moodie, R.B.; Penton, J.R.; Schofield, K. *Nitration and Aromatic Reactivity*, Cambridge University Press, Cambridge, ***1971***, pp. 122–145, 163–220.

the product is usually kinetically and not thermodynamically controlled (see p. 307). Some of the reactions are irreversible and the others are usually stopped well before equilibrium is reached. *Therefore, which of the three possible intermediates is formed is dependent not on the thermodynamic stability of the products, but on the activation energy necessary to form each of the three intermediates.* It is not easy to predict which of the three activation energies is lowest, but we make the assumption that the free-energy profile resembles either Fig. 6.2(*a* or *b*). In either case, the transition state is closer in energy to the arenium ion intermediate than to the starting compounds. Invoking the Hammond postulate (p. 308), we can then assume that the geometry of the transition state also resembles that of the intermediate and that anything that increases the stability of the intermediate will also lower the activation energy necessary to attain it. Since the intermediate, once formed, is rapidly converted to products, we can use the relative stabilities of the three intermediates as guides to predict which products will predominantly form. Of course, if reversible reactions are allowed to proceed to equilibrium, we may get product ratios that are quite different. For example, the sulfonation of naphthalene at 80°C, where the reaction does not reach equilibrium, gives mostly α-naphthalenesulfonic acid,[34] while at 160°C, where equilibrium is attained, the β isomer predominates[35] (the α isomer is thermodynamically less stable because of steric interaction between the SO_3H group and the hydrogen at the 8 position).

The three possible ions from incorporation of Y at the ortho, meta, and para positions are shown, and each arenium in obviously has a positive charge in the ring.



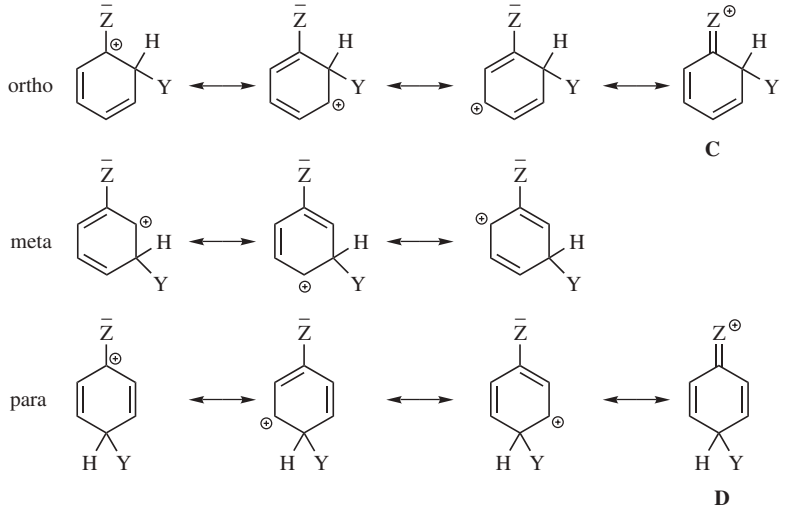
We can therefore predict that any group Z that has an electron-donating field effect (+*I*, Z will have a − charge or a δ− dipole in most cases) should stabilize all three

[34]Fierz, H.E.; Weissenbach, P. *Helv. Chim. Acta* ***1920***, *3*, 312.
[35]Witt, O.N. *Berchti* ***1915***, *48*, 743.

ions (relative to **1**), since electron donation to a positive center is stabilizing. On the other hand, electron-withdrawing groups ($-I$, Z will have a + charge or a $\delta+$ dipole in most cases) will increase the positive charge on the ring (like charges repel), and destabilize the arenium ion. Formation of a stabilized ion should be faster than benzene (which generates **1**), or activating, but formation of a destabilized ion should be slower, or deactivating. Such field effects should taper off with distance and are thus strongest at the carbon connected to the group Z (known as the ipso carbon). Of the three arenium ions, only the ortho and para have any positive charge at this carbon. None of the canonical forms of the meta ion has a positive charge at the ipso carbon. Therefore, $+I$ groups should stabilize all three ions but mostly the ortho and para, so they should be not only activating but ortho–para-directing as well. On the other hand, $-I$ groups, by removing electron density, should destabilize all three ions but mostly the ortho and para, and should be not only deactivating but also meta-directing.

These conclusions are correct as far as they go, but they do not lead to the proper results in all cases. In many cases, there is *resonance interaction* between Z and the ring; this also affects the relative stability, in some cases in the same direction as the field effect, in others differently.

Some substituents have a pair of electrons (usually unshared) that may be contributed *toward* the ring. The three arenium ions would then look like this:



C

D

For each ion the same three canonical forms can be drawn as before, but now we can draw an extra form for the ortho and para ions. The stability of these two ions is increased by the extra form not only because it is another canonical form, but because it is more stable than the others and makes a greater contribution to the hybrid. Every atom (except of course hydrogen) in these forms (**C** and **D**) has a complete octet, while all the other forms have one carbon atom with a sextet. No corresponding form can be drawn for the meta isomer. The inclusion of this form in

the hybrid lowers the energy not only because of rule 6 (p. 47), but also because it spreads the positive charge over a larger area—out onto the group Z. Groups with a pair of electrons (e.g., as the halogens) to contribute would be expected, then, in the absence of field effects, not only to direct ortho and para, but also to activate these positions for electrophilic attack.

On the basis of these discussions, we can distinguish three types of groups.

1. Groups that contain an unshared pair of electrons on the atom connected to the ring. In this category are O^-, NR_2, NHR, NH_2,[36] OH, OR, NHCOR, OCOR, SR, and the four halogens.[37] The halogens deactivate the aromatic ring to substitution (the rate of reaction is slower than that of benzene), and this effect may arise from the unique energy level of the halogen lone-pair orbital, which is higher than the adjacent π-molecular orbital of benzene (π_1).[38] The widely held explanation for this, however, is that the halogens have a $-I$ effect. The SH group would probably belong here too, except that in the case of thiophenols electrophiles usually attack the sulfur rather than the ring, and ring substitution is not feasible with these substrates. [39] The resonance explanation predicts that all these groups should be ortho–para directing, and they are, though all except O^- are electron withdrawing by the field effect (p. 20). Therefore, for these groups, resonance is more important than the field effect. This is especially true for NR_2, NHR, NH_2, and OH, which are *strongly* activating, as is O^-. The other groups are mildly activating, except for the halogens, which are deactivating. Fluorine is the least deactivating, and fluorobenzenes usually show a reactivity approximating that of benzene itself. The other three halogens deactivate about equally. In order to explain why chlorine, bromine, and iodine deactivate the ring, even though they direct ortho–para, we must assume that the canonical forms **C** and **D** make such great contributions to the respective hybrids that they make the ortho and para arenium ions more stable than the meta, even though the $-I$ effect of the halogen is withdrawing sufficient electron density from the ring to deactivate it. The three halogens make the ortho and para ions more stable than the meta, but less stable than the unsubstituted arenium ion (**1**). For the other groups that contain an unshared pair, the ortho and para ions are more stable than either the meta ion or the unsubstituted ion. For most of

[36]It must be remembered that in acid solution amines are converted to their conjugate acids, which for the most part are meta-directing (type 2). Therefore in acid (which is the most common medium for electrophilic substitutions) amino groups may direct meta. However, unless the solution is highly acidic, there will be a small amount of free amine present, and since amino groups are activating and the conjugate acids deactivating, ortho-para direction is often found even under acidic conditions.

[37]For a review of the directing and orienting effects of amino groups, see Chuchani, G., in Patai's. *The Chemistry of the Amino Group*, Wiley, NY, ***1968***, pp. 250–265; for ether groups see Kohnstam, G.; Williams, D.L.H., in Patai's. *The Chemistry of the Ether Linkage*, Wiley, NY, ***1967***, pp. 132–150.

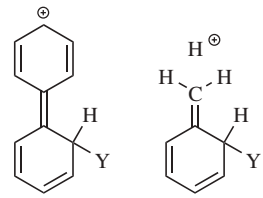
[38]Tomoda, S.; Takamatsu, K.; Iwaoka, M. *Chem. Lett.* ***1998***, 581.

[39]Tarbell, D.S.; Herz, A.H. *J. Am. Chem. Soc.* ***1953***, *75*, 4657. Ring substitution *is* possible if the SH group is protected. For a method of doing this, see Walker, D. *J. Org. Chem.* ***1966***, *31*, 835.

the groups in this category, the meta ion is more stable than **1**, so that groups, such as NH_2 and, OH, activate the meta positions too, but not as much as the ortho and para positions (see also the discussion on pp. 677–679).

2. Groups that lack an unshared pair on the atom connected to the ring and that are $-I$. In this category are, in approximate order of decreasing deactivating ability, NR_3^+, NO_2, CF_3,[40] CN, SO_3H, CHO, COR, COOH, COOR, $CONH_2$, CCl_3, and NH_3^+. Also in this category are all other groups with a positive charge on the atom directly connected to the ring[41] (SR_2^+, PR_3^+, etc.) and many groups with positive charges on atoms farther away, since often these are still powerful $-I$ groups. The field-effect explanation predicts that these should all be meta directing and deactivating, and (except for NH_3^+) this is the case. The NH_3^+ group is an anomaly, since this group directs para about as much as or a little more than it directs meta.[42] The NH_2Me^+, $NHMe_2^+$, and NMe_3^+ groups all give more meta than para substitution, the percentage of para product decreasing with the increasing number of methyl groups.[43]

3. Groups that lack an unshared pair on the atom connected to the ring and that are ortho–para directing. In this category are alkyl groups, aryl groups, and the COO^- group,[44] all of which activate the ring. We will discuss them separately. Since aryl groups are $-I$ groups, they might seem to belong to category 2. They are nevertheless ortho–para directing and activating. This can be explained in a similar manner as in category 1, with a pair of electrons from the aromatic sextet playing the part played by the unshared pair, so



E **F**

that we have forms like **E**. The effect of negatively charged groups like COO^- is easily explained by the field effect (negatively charged groups are of

[40]For the long-range electron-withdrawing effects of this group, see Castagnetti, E.; Schlosser, M. *Chem. Eur. J.* ***2002***, *8*, 799.

[41]For discussions, see Gastaminza, A.; Ridd, J.H.; Roy, F. *J. Chem. Soc. B* ***1969***, 684; Gilow, H.M.; De Shazo, M.; Van Cleave, W.C. *J. Org. Chem.* ***1971***, *36*, 1745; Hoggett, J.G.; Moodie, R.B.; Penton, J.R.; Schofield, K. *Nitration and Aromatic Reactivity*, Cambridge University Press, Cambridge, ***1971***, pp. 167–176.

[42]Hartshorn, S.R.; Ridd, J.H. *J. Chem. Soc. B* ***1968***, 1063. For a discussion, see Ridd, J.H., in *Aromaticity, Chem. Soc. Spec. Publ., no. 21*, ***1967***, 149–162.

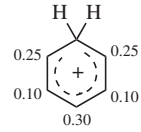
[43]Brickman, M.; Utley, J.H.P.; Ridd, J.H. *J. Chem. Soc.* ***1965***, 6851.

[44]Spryskov, A.A.; Golubkin, L.N. *J. Gen. Chem. USSR* ***1961***, *31*, 833. Since the COO^- group is present only in alkaline solution, where electrophilic substitution is not often done, it is seldom met with.

course electron donating), since there is no resonance interaction between the group and the ring. The effect of alkyl groups can be explained in the same way, but, in addition, we can also draw canonical forms, even though there is no unshared pair. These of course are hyperconjugation forms like **F** (see p. 669). This effect, like the field effect, predicts activation and ortho–para direction, so that it is not possible to say how much each effect contributes to the result. Another way of looking at the effect of alkyl groups (which sums up both field and hyperconjugation effects) is that (for Z = R) the ortho and para arenium ions are more stable because each contains a form (**A** and **B**) that is a tertiary carbocation, while all the canonical forms for the meta ion and for **1** are secondary carbocations. In activating ability, alkyl groups usually follow the Baker–Nathan order (p. 96), but not always.[45]

The Ortho/Para Ratio[46]

When an ortho–para-directing group is on a ring, it is usually difficult to predict how much of the product will be the ortho isomer and how much the para isomer. Indeed, these proportions can depend greatly on the reaction conditions. For example, chlorination of toluene gives an ortho/para ratio anywhere from 62:38 to 34:66.[47] Nevertheless, certain points can be made. On a purely statistical basis there would be 67% ortho and 33% para, since there are two ortho positions and only one para. However, the phenonium ion



12

12, which arises from protonation of benzene, has the approximate charge distribution shown[48] (see **13** as well). If we accept this as a model for the arenium ion in aromatic substitution, a para substituent would have a greater stabilizing effect on the adjacent carbon than an ortho substituent. If other effects are absent, this would mean that >33% para and <67% ortho substitution would be found. In hydrogen exchange (reaction **11-1**), where other effects are absent, it has been found for a number of substituents that the average ratio of the logarithms of the partial rate

[45]For examples of situations where the Baker–Nathan order is not followed, see Eaborn, C.; Taylor, R. *J. Chem. Soc.* ***1961***, 247; Utley, J.H.P.; Vaughan, T.A. *J. Chem. Soc. B* ***1968***, 196; Schubert, W.M.; Gurka, D.F. *J. Am. Chem. Soc.* ***1969***, *91*, 1443; Himoe, A.; Stock, L.M. *J. Am. Chem. Soc.* ***1969***, *91*, 1452.

[46]For a discussion, see Pearson, D.E.; Buehler, C.A. *Synthesis* ***1971***, 455 see pp 455–464. For a discussion of the influence of reaction conditions on the ortho/para ratio, see Effenberger, F.; Maier, A.J. *J. Am. Chem. Soc.* ***2001***, *123*, 3429.

[47]Stock, L.M.; Himoe, A. *J. Am. Chem. Soc.* ***1961***, *83*, 4605.

[48]Olah, G.A. *Acc. Chem. Res.* ***1970***, *4*, 240, p. 248.

factors for these positions (see p. 677 for a definition of partial rate factor) was close to 0.865,[49] which is not far from the value predicted from the ratio of charge densities in **12**. This picture is further supported by the fact that meta-directing groups, which destabilize a positive charge, give ortho/para ratios >67:33[50] (of course the total amount of ortho and para substitution with these groups is small, but the *ratios* are generally >67:33). Another important factor is the steric effect. If either the group on the attacking ring or the group on the electrophile is large, steric hindrance inhibits formation of the ortho product and increases the amount of the para isomer. An example may be seen in the nitration, under the same conditions, of toluene and *tert*-butylbenzene. The former gave 58% of the ortho compound and 37% of the para, while the more bulky *tert*-butyl group gave 16% of the ortho product and 73% of the para.[51] Some groups are so large that they direct almost entirely para.

When the ortho–para-directing group is one with an unshared pair (this of course applies to most of them), there is another effect that increases the amount of para product at the expense of the ortho. A comparison of the intermediates involved (p. 667) shows that **C** is a canonical form with an ortho-quinoid structure, while **D** has a para-quinoid structure. Since we know that para-quinones are more stable than the ortho isomers, it seems reasonable to assume that **D** is more stable than **C**, and therefore contributes more to the hybrid and increases its stability compared to the ortho intermediate.

It has been shown that it is possible to compel regiospecific para substitution by enclosing the substrate molecules in a cavity from which only the para position projects. Anisole was chlorinated in solutions containing a cyclodextrin, a molecule in which the anisole is almost entirely enclosed (see Fig. 3.4). With a high enough concentration of cyclodextrin, it was possible to achieve a para/ortho ratio of 21.6[52] (in the absence of the cyclodextrin the ratio was only 1.48). This behavior is a model for the regioselectivity found in the action of enzymes.

Ipso Attack

We have discussed orientation in the case of monosubstituted benzenes entirely in terms of attachment at the ortho, meta, and para positions, but attachment at the

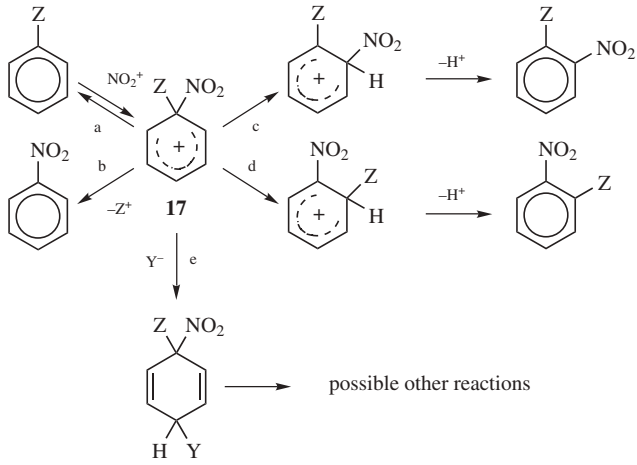
[49]Ansell, H.V.; Le Guen, J.; Taylor, R. *Tetrahedron Lett.* ***1973***, 13.

[50]Hoggett, J.G.; Moodie, R.B.; Penton, J.R.; Schofield, K. *Nitration and Aromatic Reactivity*, Cambridge University Press, Cambridge, ***1971***, pp. 176–180.

[51]Nelson, K.L.; Brown, H.C. *J. Am. Chem. Soc.* ***1951***, *73*, 5605. For product ratios in the nitration of many monoalkylbenzenes, see Baas, J.M.A.; Wepster, B.M. *Recl. Trav. Chim. Pays-Bas* ***1971***, *90*, 1081, 1089;111 ***1972***, *91*, 285, 517, 831.

[52]Breslow, R.; Campbell, P. *J. Am. Chem. Soc.* ***1969***, *91*, 3085; *Bioorg. Chem.* ***1971***, *1*, 140. See also Chen, N.Y.; Kaeding, W.W.; Dwyer, F.G. *J. Am. Chem. Soc.* ***1979***, *101*, 6783; Konishi, H.; Yokota, K.; Ichihashi, Y.; Okano, T.; Kiji, J. *Chem. Lett.* ***1980***, 1423; Komiyama, M.; Hirai, H. *J. Am. Chem. Soc.* ***1983***, *105*, 2018; ***1984***, *106*, 174; Chênevert, R.; Ampleman, G. *Can. J. Chem.* ***1987***, *65*, 307; Komiyama, M. *Polym. J. (Tokyo)* ***1988***, *20*, 439.

position bearing the substituent (called the *ipso position*[53]) can also be important. Ipso attack has mostly been studied for nitration.[54] When attack of NO_2^+ leads to incorporation at the ipso position there are at least five possible fates for the resulting arenium ion (**17**).



Path a. The arenium ion can lose NO_2^+ and revert to the starting compounds. This results in no net reaction and is often undetectable.

Path b. The arenium ion can lose Z^+, in which case this is simply aromatic substitution with a leaving group other than H (see **11-33–11-41**).

Path c. The electrophilic group (in this case NO_2^+) can undergo a 1,2-migration, followed by loss of the proton. The product in this case is the same as that obtained by direct attachment of NO_2^+ at the ortho position of PhZ. It is not always easy to tell how much of the ortho product in any individual case arises from this pathway,[55] though there is evidence that it can be a considerable proportion. Because of this possibility, many of the reported conclusions about the relat‘ive reactivity of the ortho, meta, and para positions are cast into doubt, since some of the product may have arisen not from direct attachment at the ortho position, but from attachment at the ipso position followed by rearrangement.[56]

Path d. The ipso substituent (Z) can undergo 1,2-migration, which also produces the ortho product (though the rearrangement would become apparent if there

[53]Perrin, C.L.; Skinner, G.A. *J. Am. Chem. Soc.* ***1971***, *93*, 3389. For a review of ipso substitution, see Traynham, J.G. *J. Chem. Educ.* ***1983***, *60*, 937.

[54]For a review, see Moodie, R.B.; Schofield, K. *Acc. Chem. Res.* ***1976***, *9*, 287. See also, Fischer, A.; Henderson, G.N.; RayMahasay, S. *Can. J. Chem.* ***1987***, *65*, 1233, and other papers in this series.

[55]For methods of doing so, see Gibbs, H.W.; Moodie, R.B.; Schofield, K. *J. Chem. Soc. Perkin Trans. 2* ***1978***, 1145.

[56]This was first pointed out by Myhre, P.C. *J. Am. Chem. Soc.* ***1972***, *94*, 7921.

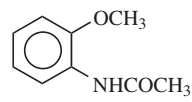
were other substituents present). The evidence is that this pathway is very minor, at least when the electrophile is NO_2^+.[57]

Path e. Attack of a nucleophile on **17**. In some cases, the products of such an attack (cyclohexadienes) have been isolated[58] (this is 1,4-addition to the aromatic ring), but further reactions are also possible.

Orientation in Benzene Rings With More Than One Substituent[59]

It is often possible in these cases to predict the correct isomer. In many cases, the groups already on the ring reinforce each other. Thus, 1,3-dimethylbenzene is substituted at the 4 position (ortho to one group and para to the other), but not at the 5 position (meta to both). Likewise, the incoming group in *p*-chlorobenzoic acid goes to the position ortho to the chloro and meta to the carboxyl group.

When the groups oppose each other, predictions may be more difficult. In a case such as where two



groups of about equal directing ability are in competing positions, all four products can be expected, and it is not easy to predict the proportions, except that steric hindrance should probably reduce the yield of substitution ortho to the acetamido group, especially for large electrophiles. Mixtures of about equal proportions are frequent in such cases. Nevertheless, even when groups on a ring oppose each other, there are some regularities.

1. If a strong activating group competes with a weaker one or with a deactivating group, the former controls. Thus *o*-cresol gives substitution mainly ortho and para to the *hydroxyl* group and not to the methyl. For this purpose we can arrange the groups in the following order: NH_2, OH, NR_2, O^- > OR, OCOR, NHCOR > R, Ar > halogen > meta-directing groups.

2. All other things being equal, a third group is least likely to enter between two groups in the meta relationship. This is the result of steric hindrance and increases in importance with the size of the groups on the ring and with the size of the attacking species.[60]

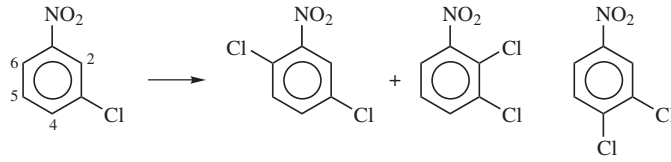
[57]For examples of such migration, where Z = Me, see Hartshorn, M.P.; Readman, J.M.; Robinson, W.T.; Sies, C.W.; Wright, G.J. *Aust. J. Chem.* ***1988***, *41*, 373.

[58]For examples, see Banwell, T.; Morse, C.S.; Myhre, P.C.; Vollmar, A. *J. Am. Chem. Soc.* ***1977***, *99*, 3042; Fischer, A.; Greig, C.C. *Can. J. Chem.* ***1978***, *56*, 1063.

[59]For a quantitative discussion, see pp. 677–678.

[60]In some cases, attack at an electrophile preferentially leads to attachment at the position between two groups in the meta relationship. For a list of some of these cases and a theory to explain them, see Kruse, L.I.; Cha, J.K. *J. Chem. Soc., Chem. Commun.* ***1982***, 1333.

3. When a meta-directing group is meta to an ortho–para-directing group, the incoming group primarily goes ortho to the meta-directing group rather than para. For example, chlorination of **18** gives mostly **19**.



18 **19** **20** **21**

The importance of this effect is underscored by the fact that **20**, which is in violation of the preceding rule, is formed in smaller amounts, but **21** is not formed at all. This is called the *ortho effect*,[61] and many such examples are known.[62] Another is the nitration of *p*-bromotoluene, which gives 2,3-dinitro-4-bromotoluene. In this case, once the first nitro group came in, the second was directed ortho to it rather than para, even though this means that the group has to come in between two groups in the meta position. There is no good explanation yet for the ortho effect, though possibly there is intramolecular assistance from the meta-directing group.

It is interesting that chlorination of **18** illustrates all three rules. Of the four positions open to the electrophile, the 5 position violates rule 1, the 2 position rule 2, and the 4 position rule 3. The principal attachment is therefore at position 6.

Orientation in Other Ring Systems[63]

In fused ring systems, the positions are not equivalent and there is usually a preferred orientation, even in the unsubstituted hydrocarbon. The preferred positions may often be predicted as for benzene rings. Thus it is possible to draw more canonical forms for the arenium ion when attack by naphthalene leads to attachment of the electrophile at the α position than when attack by naphthalene leads to attachment of the electrophile at the β position. Therefore, the α position is the preferred site of attachment,[64] though, as previously mentioned (p. 666), the isomer formed by substitution at the β-position is thermodynamically more stable and is the product if the reaction is reversible and equilibrium is reached. Because of the more extensive delocalization of charges in the corresponding arenium ions, naphthalene is more reactive than benzene and substitution is faster at both positions. Similarly,

[61]This is not the same as the ortho effect mentioned on p. 412.

[62]See Hammond, G.S.; Hawthorne, M.F., in Newman, M.S. *Steric Effects in Organic Chemistry*, Wiley, NY, ***1956***, pp. 164–200, 178–182.

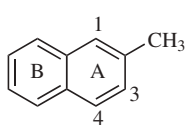
[63]For a review of substitution on nonbenzenoid aromatic systems, see Hafner, H.; Moritz, K.L., in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 4, Wiley, NY, ***1965***, pp. 127–183. For a review of aromatic substitution on ferrocenes, see Bublitz, D.E.; Rinehart Jr., K.L. *Org. React.* ***1969***, *17*, 1.

[64]For a discussion on the preferred site of attachment for many ring systems, see de la Mare, P.B.D.; Ridd, J.H. *Aromatic Substitution Nitration and Halogenation*, Academic Press, NY, ***1959***, pp. 169–209.

anthracene, phenanthrene, and other fused polycyclic aromatic hydrocarbons are also substituted faster than benzene.

Heterocyclic compounds, too, have nonequivalent positions, and the principles are similar,[65] in terms of mechanism, and rate data is available.[66] Furan, thiophene, and pyrrole are chiefly substituted at the 2 position, and all are substituted faster than benzene.[67] Pyrrole is particularly reactive, with a reactivity approximating that of aniline or the phenoxide ion. For pyridine,[68] it is not the free base that must attack the electrophile, but the conjugate acid (the pyridinium ion),[69] making the reactivity much less than that of benzene, being similar to that of nitrobenzene. The 3 position is most reactive in electrophilic substitution reactions of pyridine. However, groups can be introduced into the 4 position of a pyridine ring indirectly, by performing the reaction on the corresponding pyridine *N*-oxide.[70] Note that calculations show that the 2-pyridyl and 2-pyrimidyl cations are best represented as *ortho*-hetarynium ions, being more stable than their positional, nonconjugated isomers by as much as 18–28 kcal mol^{-1} (75-11) kJ mol^{-1}.[71]

When fused ring systems contain substituents, successful predictions can often be made by using a combination of the above principles. Thus, ring A of 2-methylnaphthalene (**22**) is activated by the methyl



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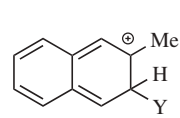
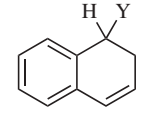


23



24

group; ring B is not (though the presence of a substituent in a fused ring system affects all the rings,[72] the effect is generally greatest on the ring to which it is attached). We therefore expect substitution in ring A. The methyl group activates positions 1 and 3, which are ortho to itself, but not position 4, which is meta to it.

[65]For a monograph, see Katritzky, A.R.; Taylor, R. *Electrophilic Substitution of Heterocycles: Quantitative Aspects* (Vol. 47 of *Adv. Heterocycl. Chem.*), Academic Press, NY, ***1990***.

[66]Katritzky, A.R.; Fan, W.-Q. *Heterocycles* ***1992***, *34*, 2179.

[67]For a review of electrophilic substitution on five-membered aromatic heterocycles, see Marino, G. *Adv. Heterocycl. Chem.* ***1971***, *13*, 235.

[68]For reviews of substitution on pyridines and other six-membered nitrogen-containing aromatic rings, see Comins, D.L.; O'Connor, S. *Adv. Heterocycl. Chem.* ***1988***, *44*, 199; Aksel'rod, Zh.I.; Berezovskii, V.M. *Russ. Chem. Rev.* ***1970***, *39*, 627; Katritzky, A.R.; Johnson, C.D. *Angew. Chem. Int. Ed.* ***1967***, *6*, 608; Abramovitch, R.A.; Saha, J.G. *Adv. Heterocycl. Chem.* ***1966***, *6*, 229. For a review of methods of synthesizing 3-substituted pyrroles, see Anderson, H.J.; Loader, C.E. *Synthesis* ***1985***, 353.

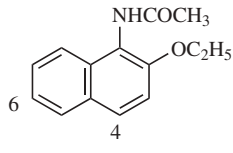
[69]Olah, G.A.; Olah, J.A.; Overchuk, N.A. *J. Org. Chem.* ***1965***, *30*, 3373; Katritzky, A.R.; Kingsland, M. *J. Chem. Soc. B* ***1968***, 862.

[70]Jaffé, H.H. *J. Am. Chem. Soc.* ***1954***, *76*, 3527.

[71]Gozzo, F.C.; Eberlin, M.N. *J. Org. Chem.* ***1999***, *64*, 2188.

[72]See, for example, Ansell, H.V.; Sheppard, P.J.; Simpson, C.F.; Stroud, M.A.; Taylor, R. *J. Chem. Soc. Perkin Trans. 2* ***1979***, 381.

However, substitution at the 3 position gives rise to an arenium ion for which it is impossible to write a low-energy canonical form in which ring B has a complete sextet. All we can write are forms like **23**, in which the sextet is no longer intact. In contrast, substitution at the 1 position gives rise to a more stable arenium ion, for which two canonical forms (one of them is **24**) can be written in which ring B is benzenoid. We thus predict predominant substitution at C-1, and that is what is generally found.[73] However, in some cases predictions are much harder to make. For example, chlorination or nitration of **25** gives mainly the 4 derivative, but bromination yields chiefly the 6 compound.[74]



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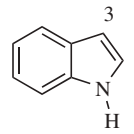
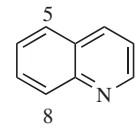
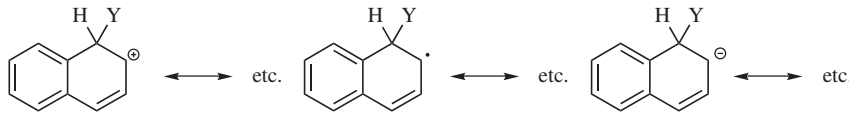


Indole



Quinoline

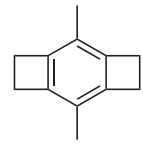
For fused heterocyclic systems too, we can often make predictions based on the above principles, though many exceptions are known. Thus, indole is chiefly substituted in the pyrrole ring (at position 3) and reacts faster than benzene, while quinoline generally reacts in the benzene ring, at the 5 and 8 positions, and slower than benzene, though faster than pyridine.



24 **26** **27**

In alternant hydrocarbons (p. 69), the reactivity at a given position is similar for electrophilic, nucleophilic, and free-radical substitution, because the same kind of resonance can be shown in all three types of intermediate (cf. **24**, **26**, and **27**). Attachment of the electrophile at the position that will best delocalize a positive charge will also best delocalize a negative charge or an unpaired electron. Most results are in accord with these predictions. For example, naphthalene is attacked primarily at the 1 position by NO_2^+, NH_2-, and Ph•, and always more readily than benzene.

[73]For example, see Alcorn, P.G.E.; Wells, P.R. *Aust. J. Chem.* ***1965***, *18*, 1377, 1391; Eaborn, C.; Golborn, P.; Spillett, R.E.; Taylor, R. *J. Chem. Soc. B* ***1968***, 1112; Kim, J.B.; Chen, C.; Krieger, J.K.; Judd, K.R.; Simpson, C.C.; Berliner, E. *J. Am. Chem. Soc.* ***1970***, *92*, 910. For discussions, see Taylor, R. *Chimia* ***1968***, *22*, 1; Gore, P.H.; Siddiquei, A.S.; Thorburn, S. *J. Chem. Soc. Perkin Trans. 1* ***1972***, 1781.
[74]Bell, F. *J. Chem. Soc.* ***1959***, 519.

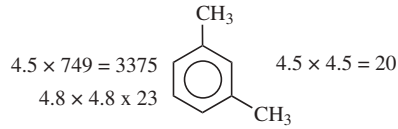


28

When strain due to a ring fused on an aromatic ring deforms that ring out of planarity, the molecule is more reactive to electrophilic aromatic substitution.[75] This has been explained by the presence of a shortened bond for the sp^2 hybridized carbon, increasing the strain at that position, and this is known as the *Mills–Nixon effect*.[76] There is EPR evidence (see p. 267) for 3,6-dimethyl-1,2,4,5-tetrahydrobenzo-bis (cyclobutene) (**28**) that supports the Mills–Nixon effect,[77] and a theoretical study supports this.[78] However, *ab initio* studies of triannelated benzene rings shows *no evidence* for the Mills–Nixon effect, and an new motif for bond-alternating benzenes was proposed.[79] Indeed, it is argued that the Mills–Nixon effect is not real.[80]

Quantitative Treatments of Reactivity in the Substrate

Quantitative rate studies of aromatic substitutions are complicated by the fact that there are usually several hydrogens that can leave, so that measurements of overall rate ratios do not give a complete picture as they do in nucleophilic substitutions, where it is easy to compare substrates that have only one possible leaving group in a molecule. What is needed is not, say, the overall rate ratio for acetylation of toluene versus that for benzene, but the *rate ratio at each position*. These can be calculated from the overall rates and a careful determination of the proportion of isomers formed, provided that the products are kinetically controlled, as is usually the case. We may thus define the *partial rate factor* for a given group and a given reaction as the rate of substitution at a single position relative to a single position in benzene. For example, for acetylation



of toluene the partial rate factors are: for the ortho position $o_f^{Me} = 4.5$, for the meta $m_f^{Me} = 4.8$, and for the para $p_f^{Me} = 749$.[81] This means that toluene is acetylated at

[75]Taylor, R. *Electrophilic Aromatic Substitution*, Wiley, Chichester, ***1990***, pp. 53.
[76]Mills, W.H.; Nixon, I.G. *J. Chem. Soc.* ***1930***, 2510.
[77]Davies, A.G.; Ng, K.M. *J. Chem. Soc. Perkin Trans. 2* ***1992***, 1857.
[78]Eckert-Maksić, M.; Maksić, Z.B.; Klessinger, M. *J. Chem. Soc. Perkin Trans. 2* ***1994***, 285; Eckert-Maksić, M.; Lesar, A.; Maksić, Z.B. *J. Chem. Soc. Perkin Trans. 2* ***1992***, 993.
[79]Baldridge, K.K.; Siegel, J.J. *J. Am. Chem. Soc.* ***1992***, *114*, 9583.
[80]Siegel, J.S. *Angew. Chem. Int. Ed.* ***1994***, *33*, 1721.
[81]Brown, H.C.; Marino, G.; Stock, L.M. *J. Am. Chem. Soc.* ***1959***, *81*, 3310.

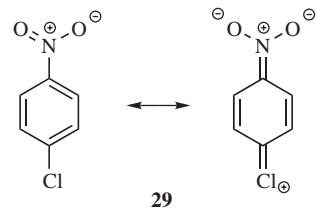
the ortho position 4.5 times as fast as a single position in benzene, or 0.75 times as fast as the overall rate of acetylation of benzene. A partial rate factor >1 for a given position indicates that the group in question activates that position for the given reaction. Partial rate factors differ from one reaction to another and are even different, though less so, for the same reaction under different conditions.

Once we know the partial rate factors, we can predict the proportions of isomers to be obtained when two or more groups are present on a ring, *if we make the assumption that the effect of substituents is independent*. For example, if the two methyl groups in *m*-xylene have the same effect as the methyl group in toluene, we can calculate the theoretical partial rate factors at each position by multiplying those from toluene, so they should be as indicated:

TABLE 11.2. Calculated and Experimental Isomer Distributions in the Acetylation of *m*-Xylene[81]

	Isomer Distribution, %	
Position	Calculated	Observed
2	0.30	0
4	9.36	97.5
5	0.34	2.5

From this, it is possible to calculate the overall theoretical rate ratio for acetylation of *m*-xylene relative to benzene, since this is one-sixth the sum of the partial rate factors (in this case 1130), and the isomer distribution if the reaction is kinetically controlled. The overall rate ratio actually is 347[82] and the calculated and observed isomer distributions are listed in Table 11.2.[76] In this case, and in many others, agreement is fairly good, but many cases are known where the effects are not additive (as on p. 671).[83] For example, this treatment predicts that for 1,2,3-trimethylbenzene



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[82]Marino, G.; Brown, H.C. *J. Am. Chem. Soc.* ***1959***, *81*, 5929.

[83]For some examples where additivity fails, see Fischer, A.; Vaughan, J.; Wright, G.J. *J. Chem. Soc. B* ***1967***, 368; Coombes, R.G.; Crout, D.H.G.; Hoggett, J.G.; Moodie, R.B.; Schofield, K. *J. Chem. Soc. B* ***1970***, 347; Richards, K.E.; Wilkinson, A.L.; Wright, G.J. *Aust. J. Chem.* ***1972***, *25*, 2369; Cook, R.S.; Phillips, R.; Ridd, J.H. *J. Chem. Soc. Perkin Trans. 2* ***1974***, 1166. For a theoretical treatment of why additivity fails, see Godfrey, M. *J. Chem. Soc. B* ***1971***, 1545.

there should be 35% 5 substitution and 65% 4 substitution, but acetylation gave 79% 5 substitution and 21% of the 4 isomer. The treatment is thrown off by steric effects, such as those mentioned earlier (p. 673), by-products arising from ipso attack (p. 671) and by resonance interaction *between* groups (e.g., **29**), which must make the results deviate from simple additivity of the effects of the groups.

Another approach that avoids the problem created by having competing leaving groups present in the same substrate is the use of substrates that contain only one leaving group. This is most easily accomplished by the use of a leaving group other than hydrogen. By this means overall rate ratios can be measured for specific positions.[84] Results obtained in this way[85] give a reactivity order quite consistent with that for hydrogen as leaving group.

A quantitative scale of reactivity for aromatic substrates (fused, heterocyclic, and substituted rings) has been devised, based on the hard–soft acid–base concept (p. 375).[86] From molecular-orbital theory, a quantity called *activation hardness* can be calculated for each position of an aromatic ring. The smaller the activation hardness, the faster the attachment at that position; hence the treatment predicts the most likely orientations for incoming groups.

A Quantitative Treatment of Reactivity of the Electrophile: The Selectivity Relationship

Not all electrophiles are equally powerful. The nitronium ion attacks not only benzene but also aromatic rings that contain a strongly deactivating group. On the other hand, diazonium ions couple only with rings containing a powerful activating group. Attempts have been made to correlate the influence of substituents with the power of the attacking group. The most obvious way to do this is with the Hammett equation (p. 392):

$$\log \frac{k}{k_0} = \rho\,\sigma$$

For aromatic substitution,[87] k_0 is divided by 6 and, for meta substitution, k is divided by 2, so that comparisons are made for only one position (consequently, k/k_0 for, say, the methyl group at a para position is identical to the partial rate factor p_f^{Me}). It was soon found that, while this approach worked fairly well for electron-withdrawing groups, it failed for those that are electron donating. However, if the equation is modified by the insertion of the Brown σ^+ values instead of the Hammett σ values (because a positive charge develops during the transition state), more satisfactory correlations can be made, even for electron-donating groups (see Table 9.4

[84]For a review of aryl-silicon and Related cleavages, see Eaborn, C. *J. Organomet. Chem.* ***1975***, *100*, 43.
[85]See, for example, Deans, F.B.; Eaborn, C. *J. Chem. Soc.* ***1959***, 2299; Eaborn, C.; Jackson, P.M. *J. Chem. Soc. B* **1969**, 21.
[86]Zhou, Z.; Parr, R.G. *J. Am. Chem. Soc.* ***1990***, *112*, 5720.
[87]See Exner, O.; Böhm, S. *J. Org. Chem.* ***2002***, *67*, 6320.

TABLE 11.3. Relative Rates and Product Distributions in Some Electrophilic Substitutions on Toluene and Benzene[89]

Reaction	Relative Rate $k_{toluene}/k_{benzene}$	Product Distribution, %	
		m	*p*
Bromination	605	0.3	66.8
Chlorination	350	0.5	39.7
Benzoylation	110	1.5	89.3
Nitration	23	2.8	33.9
Mercuration	7.9	9.5	69.5
Isopropylation	1.8	25.9	46.2

for a list of σ^+ values).[88] Groups with a negative value of σ_p^+ or σ_m^+ are activating for that position; groups with a positive value are deactivating. The ρ values correspond to the susceptibility of the reaction to stabilization or destabilization by the Z group and to the reactivity of the electrophile. The ρ values vary not only with the electrophile, but also with conditions. A large negative value of ρ means an electrophile of relatively low reactivity. Of course, this approach is completely useless for ortho substitution, since the Hammett equation does not apply there.

A modification of the Hammett approach, suggested by Brown, called the *selectivity relationship*,[89] is based on the principle that reactivity of a species varies inversely with selectivity. Table 11.3 shows how electrophiles can be arranged in order of selectivity as measured by two indexes: (*1*) their selectivity in attacking toluene rather than benzene, and (*2*) their selectivity between the meta and para positions in toluene.[90] As the table shows, an electrophile more selective in one respect is also more selective in the other. In many cases, electrophiles known to be more stable (hence less reactive) than others show a higher selectivity, as would be expected. For example, the *tert*-butyl cation is more stable and more selective than the isopropyl (p. 236), and Br_2 is more selective than Br^+. However, deviations from the relationship are known.[91] Selectivity depends not only on the nature of the electrophile but also on the temperature. As expected, it normally decreases with increasing temperature.

Brown assumed that a good measurement of selectivity was the ratio of the para and meta partial rate factors in toluene. He defined the selectivity S_f of a reaction as

$$S_f = \log \frac{p_f^{Me}}{m_f^{Me}}$$

[88]For a discussion of the limitations of the Hammett equation approach, see Koptyug, V.A.; Salakhutdinov, N.F.; Detsina, A.N. *J. Org. Chem. USSR* ***1984***, *20*, 1039.
[89]Stock, L.M.; Brown, H.C. *Adv. Phys. Org. Chem.* ***1963***, *1*, 35.
[90]Stock, L.M.; Brown, H.C. *Adv. Phys. Org. Chem.* ***1963***, *1*, 35, see p. 45.
[91]At least some of these may arise from migration of groups already on the ring; see Olah, G.A.; Olah, J.A.; Ohyama, T. *J. Am. Chem. Soc.* ***1984***, *106*, 5284.

That is, the more reactive an attacking species, the less preference it has for the para position compared to the meta. If we combine the Hammett–Brown $\sigma^+\rho$ relationship with the linearity between log S_f and log p_f^{Me} and between log S_f and log m_f^{Me}, it is possible to derive the following expressions:

$$\log p_f^{Me} = \frac{\sigma_p^+}{\sigma_p^+ - \sigma_m} S_f$$

$$\log m_f^{Me} = \frac{\sigma_m^+}{\sigma_p^+ - \sigma_m^+} S_f$$

S_f is related to ρ by

$$S_f = \rho(\sigma_p^+ - \sigma_m^+)$$

The general validity of these equations is supported by a great deal of experimental data on aromatic substitution reactions of toluene. Examples of values for some reactions obtained from these equations are given in Table 11.4.[92] For other substituents, the treatment works well with groups that, like methyl, are not very polarizable. For more polarizable groups the correlations are sometimes satisfactory and sometimes not, probably because each electrophile in the transition state makes a different demand on the electrons of the substituent group.

Not only are there substrates for which the treatment is poor, but it also fails with very powerful electrophiles; this is why it is necessary to postulate the encounter complex mentioned on p. 664. For example, relative rates of nitration of *p*-xylene, 1,2,4-trimethylbenzene, and 1,2,3,5-tetramethylbenzene were 1.0, 3.7, and 6.4,[93] though the extra methyl groups should enhance the rates much more (*p*-xylene itself reacted 295 times faster than benzene). The explanation is that with powerful electrophiles the reaction rate is so rapid (reaction taking place at virtually every

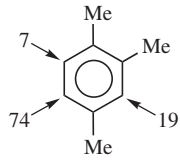
TABLE 11.4. Values of m_f^{Me}, p_f^{Me}, S_f, and ρ for Three Reactions of Toluene[92]

Reaction	m_f^{Me}	p_f^{Me}	S_f	ρ
PhMe + EtBr $\xrightarrow[\text{benzene, } 25^\circ\text{C}]{GaBr_3}$	1.56	6.02	0.587	−2.66
PhMe + HNO_3 $\xrightarrow[45^\circ\text{C}]{90\%\ HOAc}$	2.5	58	1.366	−6.04
PhMe + BR_2 $\xrightarrow[25^\circ\text{C}]{85\%\ HOAc}$	5.5	2420	2.644	−11.40

[92]Stock, L.M.; Brown, H.C. *J. Am. Chem. Soc.* ***1959***, *81*, 3323. Stock, L.M.; Brown, H.C. *Adv. Phys. Org. Chem.* ***1963***, *1*, 35 presents many tables of these kinds of data. See also, DeHaan, F.P.; Chan, W.H.; Chang, J.; Ferrara, D.M.; Wainschel, L.A. *J. Org. Chem.* ***1986***, *51*, 1591, and other papers in this series.
[93]Olah, G.A.; Lin, H.C. *J. Am. Chem. Soc.* ***1974***, *96*, 2892.

encounter[94] between an electrophile and substrate molecule)[95] that the presence of additional activating groups can no longer increase the rate.[96]

Given this behavior (little selectivity in distinguishing between different substrate molecules), the selectivity relationship would predict that positional selectivity should also be very small. However, it is not. For example, under conditions where nitration of *p*-xylene and 1,2,4-trimethylbenzene takes place at about equal rates, there was no corresponding lack of selectivity at positions *within* the latter.[97] Though



Relative rate ratios

steric effects are about the same at both positions, >10 times as much 5-nitro product was formed as 6-nitro product. It is clear that the selectivity relationship has broken down and it becomes necessary to explain why such an extremely rapid reaction should occur with positional selectivity. The explanation offered is that the rate-determining step is formation of an encounter complex (**12**, p. 664).[98] Since the position of attachment is not determined in the rate-determining step, the 5:6 ratio is not related to the reaction rate. Essentially the same idea was suggested earlier[99] and for the same reason (failure of the selectivity relationship in some cases), but the earlier explanation specifically pictured the complex as a π complex, and we have seen (p. 664) that there is evidence against this.

One interesting proposal[100] is that the encounter pair is a radical pair $\overline{\text{NO}_2\bullet\text{ArH}\bullet^+}$ formed by an electron transfer (SET), which would explain why the electrophile, once in the encounter complex, can acquire the selectivity that the free NO_2^+ lacked (it is not proposed that a radical pair is present in all aromatic substitutions; only in those that do not obey the selectivity relationship). The radical

[94]See Coombes, R.G.; Moodie, R.B.; Schofield, K. *J. Chem. Soc. B* ***1968***, 800; Moodie, R.B.; Schofield, K.; Thomas, P.N. *J. Chem. Soc. Perkin Trans. 2* ***1978***, 318.

[95]For a review of diffusion control in electrophilic aromatic substitution, see Ridd, J.H. *Adv. Phys. Org. Chem.* ***1978***, *16*, 1.

[96]Coombes, R.G.; Moodie, R.B.; Schofield, K. *J. Chem. Soc. B* ***1968***, 800; Hoggett, J.G.; Moodie, R.B.; Schofield, K. *J. Chem. Soc. B* ***1969***, 1; Manglik, A.K.; Moodie, R.B.; Schofield, K.; Dedeoglu, E.; Dutly, A.; Rys, P. *J. Chem. Soc. Perkin Trans. 2* ***1981***, 1358.

[97]Barnett, J.W.; Moodie, R.B.; Schofield, K.; Taylor, P.G.; Weston, J.B. *J. Chem. Soc. Perkin Trans. 2* ***1979***, 747.

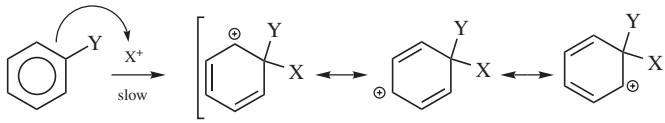
[98]For kinetic evidence in favor of encounter complexes, see Sheats, G.F.; Strachan, A.N. *Can. J. Chem.* ***1978***, *56*, 1280. For evidence for such complexes in the gas phase, see Attinà, M.; Cacace, F.; de Petris, G. *Angew. Chem. Int. Ed.* ***1987***, *26*, 1177.

[99]Olah, G.A. *Acc. Chem. Res.* ***1971***, *4*, 240.

[100]Perrin, C.L. *J. Am. Chem. Soc.* ***1977***, *99*, 5516.

pair subsequently collapses to the arenium ion. There is evidence[101] both for and against this proposal.[102]

The Effect of the Leaving Group



30

In the vast majority of aromatic electrophilic substitutions, the leaving group is H^+ as indicated above, and very little work has been done on the relative electrofugal ability of other leaving groups. However, the following orders of leaving-group ability have been suggested:[103] (*1*) for leaving groups that depart without assistance (S_N1 process with respect to the leaving group), NO_2^+[104] $< i\text{Pr}^+ \sim SO_3 < t\text{-Bu}^+ \sim ArN_2^+ < ArCHOH^+ < NO^+ < CO_2$; (*2*) for leaving groups that depart with assistance from an outside nucleophile (S_N2 process), $Me^+ < Cl^+ < Br^+ < D^+ \sim RCO^+ < H^+ \sim I^+ < Me_3Si^+$. We can use this kind of list to help predict which group, X or Y, will cleave from an arenium ion **30** (see **1**, where Y = H) once it has been formed, and so obtain an idea of which electrophilic substitutions are feasible. However, a potential leaving group can also affect a reaction in another way: by influencing the rate at which attack of the original electrophile leads to attachment directly at the ipso position. Partial rate factors for electrophilic attack at a position substituted by a group other than hydrogen are called ipso partial rate factors (i_f^X).[53] Such factors for the nitration of *p*-haloanisoles are 0.18, 0.08, and 0.06, for *p*-iodo, *p*-bromo-, and *p*-chloroanisole, respectively.[105] This means, for example, that attack at the electrophile in this case leads to attachment at the 4 position of 4-iodoanisole 0.18 times as fast as a single position of benzene. Note that this is far slower than attachment at the 4 position resulting from attack of anisole itself so that the presence of the iodo group greatly slows the reaction at that position. A similar experiment on *p*-cresol showed that ipso

[101]For evidence in favor of the proposal, see Reents, Jr., W.D.; Freiser, B.S. *J. Am. Chem. Soc.* ***1980***, *102*, 271; Morkovnik, A.S.; Dobaeva, N.M.; Panov, V.B.; Okhlobystin, O.Yu. *Doklad. Chem.* ***1980***, *251*, 116; Sankararaman, S.; Haney, W.A.; Kochi, J.K. *J. Am. Chem. Soc.* ***1987***, *109*, 5235; Keumi, T.; Hamanaka, K.; Hasegawa, K.; Minamide, N.; Inoue, Y.; Kitajima, H. *Chem. Lett.* ***1988***, 1285; Johnston, J.F.; Ridd, J.H.; Sandall, J.P.B. *J. Chem. Soc., Chem. Commun.* ***1989***, 244. For evidence against it, see Barnes, C.E.; Myhre, P.C. *J. Am. Chem. Soc.* ***1978***, *100*, 975; Eberson, L.; Radner, F. *Acc. Chem. Res.* ***1987***, *20*, 53; Baciocchi, E.; Mandolini, L. *Tetrahedron* ***1987***, *43*, 4035.

[102]For a review, see Morkovnik, A.S. *Russ. Chem. Rev.* ***1988***, *57*, 144.

[103]Perrin, C.L. *J. Org. Chem.* ***1971***, *36*, 420.

[104]For examples where NO_2^+ is a leaving group (in a migration), see Bullen, J.V.; Ridd, J.H.; Sabek, O. *J. Chem. Soc. Perkin Trans. 2* ***1990***, 1681, and other papers in this series.

[105]Perrin, C.L.; Skinner, G.A. *J. Am.Chem. Soc.* ***1971***, *93*, 3389. See also, Fischer, P.B.; Zollinger, H. *Helv. Chim. Acta* ***1972***, *55*, 2139.

attack at the methyl position was 6.8 times slower than attack of phenol leading to attachment at the para position.[106] Thus, in these cases, both an iodo and a methyl group deactivate the ipso position.[107]

REACTIONS

The reactions in this chapter are classified according to leaving group. Hydrogen replacements are treated first, then rearrangements in which the attacking entity is first cleaved from another part of the molecule (hydrogen is also the leaving group in these cases), and finally replacements of other leaving groups.

Hydrogen as the Leaving Group in Simple Substitution Reactions

A. Hydrogen as the Electrophile

11-1 Hydrogen Exchange

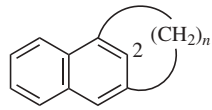
Deuterio-de-hydrogenation or Deuteriation

$$ArH + D^+ \rightleftharpoons ArD + H^+$$

Aromatic compounds can exchange hydrogens when treated with acids. The reaction is used chiefly to study mechanistic questions[108] (including substituent effects), but can also be useful to deuterate (add ^2H) or tritiate (add ^3H) aromatic rings selectively. The usual directive effects apply and, for example, phenol treated with D_2O gives slow exchange on heating, with only ortho and para hydrogens being exchanged.[109] Strong acids, of course, exchange faster with aromatic substrates, and this exchange must be taken into account when studying the mechanism of any aromatic substitution catalyzed by acids. There is a great deal of evidence that exchange takes place by the ordinary arenium ion mechanism. Among the evidence are the orientation effects noted above and the finding that the reaction is general acid catalyzed, which means that a proton is transferred in the slow step[110] (p. 373). Furthermore, many examples have been reported of stable solutions of arenium ions formed by attack of a proton on an aromatic ring.[4] Simple aromatic compounds can be extensively deuterated in a convenient fashion by

[106]Tee, O.; Iyengar, N.R.; Bennett, J.M. *J. Org. Chem.* ***1986***, *51*, 2585.
[107]For other work on ipso reactivity, see Baciocchi, E.; Illuminati, G. *J. Am. Chem. Soc.* ***1967***, *89*, 4017; Berwin, H.J. *J. Chem. Soc., Chem. Commun.* ***1972***, 237; Galley, M.W.; Hahn, R.C. *J. Am. Chem. Soc.* ***1974***, *96*, 4337; Clemens, A.H.; Hartshorn, M.P.; Richards, K.E.; Wright, G.J. *Aust. J. Chem.* ***1977***, *30*, 103, 113.
[108]For a review, see Taylor, R., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, ***1972***, pp. 194–277.
[109]Small, P.A.; Wolfenden, J.H. *J. Chem. Soc.* ***1936***, 1811.
[110]For example, see Challis, B.C.; Long, F.A. *J. Am. Chem. Soc.* ***1963***, *85*, 2524; Batts, B.D.; Gold, V. *J. Chem. Soc.* ***1964***, 4284; Kresge, A.J.; Chiang, Y.; Sato, Y. *J. Am. Chem. Soc.* ***1967***, *89*, 4418; Gruen, L.C.; Long, F.A. *J. Am. Chem. Soc.* ***1967***, *89*, 1287; Butler, A.B.; Hendry, J.B. *J. Chem. Soc. B* ***1970***, 852.

treatment with D_2O and BF_3.[111] It has been shown that tritium exchange takes place readily at the 2 position of **31**, despite the fact that this position is hindered by the bridge. The rates were not very different from the comparison compound 1,3-dimethylnaphthalene.[112]



n=7, 8, 10

31

Hydrogen exchange can also be effected with strong bases,[113] such as NH_2-. In these cases, the slow step is the proton transfer:

$$ArH + B \longrightarrow Ar^- + BH^+$$

so the S_E1 mechanism and not the usual arenium ion mechanism is operating.[114] Aromatic rings can also be deuterated by treatment with D_2O and a rhodium(III) chloride[115] or platinum[116] catalyst or with C_6D_6 and an alkylaluminum dichloride catalyst,[117] though rearrangements may take place during the latter procedure. Tritium (^3H, abbreviated T) can be introduced by treatment with T_2O and an alkylaluminum dichloride catalyst.[117] Tritiation at specific sites (e.g., >90% para in toluene) has been achieved with T_2 gas and a microporous aluminophosphate catalyst.[118]

B. Nitrogen Electrophiles

11-2 Nitration or Nitro-de-hydrogenation

$$ArH + HNO_3 \xrightarrow{H_2SO_4} ArNO_2$$

[111]Larsen, J.W.; Chang, L.W. *J. Org. Chem.* ***1978***, *43*, 3602.
[112]Laws, A.P.; Neary, A.P.; Taylor, R. *J. Chem. Soc. Perkin Trans. 2* ***1987***, 1033.
[113]For a review of base-catalyzed hydrogen exchange on heterocycles, see Elvidge, J.A.; Jones, J.R.; O'Brien, C.; Evans, E.A.; Sheppard, H.C. *Adv. Heterocycl. Chem.* ***1974***, *16*, 1.
[114]Shatenshtein, A.I. *Tetrahedron* ***1962***, *18*, 95.
[115]Lockley, W.J.S. *Tetrahedron Lett.* ***1982***, *23*, 3819; *J. Chem. Res. (S)* ***1985***, 178.
[116]See, for example, Leitch, L.C. *Can. J. Chem.* ***1954***, *32*, 813; Fraser, R.R.; Renaud, R.N. *J. Am. Chem. Soc.* ***1966***, *88*, 4365; Fischer, G.; Puza, M. *Synthesis* ***1973***, 218; Blake, M.R.; Garnett, J.L.; Gregor, I.K.; Hannan, W.; Hoa, K.; Long, M.A. *J. Chem. Soc., Chem. Commun.* ***1975***, 930. See also, Parshall, G.W. *Acc. Chem. Res.* ***1975***, *8*, 113.
[117]Long, M.A.; Garnett, J.L.; West, J.C. *Tetrahedron Lett.* ***1978***, 4171.
[118]Garnett, J.L.; Kennedy, E.M.; Long, M.A.; Than, C.; Watson, A.J. *J. Chem. Soc., Chem. Commun.* ***1988***, 763.

Most aromatic compounds, whether of high or low reactivity, can be nitrated, because a wide variety of nitrating agents is available.[119] For benzene, the simple alkylbenzenes, and less reactive compounds, the most common reagent is a mixture of concentrated nitric and sulfuric acids,[120] but for active substrates, the reaction can be carried out with nitric acid alone,[121] or in water, acetic acid, acetic anhydride, or chloroform.[122] Nitric acid in acetic anhydride/trifluoroacetic anhydride on zeolite H-β was used to convert toluene to 2,4-dinitrotoluene,[123] and $AcONO_2$ on clay converted ethylbenzene to ortho–para nitro ethylbenzene.[124] In fact, these milder conditions are necessary for active compounds, such as amines, phenols, and pyrroles, since reaction with mixed nitric and sulfuric acids would oxidize these substrates. With active substrates, such as amines and phenols, nitration can be accomplished by nitrosation under oxidizing conditions with a mixture of dilute nitrous and nitric acids.[125] A mixture of $NO_2/O_2/Fe(acac)_3$ can be used for active compounds,[126] as can $NaNO_2$ with trichloroisocyanuric acid on wet silica gel,[127] or N_2O_4 and silica acetate.[128] Trimethoxybenzenes were nitrated easily with ceric ammonium nitrate on silica gel,[129] and mesitylene was nitrated in an

[119]For a discussion of a unified mechansim, see Esteves, P.M.; de M. Carneiro, J.W.; Cardoso, S.P.; Barbosa, A.G.H.; Laali, K.K.; Rasul, G.; Prakash, G.K.S.; Olah, G.A. J. *Am. Chem. Soc.* ***2003***, *125*, 4836. For monographs, see Olah, G.A.; Malhotra, R.; Narang, S.C. *Nitration: Methods and Mechanisms*, VCH, NY, ***1989***; Schofield, K. *Aromatic Nitration*; Cambridge University Press, Cambridge, ***1980***; Hoggett, J.H.; Moodie, R.B.; Penton, J.R.; Schofield, K. *Nitraton and aromatic Reactivity*, Cambridge University Press, Cambridge, ***1971***. For reviews, see Weaver, W.M., in Feuer, H. *Chemistry of the Nitro and Nitroso Groups*, pt. 2, Wiley, NY, ***1970***, pp. 1–48; de la Mare, P.B.D.; Ridd, J.H. *Aromatic Substitution Nitration and Halogenation*, Academic Press, NY, ***1959***, pp. 48–93. See also, Ref. 1. For a review of side reactions, see Suzuki, H. *Synthesis* ***1977***, 217. Also see, Bosch, E.; Kochi, J.K. *J. Org. Chem.* ***1994***, *59*, 3314; Olah, G.A.; Wang, Q.; Li, X.; Bucsi, I. *Synthesis* ***1992***, 1085; Olah, G.A.; Reddy, V.P.; Prakash, G.K.S. *Synthesis* ***1992***, 1087.

[120]For the use of sulfuric acid/nitric acid on silica, see Smith, A.C.; Narvaez, L.D.; Akins, B.G.; Langford, M.M.; Gary, T.; Geisler, V.J.; Khan, F.A. *Synth. Commun.* ***1999***, *29*, 4187. For a reaction with guanidine–nitric acid with sulfric acid, see Ramana, M.M.V.; Malik, S.S.; Parihar, J.A. *Tetrahedron Lett.* ***2004***, *45*, 8681.

[121]For a reaction with nitric acid and a lanthanum salt, see Parac-Vogt, T.N.; Binnesmans, K. *Tetrahedron Lett.* ***2004***, *45*, 3137.

[122]Used with $(NH_4)_2SO_4 \bullet NiSO_4 \bullet 6\ H_2O$: Tasneem, Ali, M.M.; Rajanna, K.C.; Saiparakash, P.K. *Synth. Commun.* ***2001***, *31*, 1123.

[123]Smith, K.; Gibbons, T.; Millar, R.W.; Claridge, R.P. *J. Chem. Soc., Perkin Trans. 1*, ***2000***, 2753.

[124]Rodrigues, J.A.R.; Filho, A.P.O.; Moran, P.J.S. *Synth. Commun.* ***1999***, *29*, 2169.

[125]For discussions of the mechanism in this case, see Giffney, J.C.; Ridd, J.H. *J. Chem. Soc. Perkin Trans. 2* ***1979***, 618; Bazanova, G.V.; Stotskii, A.A. *J. Org. Chem. USSR* ***1980***, *16*, 2070, 2075; Ross, D.S.; Moran, K.D.; Malhotra, R. *J. Org. Chem.* ***1983***, *48*, 2118; Dix, L.R.; Moodie, R.B. *J. Chem. Soc. Perkin Trans. 2* ***1986***, 1097; Leis, J.R.; Peña, M.E.; Ridd, J.H. *Can. J. Chem.* ***1989***, *67*, 1677. For a review, see Ridd, J.H. *Chem. Soc. Rev.* ***1991***, *20*, 149.

[126]Suzuki, H.; Yonezawa, S.; Nonoyama, N.; Mori, T. *J. Chem. Soc. Perkin Trans. 1* ***1996***, 2385.

[127]Zolfigol, M.A.; Madrakian, E.; Ghaemi, E. *Synlett* ***2003***, 2222.

[128]Iranpoor, N.; Firouzabadi, H.; Heydari, R. *Synth. Commun.* ***2003***, *33*, 703.

[129]Khadilkar, B.M.; Madyar, V.R. *Synth. Commun.* ***1999***, *29*, 1195.

ionic liquid using nitric acid–acetic anhydride.[130] Phenol can be nitrated in an ionic liquid.[131]

If anhydrous conditions are required, nitration can be effected with N_2O_5[132] in CCl_4 in the presence of P_2O_5, which removes the water formed in the reaction.[133] These reagents can also be used with proton or Lewis acid catalysts. Representative nitrating agents are $NaNO_2$ and trifluoroacetic acid,[134] N_2O_4 (which gives good yields with polycyclic hydrocarbons[135]), N_2O_4/O_2 and a catalytic amount of zeolite Hβ,[136] $Yb(OTf)_3$,[137] and nitronium salts,[138] such as $NO_2^+BF_4^-$, $NO_2^+PF_6^-$, and $NO_2^+CF_3SO_3^-$.[139] A mixture of NO_2 and ozone has also been used.[140] Clays, such as clay-supported cupric nitrate (Claycop),[141,142] or Montmorillonite KSF—$Bi(NO_3)$[143] can be used to nitrate aromatic rings. Nitration of styrene poses a problem since addition occurs to the C=C unit to give a 1-nitroethyl aryl.[144] Heterocycles, such as pyridine, are nitrated with N_2O_5 and SO_2.[145] Deactivated aromatic rings, as in acetophenone, were nitrated with N_2O_5 and $Fe(acac)_2$.[146]

[130]In bmpy NTf_2, 1-butyl-4-methylpyridinium triflimide: Lancaster, N.L.; Llopis-Mestre, V. *Chem. Commun.* ***2003***, 2812.

[131]In bbim BF_4, 1,3-dibutylimidazoliiuum tetrafluoroborate: Rajogopal, R.; Srinivasan, K.V. *Synth. Commun.* ***2004***, *34*, 961.

[132]For a review of N_2O_5, see Fischer, J.W. in Feuer, H.; Nielsen, A.T. *Nitro Compounds, Recent Advances in synthesis and Chemistry*; VCH, NY, ***1990***, pp. 267–365.

[133]For another method, see Olah, G.A.; Krishnamurthy, V.V.; Narang, S.C. *J. Org. Chem.* ***1982***, *47*, 596.

[134]Uemura, S.; Toshimitsu, A.; Okano, M. *J. Chem. Soc. Perkin Trans. 1* ***1978***, 1076. For a reaction with $NaNO_2$ and wet silica, see Zolfigol, M.A.; Ghaemi, E.; Madrakian, E. *Synth. Commun.* ***2000***, *30* , 1689; Zolfigol, M.A.; Bagherzadeh, M.; Madrakian, E.; Gaemi, E.; Taqian-Nasab, A. *J. Chem. Res. (S)* ***2001***, 140.

[135]Radner, F. *Acta Chem. Scand. Ser. B* ***1983***, *37*, 65.

[136]Smith, K.; Almeer, S.; Black, S.J. *Chem. Commun.* ***2000***, 1571. See also, Smith, K.; Musson, A.; DeBoos, G.A. *J. Org. Chem.* ***1998***, *63*, 8448.

[137]Barrett, A.G.M.; Braddock, D.C.; Ducray, R.; McKinnell, R.M.; Waller, F.J. *Synlett* ***2000***, 57.

[138]Olah, G.A.; Kuhn, S.J. *J. Am. Chem. Soc.* ***1962***, *84*, 3684. These have also been used together with crown ethers: Masci, B. *J. Org. Chem.* ***1985***, *50*, 4081; Iranpoor, N.; Firouzabadi, H.; Heydari, R. *Synth. Commun.* ***1999***, *29*, 3295. For a review of nitronium salts in organic chemistry, see Guk,Yu. V.; Ilyushin, M.A.; Golod, E.L.; Gidaspov, B.V. *Russ. Chem. Rev.* ***1983***, *52*, 284.

[139]This salt gives a very high yield of products at low temperatures, see Coon, C.L.; Blucher, W.G.; Hill, M.E. *J. Org. Chem.* ***1973***, *38*, 4243; Effenberger, F.; Geke, J. *Synthesis* ***1975***, 40.

[140]Nose, M.; Suzuki, H.; Suzuki, H. *J. Org. Chem.* ***2001***, *66*, 4356; Peng, X.; Suzuki, H. *Org. Lett.* ***2001***, *3*, 3431; Suzuki, H.; Tomaru, J.-i.; Murashima, T. *J. Chem. Soc. Perkin Trans. 1* ***1994***, 2413; Suzuki, H.; Tatsumi, A.; Ishibashi, T.; Mori, T. *J. Chem. Soc. Perkin Trans. 1* ***1995***, 339.

[141]For reviews of clay-supported nitrates, see Cornélis, A.; Laszlo, P. *Synthesis* ***1985***, 909; Laszlo, P. *Acc. Chem. Res.* ***1986***, 121; Laszlo, P.; Cornélis, A. *Aldrichimica Acta* ***1988***, *21*, 97.

[142]Cornélis, A.; Delaude, L.; Gerstmans, A.; Laszlo, P. *Tetrahedron Lett.* ***1988***, *29*, 5657. See also, Smith, K.; Fry, K.; Butters, M.; Nay, B. *Tetrahedron Lett.* ***1989***, *30*, 5333; Cornélis, A.; Laszlo, P.; Pennetreau, P. *Bull. Soc. Chim. Belg.*, ***1984***, *93*, 961; Poirier, J.; Vottero, C. *Tetrahedron* ***1989***, *45*, 1415. For a method of nitrating phenols in the ortho position, see Pervez, H.; Onyiriuka, S.O.; Rees, L.; Rooney, J.R.; Suckling, C.J. *Tetrahedron* ***1988***, *44*, 4555.

[143]Samajdar, S.; Becker, F.F.; Banik, B.K. *Tetrahedron Lett.* ***2000***, *41*, 8017.

[144]Lewis, R.J.; Moodie, R.B. *J. Chem. Soc. Perkin Trans. 2* ***1997***, 563.

[145]Arnestad, B.; Bakke, J.M.; Hegbom, I.; Ranes, E. *Acta Chem. Scand. B* ***1996***, *50*, 556.

[146]Bak, R.R.; Smallridge, A.J. *Tetrahedron Lett.* ***2001***, *42*, 6767.

An alternative route for the nitration of activated aromatic compounds, such as anisole, used a nitrate ester ($RONO_2$) with triflic acid in an ionic liquid for ortho-selective nitration.[147] Nitration in alkaline media can be accomplished with esters of nitric acid, such as ethyl nitrate ($EtONO_2$).

When anilines are nitrated under strong acid conditions, meta orientation is generally observed, because the species undergoing nitration is actually the conjugate acid of the amine. If the conditions are less acidic, the free amine is nitrated and the orientation is ortho–para. Although the free base may be present in much smaller amounts than the conjugate acid, it is far more susceptible to aromatic substitution (see also p. 668). Because of these factors and because they are vulnerable to oxidation by nitric acid, primary aromatic amines are often protected before nitration by treatment with acetyl chloride (**16-72**) or acetic anhydride (**16-73**). Nitration of the resulting acetanilide derivative avoids all these problems. There is evidence that when the reaction takes place on the free amine, it is the nitrogen that is attacked to give an *N*-nitro compound Ar—NH–NO_2 which rapidly undergoes rearrangement (see **11-28**) to give the product.[148]

Since the nitro group is deactivating, it is usually easy to stop the reaction after one group has entered the ring, but a second and a third group can be introduced if desired, especially when an activating group is also present. Even *m*-dinitrobenzene can be nitrated if vigorous conditions are applied. This has been accomplished with $NO_2^+BF_4^-$ in FSO_3H at 150°C.[149]

With most of the reagents mentioned, the attacking species is the nitronium ion NO_2^+. Among the ways in which this ion is formed are

1. In concentrated sulfuric acid, by an acid–base reaction in which nitric acid is the base:

$$HNO_3 + 2\,H_2SO_4 \rightleftharpoons NO_2^+ + H_3O^+ + 2\,HSO_4^-$$

This ionization is essentially complete.

2. In concentrated nitric acid alone,[150] by a similar acid–base reaction in which one molecule of nitric acid is the acid and another the base:

$$2\,HNO_3 \rightleftharpoons NO_2^+ + NO_3^- + H_2O$$

This equilibrium lies to the left (~4% ionization), but enough NO_2^+ is formed for nitration to occur.

[147]In emim OTf, 1-ethyl-3-methylimidazolium triflate: Laali, K.K.; Gettwert, V.J. *J. Org. Chem.* ***2001***, *66*, 35.

[148]Ridd, J.H.; Scriven, E.F.V. *J. Chem. Soc., Chem. Commun.* ***1972***, 641. See also, Helsby, P.; Ridd, J.H. *J. Chem. Soc. Perkin Trans. 2* ***1983***, 1191.

[149]Olah, G.A.; Lin, H.C. *Synthesis* ***1974***, 444.

[150]See Belson, D.J.; Strachan, A.N. *J. Chem. Soc. Perkin Trans. 2* ***1989***, 15.

3. The equilibrium just mentioned occurs to a small extent even in organic solvents.
4. With N_2O_5 in CCl_4, there is spontaneous dissociation:

$$N_2O_5 \rightleftharpoons NO_2^+ + NO_3^-$$

but in this case there is evidence that some nitration also takes place with undissociated N_2O_5 as the electrophile.

5. When nitronium salts are used, NO_2^+ is of course present to begin with. Esters and acyl halides of nitric acid ionize to form NO_2^+. Nitrocyclohexadienones are converted to NO_2^+ and the corresponding phenol.[132]

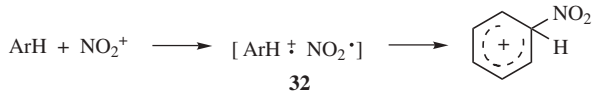
There is a great deal of evidence that NO_2^+ is present in most nitration reactions and that it is the attacking entity,[151] for example,

1. Nitric acid has a peak in the Raman spectrum. When nitric acid is dissolved in concentrated sulfuric acid, the peak disappears and two new peaks appear, one at 1400 cm^{-1} attributable to NO_2^+ and one at 1050 cm^{-1} due to HSO_4-.[152]
2. On addition of nitric acid, the freezing point of sulfuric acid is lowered about four times the amount expected if no ionization has taken place.[153] This means that the addition of one molecule of nitric acid results in the production of four particles, which is strong evidence for the ionization reaction between nitric and sulfuric acids given above.
3. The fact that nitronium salts in which nitronium ion is known to be present (by X-ray studies) nitrate aromatic compounds shows that this ion does attack the ring.
4. The rate of the reaction with most reagents is proportional to the concentration of NO_2^+, not to that of other species.[154] When the reagent produces this ion in small amounts, the attack is slow and only active substrates can be nitrated. In concentrated and aqueous mineral acids, the kinetics are second order: first order each in aromatic substrate and in nitric acid (unless pure nitric acid is used in which case there are pseudo-first-order kinetics). But in organic solvents such as nitromethane, acetic acid, and CCl_4, the kinetics are first order in nitric acid alone and zero order in aromatic substrate, because the rate-determining step is formation of NO_2^+ and the substrate does not take part in this.

[151]For an exhaustive study of this reaction, see Hughes, E.D.; Ingold, C.K.in a series of several papers with several different co-workers, see *J. Chem. Soc.* ***1950***, 2400.
[152]Ingold, C.K.; Millen, D.J.; Poole, H.G. *J. Chem. Soc.* ***1950***, 2576.
[153]Gillespie, R.J.; Graham, J.; Hughes, E.D.; Ingold, C.K.; Peeling, E.R.A. *J. Chem. Soc.* ***1950***, 2504.
[154]This is not always strictly true. See Ross, D.S.; Kuhlmann, K.F.; Malhotra, R. *J. Am. Chem. Soc.* ***1983***, *105*, 4299.

An interesting route to nitrobenzene begins with bromobenzene. Reaction with butyllithium gives phenyllithium, which reacts with an excess of N_2O_4 to give nitrobenzene.[155]

In a few cases, depending on the substrate and solvent, there is evidence that the arenium ion is not formed directly, but via the intermediacy of a radical pair (see p. 682) such as **32**.[156]

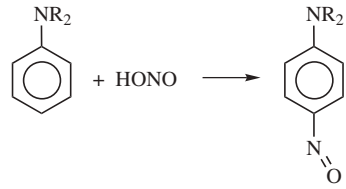


32

Arylboronic acids have been shown to react with ammonium nitrate and trifluoroacetic acid to give the corresponding nitrobenzene.[157]

OS **I**, 372, 396, 408 (see also OS **53**, 129); **II**, 254, 434, 438, 447, 449, 459, 466; **III**, 337, 644, 653, 658, 661, 837; **IV**, 42, 364, 654, 711, 722, 735; **V**, 346, 480, 829, 1029, 1067.

11-3 Nitrosation or Nitroso-de-hydrogenation



Ring nitrosation[158] with nitrous acid is normally carried out only with active substrates, such as amines and phenols. However, primary aromatic amines give diazonium ions (**13-19**) when treated with nitrous acid,[159] and secondary amines tend to give *N*-nitroso rather than *C*-nitroso compounds (**12-50**); hence this reaction is normally limited to phenols and tertiary aromatic amines. Nevertheless, secondary aromatic amines can be *C*-nitrosated in two ways. The *N*-nitroso compound first obtained can be isomerized to a *C*-nitroso compound (**11-29**), or it can be treated with another equivalent of nitrous acid to give an *N,C*-dinitroso compound. Also, a successful nitrosation of anisole has been reported, where the solvent was $CF_3COOH—CH_2Cl_2$.[160]

[155]Tani, K.; Lukin, K.; Eaton, P.E. *J. Am. Chem. Soc.* ***1997***, *119*, 1476.

[156]For a review of radical processes in aromatic nitration, see Ridd, J.H. *Chem. Soc. Rev.* ***1991***, *20*, 149. For a review of aromatic substitutions involving radical cations, see Kochi, J.K. *Adv. Free Radical Chem. (Greenwich, Conn.)* ***1990***, *1*, 53.

[157]Salzbrunn, S.; Simon, J.; Prakash, G.K.S.; Petasis, N.A.; Olah, G.A. *Synlett* ***2000***, 1485; Prakash, G.K.S.; Panja, C.; Mathew, T.; Surampudi, V.; Petasis, N.A.; Olah, G.A. *Org. Lett.* ***2004***, *6*, 2205.

[158]For a review, see Williams, D.L.H. *Nitrosation*, Cambridge University Press, Cambridge, ***1988***, pp. 58–76. Also see Atherton, J.H.; Moodie, R.B.; Noble, D.R.; O'Sullivan, B. *J. Chem. Soc. Perkin Trans. 2* ***1997***, 663.

[159]For examples of formation of *C*-nitroso compounds from primary and secondary amines, see Hoefnagel, M.A.; Wepster, B.M. *Recl. Trav. Chim. Pays-Bas* ***1989***, *108*, 97.

[160]Radner, F.; Wall, A.; Loncar, M. *Acta Chem. Scand.* ***1990***, *44*, 152.

Much less work has been done on the mechanism of this reaction than on **11-2**.[161] In some cases, the attacking entity is NO^+, but in others it is apparently NOCl, NOBr, N_2O_3, and so on, in each of which there is a carrier of NO^+. Both NOCl and NOBr are formed during the normal process of making nitrous acid (the treatment of sodium nitrite with HCl or HBr). Nitrosation requires active substrates because NO^+ is much less reactive than NO_2^+. Kinetic studies have shown that NO^+ is at least 10^{14} times less reactive than NO_2^+.[162] A consequence of the relatively high stability of NO^+ is that this species is easily cleaved from the arenium ion, so that k_{-1} competes with k_2 (p. 660) and isotope effects are found.[163] With phenols, there is evidence that nitrosation may first take place at the OH group, after which the nitrite ester thus formed rearranges to the C-nitroso product.[164] Tertiary aromatic amines substituted in the ortho position generally do not react with HONO, probably because the ortho substituent prevents planarity of the dialkylamino group, without which the ring is no longer activated. This is an example of steric inhibition of resonance (p. 48).

OS **I**, 214, 411, 511; **II**, 223; **IV**, 247.

11-4 Diazonium Coupling

Arylazo-de-hydrogenation

$$ArH + Ar'N_2^+ \longrightarrow Ar{-}N{=}N{-}Ar'$$

Aromatic diazonium ions normally couple only with active substrates, such as amines and phenols.[165] Many of the products of this reaction are used as dyes (*azo dyes*).[166] Presumably because of the size of the attacking species, substitution is mostly para to the activating group, unless that position is already occupied, in which case ortho substitution takes place. The pH of the solution is important both for phenols and amines. For amines, the solutions may be mildly acidic or neutral. The fact that amines give ortho and para products shows that even in mildly acidic solution they react in their un-ionized form. If the acidity is too high, the reaction does not occur, because the concentration of free amine becomes too small. Phenols must be coupled in slightly alkaline solution where they are converted to the more reactive phenoxide ions, because phenols themselves are not active enough for the

[161]For a review of nitrosation mechanisms at C and other atoms, see Williams, D.L.H. *Adv. Phys. Org. Chem.* ***1983***, *19*, 381. See Williams, D.L.H. *Nitrosation*, Cambridge University Press, Cambridge, ***1988***, pp. 58–76; Atherton, J.H.; Moodie, R.B.; Noble, D.R.; O'Sullivan, B. *J. Chem. Soc. Perkin Trans. 2* ***1997***, 663.

[162]Challis, B.C.; Higgins, R.J.; Lawson, A.J. *J. Chem. Soc. Perkin Trans. 2* ***1972***, 1831; Challis, B.C.; Higgins, R.J. *J. Chem. Soc. Perkin Trans. 2* ***1972***, 2365.

[163]Challis, B.C.; Higgins, R.J. *J. Chem. Soc. Perkin Trans. 2* ***1973***, 1597.

[164]Gosney, A.P.; Page, M.I. *J. Chem. Soc. Perkin Trans. 2* ***1980***, 1783.

[165]For reviews, see Szele, I.; Zollinger, H. *Top. Curr. Chem.* ***1983***, *112*, 1; Hegarty, A.F., in Patai's. *The Chemistry of Diazonium and Diazo Groups*, pt. 2, Wiley, NY, ***1978***, pp. 545–551.

[166]For reviews of azo dyes, see Zollinger, H. *Color Chemistry*, VCH, NY, ***1987***, pp. 85–148; Gordon, P.F.; Gregory, P. *Organic Chemistry in Colour*, Springer, NY, ***1983***, pp. 95–162.

reaction. However, neither phenols nor amines react in moderately alkaline solution, because the diazonium ion is converted to a diazo hydroxide Ar—N=N—OH. Primary and secondary amines face competition from attack at the nitrogen.[167] However, the resulting *N*-azo compounds (aryl triazenes) can be isomerized to *C*-azo compounds (**11-30**). In at least some cases, even when the *C*-azo compound is isolated, it is the result of initial *N*-azo compound formation followed by isomerization. It is therefore possible to synthesize the *C*-azo compound directly in one laboratory step.[168] Acylated amines and phenolic ethers and esters are ordinarily not active enough for this reaction, though it is sometimes possible to couple them (as well as such polyalkylated benzenes as mesitylene and pentamethylbenzene) to diazonium ions containing electron-withdrawing groups in the para position, since such groups increase the concentration of the positive charge and thus the electrophilicity of the ArN_2^+. Some coupling reactions which are otherwise very slow (in cases where the coupling site is crowded) are catalyzed by pyridine for reasons discussed on p. 661. Phase transfer catalysis has also been used.[169]

Coupling of a few aliphatic diazonium compounds to aromatic rings has been reported. All the examples reported so far involve cyclopropanediazonium ions and bridgehead diazonium ions, in which loss of N_2 would lead to very unstable carbocations.[170] Azobenzenes have been prepared by Pd-catalyzed coupling of aryl hydrazides with aryl halides, followed by direct oxidation.[171]

The mechanism of Z/E isomerization in Ar-N=NAr systems has been studied.[172]

OS **I**, 49, 374; **II**, 35, 39, 145.

11-5 Direct Introduction of the Diazonium Group

Diazoniation or Diazonio-de-hydrogenation

$$ArH \xrightarrow[HX]{2\,HONO} ArN_2^+X^-$$

Diazonium salts can be prepared directly by replacement of an aromatic hydrogen without the necessity of going through the amino group.[173] The reaction is essentially limited to active substrates (amines and phenols), since otherwise poor yields are obtained. Since the reagents and the substrate are the same as in reaction **11-3**, the first species formed is the nitroso compound. In the presence of excess nitrous acid, this is converted to the diazonium ion.[174] The reagent

[167]See Penton, J.R.; Zollinger, H. *Helv. Chim. Acta* ***1981***, *64*, 1717, 1728.
[168]Kelly, R.P.; Penton, J.R.; Zollinger, H. *Helv. Chim. Acta* ***1982***, *65*, 122.
[169]Hashida, Y.; Kubota, K.; Sekiguchi, S. *Bull. Chem. Soc. Jpn.* ***1988***, *61*, 905.
[170]See Szele, I.; Zollinger, H. *Top. Curr. Chem.* ***1983***, *112*, 1, see pp. 3–6.
[171]Lim, Y.-K.; Lee, K.-S.; Cho, C.-G. *Org. Lett.* ***2003***, *5*, 979.
[172]Asano, T.; Furuta, H.; Hofmann, H.-J.; Cimiraglia, R.; Tsuno, Y.; Fujio, M. *J. Org. Chem.* ***1993***, *58*, 4418.
[173]Tedder, J.M. *J. Chem. Soc.* ***1957***, 4003.
[174]Tedder, J.M.; Theaker, G. *Tetrahedron* ***1959***, *5*, 288; Kamalova, F.R.; Nazarova, N.E.; Solodova, K.V. ; Yaskova, M.S. *J. Org. Chem. USSR* ***1988***, *24*, 1004.

(azidochloromethylene)dimethylammonium chloride [$Me_2N{=}C(Cl)N_3\ Cl^-$] can also introduce the diazonium group directly into a phenol.[175] A synthesis of solid aryldiazonium chlorides is now available.[176]

11-6 Amination or Amino-de-hydrogenation[177]

$$ArH + HN_3 \xrightarrow{AlCl_3} ArNH_2$$

Aromatic compounds can be converted to primary aromatic amines, in 10–65% yields, by treatment with hydrazoic acid HN_3 in the presence of $AlCl_3$ or H_2SO_4.[178] Higher yields (>90%) have been reported with trimethylsilyl azide (Me_3SiN_3) and triflic acid F_3CSO_2OH.[179] Treatment of an aromatic compound with tetramethylhydrazonium iodide and then ammonium also give the aryl amine.[180] Tertiary amines have been prepared in ~50–90% yields by treatment of aromatic hydrocarbons with *N*-chlorodialkylamines; by heating in 96% sulfuric acid; or with $AlCl_3$ or $FeCl_3$ in nitroalkane solvents; or by irradiation.[181] Treatment of an aryl halide with an amine and a palladium catalyst leads to the aniline derivative.[182]

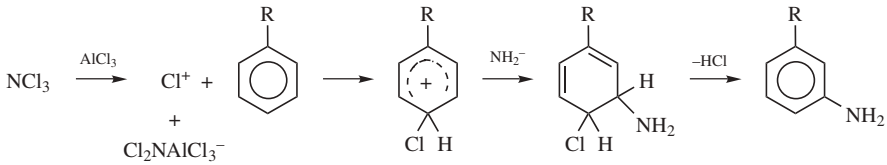
Tertiary (and to a lesser extent, secondary) aromatic amines can also be prepared in moderate to high yields by amination with an *N*-chlorodialkylamine (or an *N*-chloroalkylamine) and a metallic-ion catalyst (e.g., Fe^{2+}, Ti^{3+}, Cu^+, Cr^{2+}) in the presence of sulfuric acid.[183] The attacking species in this case is the aminium radical ion $R_2NH\bullet$ formed by[184]

$$R_2\overset{\oplus}{N}HCl + M^+ \longrightarrow R_2\overset{\oplus}{N}H\bullet + M^{2+} + Cl^-$$

Because attack is by a positive species (even though it is a free radical), orientation is similar to that in other electrophilic substitutions (e.g., phenol and acetanilide give ortho and para substitution, mostly para). When an alkyl group is present, attack at the benzylic position competes with ring substitution. Aromatic rings containing only meta-directing groups do not give the reaction at all. Fused ring systems react well.[185]

[175]Kokel, B.; Viehe, H.G. *Angew. Chem. Int. Ed.* ***1980***, *19*, 716.
[176]Mohamed, S.K.; Gomaa, M.A.-M.; El-Din, A..M.N. *J. Chem. Res. (S)* ***1997***, 166.
[177]For a review, see Kovacic, P., in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 3, Wiley, NY, ***1964***, pp. 1493–1506.
[178]Kovacic, P.; Russell, R.L.; Bennett, R.P. *J. Am. Chem. Soc.* ***1964***, *86*, 1588.
[179]Olah, G.A.; Ernst, T.D. *J. Org. Chem.* ***1989***, *54*, 1203.
[180]Rozhkov, V.V.; Shevelev, S.A.; Chervin, I.T.; Mitchel, A.R.; Schmidt, R.D. *J. Org. Chem.* ***2003***, *68*, 2498.
[181]Bock, H.; Kompa, K. *Angew. Chem. Int. Ed.* ***1965***, *4*, 783; *Chem. Ber.* ***1966***, *99*, 1347, 1357, 1361.
[182]Guram, A.S.; Rennels, R.A.; Buchwald, S.L. *Angew. Chem. Int. Ed. Engl.* ***1995***, *34*, 1348.
[183]For reviews, see Minisci, F. *Top. Curr. Chem.* ***1976***, *62*, 1, see pp. 6–16, *Synthesis* ***1973***, 1, see pp. 2–12, Sosnovsky, G.; Rawlinson, D.J. *Adv. Free-Radical Chem.* ***1972***, *4*, 203, see pp. 213–238.
[184]For a review of aminium radical ions, see Chow, Y.L. *React. Intermed. (Plenum)* ***1980***, *1*, 151.
[185]The reaction has been extended to the formation of primary aromatic amines, but the scope is narrow: Citterio, A.; Gentile, A.; Minisci, F.; Navarrini, V.; Serravalle, M.; Ventura, S. *J. Org. Chem.* ***1984***, *49*, 4479.

Unusual orientation has been reported for amination with haloamines and with NCl_3 in the presence of $AlCl_3$. For example, toluene gave predominately meta amination.[186] It has been suggested that initial attack in this case is by Cl^+ and that a nitrogen nucleophile (whose structure is not known, but is represented here as NH_2^- for simplicity) adds to the resulting arenium ion, so that the initial reaction is addition to a carbon–carbon double bond followed by elimination of HCl from **33**.[187]



33

According to this suggestion, the electrophilic attack is at the para position (or the ortho, which leads to the same product) and the meta orientation of the amino group arises indirectly. This mechanism is called the σ-*substitution mechanism*.

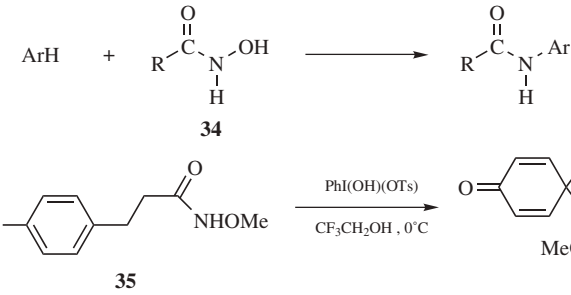
Diphenylliodonium salts react with amines in the presence of a copper catalyst. Diphenyliodonium tetrafluoroborate, $Ph_2I^+BF_4^-$, reacts with indole in DMF at 150°C with a $Cu(OAc)_2$ catalyst, for example, to give *N*-phenylindole.[188]

Aromatic compounds that do not contain meta-directing groups can be converted to diarylamines by treatment with aryl azides in the presence of phenol at −60°C: $ArH + Ar'N_3 \rightarrow ArNHAr'$.[189] Diarylamines are also obtained by the reaction of *N*-arylhydroxylamines with aromatic compounds (benzene, toluene, anisole) in the presence of F_3CCOOH: $ArH + Ar'NHOH \rightarrow ArNHAr'$.[190]

Direct *amidation* can be carried out if an aromatic compound is heated with a hydroxamic acid (**34**) in polyphosphoric acid, but the scope is essentially limited to phenolic ethers.[191] The reaction of an aromatic compound with aniline, Bu_4NF and $KMnO_4$ led to the diarylamine.[192] The formation of hydroindole derivatives was accomplished by reaction of a *N*-carbamoyl phenylethylamine derivative with phenyliodine (III) diacetate, followed by Bu_4NF.[193] Direct amidation via ipso substitution by nitrogen was accomplished when a *N*-methoxy arylethylamide (**35**) was

[186]See Strand, J.W.; Kovacic, P. *J. Am. Chem. Soc.* ***1973***, *95*, 2977, and references cited therein.
[187]Kovacic, P.; Levisky, J.A. *J. Am. Chem. Soc.* ***1966***, *88*, 1000.
[188]Zhou, T.; Chen, Z.-C. *Synth. Commun.* ***2002***, *32*, 903.
[189]Nakamura, K.; Ohno, A.; Oka, S. *Synthesis* ***1974***, 882. See also, Takeuchi, H.; Takano, K. *J. Chem. Soc. Perkin Trans. 1* ***1986***, 611.
[190]Shudo, K.; Ohta, T.; Okamoto, T. *J. Am. Chem. Soc.* ***1981***, *103*, 645.
[191]Wassmundt, F.W.; Padegimas, S.J. *J. Am. Chem. Soc.* ***1967***, *89*, 7131; March, J.; Engenito Jr., J.S. *J. Org. Chem.* ***1981***, *46*, 4304. Also see, Cablewski, T.; Gurr, P.A.; Rander, K.D.; Strauss, C.R. *J. Org. Chem.* ***1994***, *59*, 5814.
[192]Huertas, I.; Gallardo, I.; Marquet, J. *Tetrahedron Lett.* ***2001***, *42*, 3439.
[193]Pouységu, L.; Avellan, A.-V.; Quideau, S. *J. Org. Chem.* ***2002***, *67*, 3425.

treated with [hydroxyl(tosyloxy)iodo]benzene (HTIB) in 2,2,2-trifluoroethanol, giving a *N*-methoxy spirocylcic amide, **36**.[194]



Aromatic compounds add to DEAD (diethyl azodicarboxylate), in the presence of $InCl_3$–SiO_2 and microwave irradiation, to give the *N*-aryldiamino compound [$ArN(CO_2Et)$–$NHCO_2Et$].[195]

An interesting variation in the alkylation reaction used five equivalents of aluminum chloride in a reaction of *N*-methyl-*N*-phenylhydrazine and benzene to give *N*-methyl-4-phenylaniline.[196]

Also see **13-5**, **13-16**.

C. Sulfur Electrophiles

11-7 Sulfonation or Sulfo-de-hydrogenation

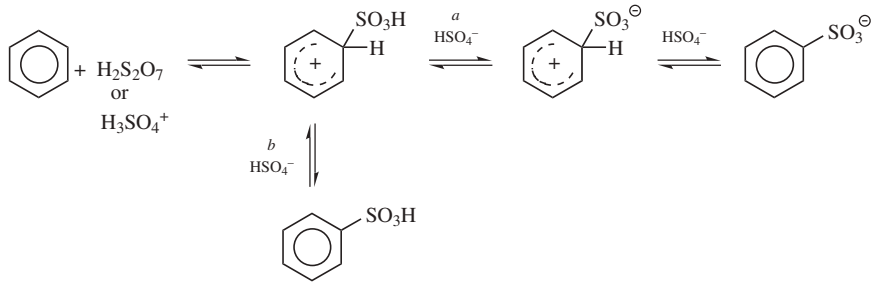
$$ArH + H_2SO_4 \longrightarrow ArSO_2OH$$

The sulfonation reaction is very broad in scope and many aromatic hydrocarbons (including fused ring systems), aryl halides, ethers, carboxylic acids, amines,[197] acylated amines, ketones, nitro compounds, and sulfonic acids have been sulfonated.[198] Phenols can also be successfully sulfonated, but attack at oxygen may compete.[199] Sulfonation is often accomplished with concentrated sulfuric acid, but it can also be done with fuming sulfuric acid, SO_3, $ClSO_2OH$, $ClSO_2NMe_2/In(OTf)_3$,[200] or other reagents.[201] As with nitration (**11-2**), reagents of a wide variety of activity are available to suit both highly active and highly inactive substrates. Since this is a reversible reaction (see **11-38**), it may be necessary to drive the reaction to completion.

[194]Miyazawa, E.; Sakamoto, T.; Kikugawa, Y. *J. Org. Chem.* ***2003***, *68*, 5429.
[195]Yadav, J.S.; Subba Reddy, B.V.; Kumar, G.M.; Madan, C. *Synlett* ***2001***, 1781.
[196]Ohwada, A.; Nara, S.; Sakamoto, T.; Kikugawa, Y. *J. Chem. Soc, Perkin Trans. 1* ***2001***, 3064.
[197]See Khelevin, R.N. *J. Org. Chem. USSR* ***1987***, *23*, 1709; ***1988***, *24*, 535, and references cited therein.
[198]For reviews, see Nelson, K.L. in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 3, Wiley, NY, ***1964***, pp. 1355–1392; Gilbert, E.E. *Sulfonation and Related Reactions*, Wiley, NY, ***1965***, pp. 62–83, 87–124.
[199]See, for example, de Wit, P.; Woldhuis, A.F.; Cerfontain, H. *Recl. Trav. Chim. Pays-Bas* ***1988***, *107*, 668.
[200]Frost, C.G.; Hartley, J.P.; Griffin, D. *Synlett* ***2002***, 1928.
[201]For a reaction using silica sulfuric acid, see Hajipour, A.R.; Mirjalili, B.B.F.; Zarei, A.; Khazdooz, L.; Ruoho, A.E. *Tetrahedron Lett.* ***2004***, *45*, 6607.

However, at low temperatures the reverse reaction is very slow and the forward reaction is practically irreversible.[202] Sulfur trioxide reacts much more rapidly than sulfuric acid with benzene it is nearly instantaneous. Sulfones are often side products. When sulfonation is carried out on a benzene ring containing four or five alkyl and/or halogen groups, rearrangements usually occur (see **11-36**).

A great deal of work has been done on the mechanism,[203] chiefly by Cerfontain and co-workers. Mechanistic study is made difficult by the complicated nature of the solutions. Indications are that the electrophile varies with the reagent, though SO_3 is involved in all cases, either free or combined with a carrier. In aqueous H_2SO_4 solutions, the electrophile is thought to be $H_3SO_4^+$ (or a combination of H_2SO_4 and H_3O^+) at concentrations below $\sim$ 80–85% H_2SO_4, and $H_2S_2O_7$ (or a combination of H_2SO_4 and SO_3) at concentrations higher than this[204] (the change-over point varies with the substrate[205]). Evidence for a change in electrophile is that in the dilute and in the concentrated solutions the rate of the reaction was proportional to the activity of $H_3SO_4^+$ and $H_2S_2O_7$, respectively. Further evidence is that with toluene as substrate the two types of solution gave very different ortho/para ratios. The mechanism is essentially the same for both electrophiles and may be shown as:[204]



The other product of the first step is HSO_4^- or H_2O from $H_2S_2O_7$ or $H_3SO_4^+$, respectively. Path *a* is the principal route, except at very high H_2SO_4 concentrations, when path *b* becomes important. With $H_3SO_4^+$ the first step is rate determining under all conditions, but with $H_2S_2O_7$ the first step is the slow step only up to $\sim$ 96% H_2SO_4, when a subsequent proton transfer becomes partially rate determining.[206] The $H_2S_2O_7$ is more reactive than $H_3SO_4^+$. In fuming sulfuric acid (H_2SO_4 containing excess SO_3), the electrophile is thought to be $H_3S_2O_7^+$ (protonated $H_2S_2O_7$) up to

[202]Spryskov, A.A. *J. Gen. Chem. USSR* ***1960***, *30*, 2433.
[203]For a monograph, see Cerfontain, H. *Mechanistic Aspects in Aromatic Sulfonation and Desulfonation*, Wiley, NY, ***1968***. For reviews, see Cerfontain, H. *Recl. Trav. Chim. Pays-Bas* ***1985***, *104*, 153; Cerfontain, H.; Kort, C.W.F. *Int. J. Sulfur Chem. C* ***1971***, *6*, 123; Taylor, R., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, ***1972***, pp. 56–77.
[204]Cerfontain, H.; Lambrechts, H.J.A.; Schaasberg-Nienhuis, Z.R.H.; Coombes, R.G.; Hadjigeorgiou, P.; Tucker, G.P. *J. Chem. Soc. Perkin Trans. 2* ***1985***, 659, and references cited therein.
[205]See, for example, Kaandorp, A.W.; Cerfontain, H. *Recl. Trav. Chim. Pays-Bas* ***1969***, *88*, 725.
[206]Kort, C.W.F.; Cerfontain, H. *Recl. Trav. Chim. Pays-Bas* ***1967***, *86*, 865.

$\sim$104% H_2SO_4 and $H_2S_4O_13$ ($H_2SO_4 + 3SO_3$) beyond this concentration.[207] Finally, when pure SO_3 is the reagent in aprotic solvents, SO_3 itself is the actual electrophile.[208] Free SO_3 is the most reactive of all these species, so that attack here is generally fast and a subsequent step is usually rate determining, at least in some solvents.

OS **II**, 42, 97, 482, 539; **III**, 288, 824; **IV**, 364; **VI**, 976.

11-8 Halosulfonation or Halosulfo-de-hydrogenation

$$ArH + ClSO_2OH \longrightarrow ArSO_2Cl$$

Aromatic sulfonyl chlorides can be prepared directly, by treatment of aromatic rings with chlorosulfuric acid.[209] Since sulfonic acids can also be prepared by the same reagent (**11-7**), it is likely that they are intermediates, being converted to the halides by excess chlorosulfuric acid.[210] The reaction has also been effected with bromo- and fluorosulfuric acids. Sulfinyl chlorides (ArSOCl) have been prepared by the reaction of thionyl chloride and an aromatic compound on Montmorillonite K10 clay.[211]

OS **I**, 8, 85.

11-9 Sulfonylation

Alkylsulfonylation or **Alkylsulfo-de-hydrogenation**

$$ArH + SOCl_2 \xrightarrow{TfOH} ArSOAr$$

$$ArH + Ar'SO_2Cl \xrightarrow{AlCl_3} ArSO_2Ar'$$

Diaryl sulfoxides can be prepared by the reaction of aromatic compounds with thionyl chloride and triflic acid.[212] Diaryl sulfones have also been prepared using thionyl chloride with the ionic liquid [bmim]Cl•$AlCl_3$.[213] Diaryl sulfones can be formed by treatment of aromatic compounds with aryl sulfonyl chlorides and a Friedel–Crafts catalyst[214] This reaction is analogous to Friedel–Crafts acylation with carboxylic acid halides (**11-17**). In a better procedure, the aromatic compound

[207]Koeberg-Telder, A.; Cerfontain, H. *J. Chem. Soc. Perkin Trans. 2* ***1973***, 633.

[208]Lammertsma, K.; Cerfontain, H. *J. Chem. Soc. Perkin Trans. 2* ***1980***, 28, and references cited therein.

[209]For a review, see Gilbert, E.E. *Sulfonaton and Related Reactions*, Wiley, NY, ***1965***, pp. 84–87.

[210]For a discussion of the mechanism with this reagent, see van Albada, M.P.; Cerfontain, H. *J. Chem. Soc. Perkin Trans. 2* ***1977***, 1548, 1557.

[211]Karade, N.N.; Kate, S.S.; Adude, R.N. *Synlett* ***2001***, 1573.

[212]Olah G.A.; Marinez, E.R.; Prakash, G.K.S. *Synlett* ***1999***, 1397.

[213]In [bmim]Cl•$AlCl_3$, 1-butyl-3-methylimidazolium chloroaluminate: Mohile, S.S.; Potdar, M.K.; Salunkhe, M.M. *Tetrahedron Lett.* ***2003***, *44*, 1255.

[214]For reviews, see Taylor, R., in Bamford, C.H.; Tipper, C.F.H *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, ***1972***, pp. 77–83; Jensen, F.R.; Goldman, G. in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 3, Wiley, NY, ***1964***, pp. 1319–1347. For a solid-state reaction using Fe^{3+}-Montmorillonite, see Choudary, B.M.; Chowdari, N.S.; Kantam, M.L. *J. Chem. Soc., Perkin Trans. 1*, ***2000***, 2689.

is treated with an aryl sulfonic acid and P_2O_5 in polyphosphoric acid.[215] Still another method uses an arylsulfonic trifluoromethanesulfonic anhydride $ArSO_2OSO_2CF_3$ (generated *in situ* from $ArSO_2Br$ and CF_3SO_3Ag) without a catalyst.[216] Indium *tris*(triflate)[217] and indium trichloride[218] give sulfonation with sulfonyl chlorides, and indium bromide was used in indoles.[219] A ferric chloride catalyzed reaction with microwave irradiation has also been reported,[220] as has the use of zinc metal with microwave irradiation.[221]

The reaction can be extended to the preparation of alkyl aryl sulfones by the use of a sulfonyl fluoride.[222]

Direct formation of diaryl sulfones from benzenesulfonic acid and benzene was accomplished using Nafion-H.[223]

OS **X**, 147.

D. Halogen Electrophiles

11-10 Halogenation[224]

Halo-de-hydrogenation

$$ArH + Br_2 \xrightarrow{\text{catalyst}} ArBr$$

1. *Chlorine and Bromine*. Aromatic compounds can be brominated or chlorinated by treatment with bromine or chlorine in the presence of a catalyst. For amines and phenols the reaction is so rapid that it is carried out with a dilute solution of Br_2 or Cl_2 in water at room temperature, or with aqueous HBr in DMSO.[225] Even so, with amines it is not possible to stop the reaction before all the available ortho and para positions are substituted, because the initially formed haloamines are weaker bases than the original amines and are less

[215]Graybill, B.M. *J. Org. Chem.* ***1967***, *32*, 2931; Sipe, Jr., H.J.; Clary, D.W.; White, S.B. *Synthesis* ***1984***, 283. See also, Ueda, M.; Uchiyama, K.; Kano, T. *Synthesis* ***1984***, 323.

[216]Effenberger, F.; Huthmacher, K. *Chem. Ber.* ***1976***, *109*, 2315. For similar methods, see Hancock, R.A.; Tyobeka, T.E.; Weigel, H. *J. Chem. Res. (S)* ***1980***, 270; Ono, M.; Nakamura, Y.; Sato, S.; Itoh, I. *Chem. Lett.* ***1988***, 395.

[217]Frost, C.G.; Hartley, J.P.; Whittle, A.J. *Synlett* ***2001***, 830.

[218]Garzya, V.; Forbes, I.T.; Lauru, S.; Maragni, P. *Tetahedron Lett.* ***2004***, *45*, 1499.

[219]Yadav, J.S.; Reddy, B.V.S.; Krishna, A.D.; Swamy, T. *Tetahedron Lett.* ***2003***, *44*, 6055.

[220]Marquié, J.; Laporterie, A.; Dubac, J.; Roques, N.; Desmurs, J.-R. *J. Org. Chem.* ***2001***, *66*, 421.

[221]Bandgar, B.P.; Kasture, S.P. *Synth. Commun.* ***2001***, *31*, 1065.

[222]Hyatt, J.A.; White, A.W. *Synthesis* ***1984***, 214.

[223]Olah, G.A.; Mathew, T.; Prakash, G.K.S. *Chem. Commun.* ***2001***, 1696.

[224]For a monograph, see de la Mare, P.B.D. *Electrophilic Halogenation*, Cambridge University Press, Cambridge, ***1976***. For reviews, see Buehler, C.A.; Pearson, D.E. *Survey of Organic Synthesis*, Wiley, NY, ***1970***, pp. 392–404; Braendlin, H.P.; McBee, E.T., in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 3, Wiley, NY, ***1964***, pp. 1517–1593. For a review of the halogenation of heterocyclic compounds, see Eisch, J.J. *Adv. Heterocycl. Chem.* ***1966***, *7*, 1. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 619–628.

[225]Srivastava, S.K.; Chauhan, P.M.S.; Bhaduri, A.P. *Chem. Commun.* ***1996***, 2679.

likely to be protonated by the liberated HX.[226] For this reason, primary amines are often converted to the corresponding anilides if monosubstitution is desired. With phenols it is possible to stop after one group has entered.[227] The rapid room-temperature reaction with amines and phenols is often used as a test for these compounds.

For less activated aromatic rings, iron was commonly used at one time for halogenation, but the real catalyst was shown not to be the iron itself, but rather the ferric bromide or ferric chloride formed in small amounts from the reaction between iron and the reagent. Indeed, ferric chloride and other Lewis acids are typically directly used as catalysts, as is iodine. For active substrates, including amines, phenols, naphthalene, and polyalkylbenzenes,[228] such as mesitylene and isodurene, no catalyst is needed. Many Lewis acids can be used, including thallium(III) acetate, which promotes bromination with high regioselectivity para to an ortho–para-directing group.[229] A mixture of $Mn(OAc)_3$ and acetyl chloride, with ultrasound, chlorinates anisole with high selectivity.[230] Bromination on NaY zeolite occurs with high para selectivity.[231]

Other acids can be used to promote chlorination or bromination. *N*-Bromosuccinimide and HBF_4 can be used to brominate phenols with high *para*-selectivity,[232] as can pyridinium bromide perbromide,[233] and NBS in acetic acid with ultrasound is effective.[234] The use of NBS with a catalytic amount of HCl has also been reported.[235] Both NCS and NBS with aqueous BF_3 gave the respective chloride or bromide.[236] Note that NBS in an ionic liquid[237] gave the brominated aromatic. Bromine on silica gel gave good yields of the brominated aromatic compound.[238] HBr with hydrogen peroxide

[226]Monobromination (para) of aromatic amines has been achieved with tetrabutylammonium tribromide: Berthelot, J.; Guette, C.; Desbène, P.; Basselier, J.; Chaquin, P.; Masure, D. *Can. J. Chem.* ***1989***, *67*, 2061. For another procedure, see Onaka, M.; Izumi, Y. *Chem. Lett.* ***1984***, 2007.

[227]For a review of the halogenation of phenols, see Brittain, J.M.; de la Mare, P.B.D., in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement D*, pt. 1, Wiley, NY, ***1983***, pp. 522–532.

[228]For a review of aromatic substitution on polyalkylbenzenes, see Baciocchi, E.; Illuminati, G. *Prog. Phys. Org. Chem.* ***1967***, *5*, 1.

[229]McKillop, A.; Bromley, D.; Taylor, E.C. *J. Org. Chem.* ***1972***, *37*, 88.

[230]Prokes, I.; Toma, S.; Luche, J.-L. *J. Chem. Res. (S)* ***1996***, 164.

[231]See Smith, K.; Bahzad, D. *Chem. Commun.* ***1996***, 467; Smith, K.; Musson, A.; DeBoos, G.A. *J. Org. Chem.* ***1998***, *63*, 8448. Also see, Paul, V.; Sudalai, A.; Daniel, T.; Srinivasan, K.V. *Tetrahedron Lett.* ***1994***, *35*, 7055.

[232]Oberhauser, T. *J. Org. Chem.* ***1997***, *62*, 4504.

[233]Reeves, W.P.; Lu, C.V.; Schulmeier, B.; Jonas, L.; Hatlevik, O. *Synth. Commun.* ***1998***, *28*, 499; Reeves, W.P.; King II, R.M. *Synth. Commun.* ***1993***, *23*, 855. Also see, Bisarya, S.C.; Rao, R. *Synth. Commun.* ***1993***, *23*, 779.

[234]Paul, V.; Sudalai, A.; Daniel, T.; Srinivasan, K.V. *Synth. Commun.* ***1995***, *25*, 2401.

[235]Andersh, B.; Murphy, D.L.; Olson, R.J. *Synth. Commun.* ***2000***, *30*, 2091.

[236]Prakash, G.K.S.; Mathew, T.; Hoole, D.; Esteves, P.M.; Wang, Q.; Rasul, G.; Olah, G.A. *J. Am. Chem. Soc.* ***2004***, *126*, 15770.

[237]In bbim BF_4, 1,3-di-*n*-butylimidazolium tetrafluoroborate: Rajagopal, R.; Jarikote, D.V.; Lahoti, R.J.; Daniel, T.; Srinivasan, K.V. *Tetrahedron Lett.* ***2003***, *44*, 1815.

[238]Ghiaci, M.; Asghari, J. *Bull. Chem. Soc. Jpn.* ***2001***, *74*, 1151.

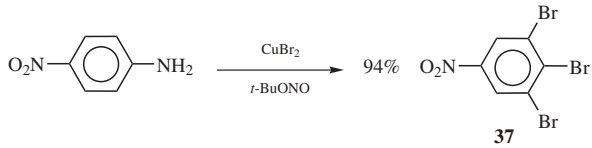
converted aniline to 2,4,6-tribromoaniline.[239] Majetich and co-workers reported the use of HBr/DMSO for the remarkably selective bromination of aniline.[240] *para*-Bromination of aniline was reported by mixing aniline with the ionic liquid, bmim Br_3.[241] Similarly, hmim Br_3[242] without another reagent is a brominating agent.

Other reagents have been used for chlorination and bromination, among them HOCl,[243] HOBr, and *N*-chloro and *N*-bromo amides (especially NBS and tetraalkylammonium polyhalides[244]). In all but the last of these cases, the reaction is catalyzed by the addition of acids. Sulfuryl chloride (SO_2Cl_2) in acetic acid effective chlorinates anisole derivatives,[245] and LiBr with ceric ammonium nitrate in acetonitrile brominates.[246] Acetyl chloride with a catalytic amount of ceric ammonium nitrate also converted aromatic compounds to the corresponding chlorinated derivative.[247] A mixture of KCl and Oxone® as chlorinated activated aromatic compounds.[248] Oxone® and KBr gave good para bromination of anisole.[249] Dibromoisocyanuric acid in H_2SO_4 is a very good brominating agent[250] for substrates with strongly deactivating substituents.[251] If the substrate contains alkyl groups, side-chain halogenation (**14-1**) is possible with most of the reagents mentioned, including chlorine and bromine. Since side-chain halogenation is catalyzed by light, the reactions should be run in the absence of light wherever possible. Both NCS in isopropanol[252] and *tert*-butyl hypochlorite[253] chlorinate aniline derivatives, and $KBr/NaBO_3 \bullet 4\ H_2O$ has been used for the bromination of aniline derivatives.[254] Anisole was brominated with para selectivity using HBr, in the presence of *tert*-butyl hydroperoxide and hydrogen peroxide.[255] Potassium bromide (KBr) with a zeolite (HZSM-5), acetic acid and 30% hydrogen peroxide was used to brominate both anisole and aniline derivatives.[256] Conversion of aniline to the *N*-$SnMe_3$ derivative allowed

[239]Vyas, P.V.; Bhatt, A.K.; Ramachandraiah, G.; Bedekar, A.V. *Tetrahedron Lett.* ***2003***, *44*, 4085.
[240]Majetich, G.; Hicks, R.; Reister, S. *J. Org. Chem.* ***1997***, *62*, 4321.
[241]1-Butyl-3-methylimidazolium tribromide: Lei, Z.-G.; Chen, Z.-C.; Hu, Y.;. Zheng, Q.-G. *Synthesis* ***2004***, 2809.
[242]In hmim, *N*-methylimidazolium: See Chiappe, C.; Leandri, E.; Pieraccini, D. *Chem. Commun.* ***2004***, 2536.
[243]For the use of calcium hypochlorite, see Nwaukwa, S.O.; Keehn, P.M. *Synth. Commun.* ***1989***, *19*, 799.
[244]See Kajigaeshi, S.; Moriwaki, M.; Tanaka, T.; Fujisaki, S.; Kakinami, T.; Okamoto, T. *J. Chem. Soc. Perkin Trans. 1* ***1990***, 897, and other papers in this series.
[245]Yu, G.; Mason, H.J.; Wu, X.; Endo, M.; Douglas, J.; Macor, J.E. *Tetrahedron Lett.* ***2001***, *42*, 3247.
[246]Roy, S.C.; Guin, C.; Rana, K.K.; Maiti, G. *Tetrahedron Lett.* ***2001***, *42*, 6941.
[247]Roy, S.C.; Rana, K.K.; Guin, C.; Banerjee, B. *Synlett* ***2003***, 221.
[248]Narender, N.; Srinivasu, P.; Kulkarni, S.J.; Raghavan, K.V. *Synth. Commun.* ***2002***, *32*, 279.
[249]Tamhankar, B.V.; Desai, U.V.; Mane, R.B.; Wadgaonkar, P.P.; Bedekar, A.V. *Synth. Commun.* ***2001***, *31*, 2021.
[250]Nitrobenzene is pentabrominated in 1 min with this reagent in 15% oleum at room temperature.
[251]Gottardi, W. *Monatsh. Chem.* ***1968***, *99*, 815; ***1969***, *100*, 42.
[252]Zanka, A.; Kubota, A. *Synlett* ***1999***, 1984.
[253]Lengyel, I.; Cesare, V.; Stephani, R. *Synth. Commun.* ***1998***, *28*, 1891.
[254]Roche, D.; Prasad, K.; Repic, O.; Blacklock, T.J. *Tetrahedron Lett.* ***2000***, *41*, 2083.
[255]Barhate, N.B.; Gajare, A.S.; Wakharkar, R.D.; Bedekar, A.V. *Tetrahedron* ***1999***, *55*, 11127.
[256]Narender, N.; Srinivasu, P.; Kulkarni, S.J.; Raghavan, K.V. *Synth. Commun.* ***2000***, *30*, 3669.

in situ bromination with bromine, with high para selectivity after conversion to the free amine with aqueous KF.[257] Pyridinium bromochromate converted phenolic derivatives to brominated phenols.[258]

Chlorine is a more active reagent than bromine. Phenols can be brominated exclusively in the ortho position (disubstitution of phenol gives 2,6-dibromophenol) by treatment with Br_2 at about $-70°C$, in the presence of *tert*-butylamine or triethylenediamine to precipitate out the liberated HBr.[259] Predominant ortho chlorination[260] of phenols has been achieved with chlorinated cyclohexadienes,[261] while para chlorination of phenols, phenolic ethers, and amines can be accomplished with *N*-chloroamines[262] and with *N*-chlorodimethylsulfonium chloride ($Me_2S^+Cl\,Cl^-$).[263] The last method is also successful for bromination when *N*-bromodimethylsufonium bromide is used. On the other hand, certain alkylated phenols can be brominated in the meta positions with Br_2 in the superacid solution SbF_5—HF.[264] It is likely that the meta orientation is the result of conversion by the super acid of the OH group to the OH_2^+ group, which should be meta directing because of its positive charge. Bromination and the Sandmeyer reaction (**14-20**) can be carried out in one laboratory step to give **37** by treatment of an aromatic primary amine with $CuBr_2$ and *tert*-butyl nitrite, for example[265]



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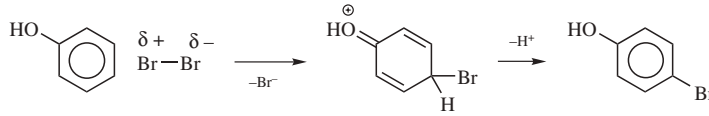
With deactivated aromatic derivatives, such as nitrobenzene, BrF_3 and Br_2 is an effective reagent, gives the *meta*-brominated product.[266] Tetrabutylammonium bromide and P_2O_5 at 100°C has been used to convert 2-hydroxypyridine derivatives to the corresponding 2-bromopyridine.[267] Bromination at C-6 of 2-aminopyridine was accomplished with NBS.[268] An alternative route

[257]Smith, M.B.; Guo, L.; Okeyo, S.; Stenzel, J.; Yanella, J.; La Chapelle, E. *Org. Lett.* ***2002***, *4*, 2321.
[258]Patwari, S.B.; Baseer, M.A.; Vibhute, Y.B.; Bhusare, S.R. *Tetrahedron Lett.* ***2003***, *44*, 4893.
[259]Pearson, D.E.; Wysong, R.D.; Breder, C.V. *J. Org. Chem.* ***1967***, *32*, 2358.
[260]For other methods of regioselective chlorination or bromination, see Kodomari, M.; Takahashi, S.; Yoshitomi, S. *Chem. Lett.* ***1987***, 1901; Kamigata, N.; Satoh, T.; Yoshida, M.; Matsuyama, H.; Kameyama, M. *Bull. Chem. Soc. Jpn.* ***1988***, *61*, 2226; de la Vega, F.; Sasson, Y. *J. Chem. Soc., Chem. Commun.* ***1989***, 653.
[261]Lemaire, M.; Guy, A.; Guette, J. *Bull. Soc. Chim. Fr.* ***1985***, 477.
[262]Lindsay Smith, J.R.; McKeer, L.C.; Taylor, J.M. *J. Chem. Soc. Perkin Trans. 2* ***1989***, 1529, 1537. See also, Minisci, F.; Vismara, E.; Fontana, F.; Platone, E.; Faraci, G. *J. Chem. Soc. Perkin Trans. 2* ***1989***, 123.
[263]Olah, G.A.; Ohannesian, L.; Arvanaghi, M. *Synthesis* ***1986***, 868.
[264]Jacquesy, J.; Jouannetaud, M.; Makani, S. *J. Chem. Soc., Chem. Commun.* ***1980***, 110.
[265]Doyle, M.P.; Van Lente, M.A.; Mowat, R.; Fobare, W.F. *J. Org. Chem.* ***1980***, *45*, 2570.
[266]Rozen, S.; Lerman, O. *J. Org. Chem.* ***1993***, *58*, 239.
[267]Kato, Y.; Okada, S.; Tomimoto, K.; Mase, T. *Tetrahedron Lett.* ***2001***, *42*, 4849.
[268]Cañibano, V.; Rodríguez, J.F.; Santos, M.; Sanz-Tejedor, A.; Carreño, M.C.; González, G.; García-Ruano, J.L. *Synthesis* ***2001***, 2175.

reacted pyridine *N*-oxide was $POCl_3$ and triethylamine to give 2-chloropyridine.[269] Pyridinium dichlorobromate with $FeCl_3$ brominates benzene.[270]

For reactions in the absence of a catalyst, the attacking entity is simply Br_2 or Cl_2 that has been polarized by the ring.[271]



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Evidence for molecular chlorine or bromine as the attacking species in these cases is that acids, bases, and other ions, especially chloride ion, accelerate the rate about equally, though if chlorine dissociated into Cl^+ and Cl^-, the addition of chloride should decrease the rate and the addition of acids should increase it. Intermediate **38** has been detected spectrally in the aqueous bromination of phenol.[272]

When a Lewis acid catalyst is used with chlorine or bromine, the attacking entity may be Cl^+ or Br^+, formed by $FeCl_3 + Br_2 \rightarrow FeCl_3Br^- + Br^+$, or it may be Cl_2 or Br_2, polarized by the catalyst. With other reagents, the attacking entity in brominations may be Br^+ or a species, such as H_2OBr^+ (the conjugate acid of HOBr), in which H_2O is a carrier of Br^+.[273] With HOCl in water the electrophile may be Cl_2O, Cl_2, or H_2OCl^+; in acetic acid it is generally AcOCl. All these species are more reactive than HOCl itself.[274] It is extremely doubtful that Cl^+ is a significant electrophile in chlorinations by HOCl.[274] It has been demonstrated in the reaction between *N*-methylaniline and calcium hypochlorite that the chlorine attacking entity attacks the *nitrogen* to give *N*-chloro-*N*-methylaniline, which rearranges (as in **11-31**) to give a mixture of ring-chlorinated *N*-methylanilines in which the ortho isomer predominates.[275] In addition to hypohalous acids and metal hypohalites, organic hypohalites are reactive. An example is *tert*-butylhypobromite (*t*-BuOBr), which brominated toluene in the presence of zeolite HNaX.[276]

[269]Jung, J.-C.; Jung, Y.-J.; Park, O.-S. *Synth. Commun.* ***2001***, *31*, 2507.

[270]Muathen, H.A. *Synthesis* ***2002***, 169.

[271]For reviews of the mechanism of halogenation, see de la Mare, P.B.D., *Electrophilic Halogenation*, Cambridge University Press, Cambridge, ***1976***; de la Mare, P.B.D.; Swedlund, B.E., in Patai. S. *The Chemistry of the Carbon–Halogen Bond*, pt. 1, Wiley, NY, ***1973***; pp. 490–536; Taylor, R., in Bamford, C.H.; Tipper, C.F.H *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, ***1972***, pp. 83–139. See also, Schubert, W.M.; Dial, J.L. *J. Am. Chem. Soc.* ***1975***, *97*, 3877; Keefer, R.M.; Andrews, L.J. *J. Am. Chem. Soc.* ***1977***, *99*, 5693; Tee, O.S.; Paventi, M.; Bennett, J.M. *J. Am. Chem. Soc.* ***1989***, *111*, 2233.

[272]Tee, O.S.; Iyengar, N.R.; Paventi, M. *J. Org. Chem.* ***1983***, *48*, 759. See also, Tee, O.S.; Iyengar, N.R. *Can. J. Chem.* ***1990***, *68*, 1769.

[273]For discussions, see Gilow, H.M.; Ridd, J.H. *J. Chem. Soc. Perkin Trans. 2* ***1973***, 1321; Rao, T.S.; Mali, S.I.; Dangat, V.T. *Tetrahedron* ***1978***, *34*, 205.

[274]Swain, C.G.; Crist, D.R. *J. Am. Chem. Soc.* ***1972***, *94*, 3195.

[275]Gassman, P.G.; Campbell, G.A. *J. Am. Chem. Soc.* ***1972***, *94*, 3891; Paul, D.F.; Haberfield, P. *J. Org. Chem.* ***1976***, *41*, 3170.

[276]Smith, K.; El-Hiti, G.A.; Hammond, M.E.W.; Bahzad, D.; Li, Z.; Siquet, C. *J. Chem. Soc., Perkin Trans. 1* ***2000***, 2745.

When chlorination or bromination is carried out at high temperatures (e.g., 300–400°C), ortho–para-directing groups direct meta and vice versa.[277] A different mechanism operates here, which is not completely understood. It is also possible for bromination to take place by the S_E1 mechanism, for example, in the *t*-BuOK-catalyzed bromination of 1,3,5-tribromobenzene.[278]

Furan and thiophene are known to polymerize in the presence of strong acid, both Brønsted–Lowry and Lewis. For such highly reactive heteroaromatic systems, alternative halogenating reagents are commonly used. Furan was converted to 2-bromofuran with a bromine•dioxane complex, for example, at <0°C.[279] 3-Butylthiophene reacted with NBS/acetic acid to give 2-bromo-3-butylthiophene.[280] *N*-Methylpyrrole reacted with NBS and a catalytic amount of PBr_3, at $-78°C \rightarrow -10°C$, to give *N*-methyl-3-bromopyrrole.[281]

2. *Iodine*. Iodine is the least reactive of the halogens in aromatic substitution.[282] Except for active substrates, an oxidizing agent must normally be present to oxidize I_2 to a better electrophile.[283] Examples of such oxidizing agents are HNO_3, HIO_3, SO_3, MnO_2,[284] hypervalent iodine compounds, such as $PhI(OTf)_2$,[285] $NaIO_4$,[286] peroxyacetic acid, H_2O_2[287] peroxydisulfates,[288] and ammonium iodide with Oxone®.[289] The ICl is a better iodinating agent than iodine itself.[290] Among other reagents used have been IF (prepared directly from the elements),[291] and benzyltrialkylammonium dichloroiodate (which iodinates phenols, aromatic amines, and *N*-acylated aromatic amines,[292] as well

[277]For a review of this type of reaction, see Kooyman, E.C. *Pure. Appl. Chem.* ***1963***, *7*, 193.

[278]Mach, M.H.; Bunnett, J.F. *J. Am. Chem. Soc.* ***1974***, *96*, 936.

[279]See Baciocchi, E.; Clementi, S.; Sebastiani, G.V. *J. Chem. Soc., Chem. Commun.* ***1975***, 875.

[280]Hoffmann, K.J.; Carlsen, P.H.J. *Synth. Commun.* ***1999***, *29*, 1607.

[281]Dvornikova, E.; Kamieńska-Trela, K. *Synlett* ***2002***, 1152.

[282]For reviews of I_2 as an electrophilic reagent, see Pizey, J.S., in Pizey, J.S. *Synthetic Reagents*, Vol. 3, Wiley, NY, ***1977***, pp. 227–276. For a review of aromatic iodination, see Merkushev, E.B. *Synthesis* ***1988***, 923.

[283]Butler, A.R. *J. Chem. Educ.* ***1971***, *48*, 508.

[284]Luliski, P.; Skulski, L. *Bull. Chem. Soc. Jpn.* ***1999***, *72*, 115.

[285]D'Auria, M.; Mauriello, G. *Tetrahedron Lett.* ***1995***, *36*, 4883; Togo, H.; Abe, S.; Nogami, G.; Yokoyama, M. *Bull. Chem. Soc. Jpn.* ***1999***, *72*, 2351; Panunzi, B.; Rotiroti, L.; Tingoli, M. *Tetrahedron Lett.* ***2003***, *44*, 8753.

[286]Luliński, P.; Skulski, L. *Bull. Chem. Soc. Jpn.* ***2000***, *73*, 951.

[287]For a discussion, see Makhon'kov, D.I.; Cheprakov, A.V.; Beletskaya, I.P. *J. Org. Chem. USSR* ***1989***, *24*, 2029. See Iskra, J.; Stavber, S.; Zupan, M. *Synthesis* ***2004***, 1869.

[288]Tajik, H.; Esmaeili, A.A.; Mohammadpoor-Baltork, I.; Ershadi, A.; Tajmehri, H. *Synth. Commun.* ***2003***, *33*, 1319.

[289]Mohan, K.V.V.K.; Narender, N.; Kulkarni, S.J. *Tetrahedron Lett.* ***2004***, *45*, 8015.

[290]For a review of ICl, see McCleland, C.W., in Pizey, J.S. *Synthetic Reagents*, Vol. 5, Wiley, NY, ***1983***, pp. 85–164. For a reaction using ICl, ZnO and an iron catalyst, see Mukaiyama, T.; Kitagawa, H.; Matsuo, J.-i. *Tetrahedron Lett.* ***2000***, *41*, 9383.

[291]Rozen, S.; Zamir, D. *J. Org. Chem.* ***1990***, *55*, 3552.

[292]See Kajigaeshi, S.; Kakinami, T.; Watanabe, F.; Okamoto, T. *Bull. Chem. Soc. Jpn.* ***1989***, *62*, 1349, and references cited therein. For a reaction of anisole with Me_4NICl_2 to give *p*-iodoanisole exclusively, see Hajipour, A.R.; Arbabian, M.; Ruoho, A.E. *J. Org. Chem.* ***2002***, *67*, 8622.

as unprotected aniline derivatives[293]). Iodination can also be accomplished by treatment of the substrate with NCI and sulfuric acid,[294] NIS and trifluoroacetic acid,[295] KI/KIO_3 in aqueous methanol,[296] I_2 in the presence of copper salts,[297] Al_2O_3,[298] and NaI with an iron catalyst.[299] Sodium periodate and iodine was used to iodinate β-carbolines.[300] Sodium iodide in liquid NO_2 can be used to iodinate aniline derivatives.[301] A solvent-free iodination was accomplished using $NaICl_2$ and an *N*-bromoammonium salt.[302] Another solvent-free iodination used I_2 with $Bi(NO_3)_3$ on silica gel.[303] Iodine with Selectfluor also leads to iodination of aromatic compounds.[304]

The actual attacking species is less clear than with bromine or chlorine. Iodine itself is too unreactive, except for active species, such as phenols, where there is good evidence that I_2 is the attacking entity.[305] There is evidence that AcOI may be the attacking entity when peroxyacetic acid is the oxidizing agent,[306] and I_3^+ when SO_3 or HIO_3 is the oxidizing agent.[307] The I^+ ion has been implicated in several procedures.[308] For an indirect method for accomplishing aromatic iodination, see **12-31**.

Note that conversion of aniline derivatives to the corresponding para aryllithium, followed by reaction with $B(OMe)_3$ and then bromine at −78°C gave *p*-bromoaniline.[309]

3. *Fluorine*. Direct fluorination of aromatic rings with F_2 is not feasible at room temperature, because of the extreme reactivity of F_2.[310] It has been accomplished at low temperatures (e.g., −70 to −20°C, depending on the

[293]Kosynkin, D.V.; Tour, J.M. *Org. Lett.* ***2001***, *3*, 991.
[294]Chaikovskii, V.K.; Shorokhodov, V.I.; Filimonov, V.D. *Russ. J. Org. Chem.* ***2001***, *37*, 1503.
[295]Castanet, A.-S.; Colobert, F.; Broutin, P.-E. *Tetrahedron Lett.* ***2002***, *43*, 5047.
[296]Adimurthy, S.; Ramachandraiah, G.; Ghosh, P.K.; Bedekar, A.V. *Tetrahedron Lett.* ***2003***, *44*, 5099.
[297]Baird Jr., W.C.; Surridge, J.H. *J. Org. Chem.* ***1970***, *35*, 3436; Horiuchi, C.A.; Satoh, J.Y. *Bull. Chem. Soc. Jpn.* ***1984***, *57*, 2691; Makhon'kov, D.I.; Cheprakov, A.V.; Rodkin, M.A.; Beletskaya, I.P. *J. Org. Chem. USSR* ***1986***, *22*, 1003.
[298]Pagni, R.M.; Kabalka, G.W.; Boothe, R.; Gaetano, K.; Stewart, L.J.; Conaway, R.; Dial, C.; Gray, D.; Larson, S.; Luidhart, T. *J. Org. Chem.* ***1988***, *53*, 4477.
[299]Firouzabadi, H.; Iranpoor, N.; Shiri, M. *Tetrahedron Lett.* ***2003***, *44*, 8781.
[300]Bonesi, S.M.; Erra-Balsells, R. *J. Heterocyclic Chem.* ***2001***, *38*, 77.
[301]Suzuki, H.; Nonoyama, N. *Tetrahedron Lett.* ***1998***, *39*, 4533.
[302]Hajipour, A.R.; Ruoho, A.E. *Org. Prep. Proceed. Int.* ***2002***, *34*, 647.
[303]Alexander, V.M.; Khandekar, A.C.; Samant, S.D. *Synlett* ***2003***, 1895.
[304]Stavber, S.; Kralj, P.; Zupan, M. *Synlett* ***2002***, 598.
[305]Grovenstein, Jr., E.; Aprahamian, N.S.; Bryan, C.J.; Gnanapragasam, N.S.; Kilby, D.C.; McKelvey Jr., J.M.; Sullivan, R.J. *J. Am. Chem. Soc.* ***1973***, *95*, 4261.
[306]Ogata, Y.; Urasaki, I. *J. Chem. Soc. C* ***1970***, 1689.
[307]Arotsky, J.; Butler, R.; Darby, A.C. *J. Chem. Soc. C* ***1970***, 1480.
[308]Galli, C. *J. Org. Chem.* ***1991***, *56*, 3238.
[309]Zhao, J.; Jia, X.; Zhai, H. *Tetrahedron Lett.* ***2003***, *44*, 9371.
[310]For a monograph on fluorinating agents, see German, L.; Zemskov, S. *New Fluorinating Agents in Organic Synthesis*, Springer, NY, ***1989***. For reviews of F_2 in organic synthesis see Purrington, S.T.; Kagen, B.S.; Patrick, T.B. *Chem. Rev.* ***1986***, *86*, 997; Grakauskas, V. *Intra-Sci. Chem. Rep.* ***1971***, *5*, 85. For a review of fluoroaromatic compounds, see Hewitt, C.D.; Silvester, M.J. *Aldrichimica Acta* ***1988***, *21*, 3.

substrate),[311] but the reaction is not yet of preparative significance. Fluorination has also been reported with acetyl hypofluorite CH_3COOF (generated from F_2 and sodium acetate),[312] with XeF_2,[313] and with an *N*-fluoroperfluoroalkyl sulfonamide, for example $(CF_3SO_2)_2NF$.[314] Pyridine has been converted to 2-fluoropyridine with $F_2/I_2/NEt_3$ in 1,1,2-trichloro-1,2,2-trifluoroethane.[315] However, none of these methods seems likely to displace the Schiemann reaction (**13-23**; heating diazonium tetrafluoroborates) as the most common method for introducing fluorine into aromatic rings.

The overall effectiveness of reagents in aromatic substitution is $Cl_2 > BrCl > Br_2 > ICl > I_2$.

OS **I**, 111, 121, 123, 128, 207, 323; **II**, 95, 97, 100, 173, 196, 343, 347, 349, 357, 592; **III**, 132, 134, 138, 262, 267, 575, 796; **IV**, 114, 166, 256, 545, 547, 872, 947; **V**, 117, 147, 206, 346; **VI**, 181, 700; **VIII**, 167; **IX**, 121, 356. Also see, OS **II**, 128.

E. Carbon Electrophiles

In the reactions in this section, a new carbon–carbon bond is formed. With respect to the aromatic ring, they are electrophilic substitutions, because a positive species attacks the ring. We treat them in this manner because it is customary. However, with respect to the electrophile, most of these reactions are nucleophilic substitutions, and what was said in Chapter 10 is pertinent to them.

11-11 Friedel–Crafts Alkylation

Alkylation or **Alkyl-de-hydrogenation**

$$ArH + RCl \xrightarrow{AlCl_3} ArCl$$

The alkylation of aromatic rings, called *Friedel–Crafts alkylation*, is a reaction of very broad scope.[316] The most important reagents are alkyl halides, alkenes, and

[311]Grakauskas, V. *J. Org. Chem.* ***1970***, *35*, 723; Cacace, F.; Giacomello, P.; Wolf, A.P. *J. Am. Chem. Soc.* ***1980***, *102*, 3511; Stavber, S.; Zupan, M. *J. Org. Chem.* ***1983***, *48*, 2223. See also, Purrington, S.T.; Woodard, D.L. *J. Org. Chem.* ***1991***, *56*, 142.

[312]See Hebel, D.; Lerman, O.; Rozen, S. *Bull. Soc. Chim. Fr.* ***1986***, 861; Visser, G.W.M.; Bakker, C.N.M.; van Halteren, B.W.; Herscheid, J.D.M.; Brinkman, G.A.; Hoekstra, A. *J. Org. Chem.* ***1986***, *51*, 1886.

[313]Shaw, M.J.; Hyman, H.H.; Filler, R. ***1970***, *92*, 6498; *J. Org. Chem.* ***1971***, *36*, 2917; Mackenzie, D.R.; Fajer, J. *J. Am. Chem. Soc.* ***1970***, *92*, 4994; Filler, R. *Isr. J. Chem.* ***1978***, *17*, 71.

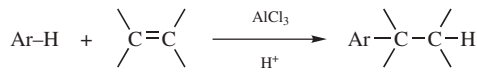
[314]Singh, S.; DesMarteau, D.D.; Zuberi, S.S.; Witz, M.; Huang, H. *J. Am. Chem. Soc.* ***1987***, *109*, 7194.

[315]Chambers, R.D.; Parsons, M.; Sandford, G.; Skinner, C.J.; Atherton, M.J.; Moilliet, J.S. *J. Chem. Soc., Perkin Trans. 1* ***1999***, 803.

[316]For a monograph, see Roberts, R.M.; Khalaf, A.A. *Friedel–Crafts Alkylation Chemistry*, Marcel Dekker, NY, ***1984***. For a treatise on Friedel–Crafts reactions in general, see Olah, G.A. *Friedel–Crafts and Related Reactions*, Wiley, NY, ***1963–1965***. Volume 1 covers general aspects, such as catalyst activity, intermediate complexes, and so on. Volume 2 covers alkylation and related reactions. In this volume, the various reagents are treated by the indicated authors as follows: alkenes and alkanes, Patinkin, S.H.; Friedman, B.S. pp. 1–288; dienes and substituted alkenes, Koncos, R.; Friedman, B.S. pp. 289–412; alkynes, Franzen, V. pp. 413–416; alkyl halides, Drahowzal, F.A. pp. 417–475; alcohols and ethers, Schriesheim, A. pp. 477–595; sulfonates and inorganic esters, Drahowzal, F.A. pp. 641–658. For a monograph in which five chapters of the above treatise are reprinted and more recent material added, see Olah, G.A. *Friedel–Crafts Chemistry*, Wiley, NY, ***1973***.

alcohols, but other types of reagent have also been employed.[316] Tertiary halides are particularly good substrates since they form relatively stable tertiary carbocations. *tert*-Butyl chloride reacts with phenetole in the presence of a $ReBr(CO)_5$ catalyst, for example, to give the 4-*tert*-butyl isomer as the major product.[317] When alkyl halides are used, the reactivity order is F > Cl > Br > I.[318] This trend can be seen in reactions of dihalo compounds, such as $FCH_2CH_2CH_2Cl$, which react with benzene to give $PhCH_2CH_2CH_2Cl$[319] when the catalyst is BCl_3. By the use of this catalyst, it is therefore possible to place a haloalkyl group on a ring (see also, **11-14**).[320] Di- and trihalides, when all the halogens are the same, usually react with more than one molecule of an aromatic compound; it is usually not possible to stop the reaction earlier.[321] Thus, benzene with CH_2Cl_2 gives not $PhCH_2Cl$, but Ph_2CH_2; benzene with $CHCl_3$ gives Ph_3CH. With CCl_4, however, the reaction stops when only three rings have been substituted to give Ph_3CCl. Functionalized alkyl halides, such as $ClCH(SEt)CO_2Et$, undergo Friedel–Crafts alkylation.[322] Interestingly, benzyl chloride was converted to diphenylmethane in benzene at 130°C with 10 atm of CO,[323] and also with a $LiB(C_6F_5)_4$ catalyst.[324]

Alkenes are especially good alkylating agents, generally proceeding by formation of an intermediate carbocation that reacts with the electron rich aromatic ring, and the final product (**39**) incorporates a H and Ar from ArH to a C=C double bond. Many variations are possible. This reaction has been accomplished in an ionic liquid, using $Sc(OTf)_3$ as the catalyst.[325] Intramolecular versions lead to polycyclic aromatic compounds.[326] Benzene reacted with 1,2,3,6-tetrahydropyridine in the presence of trifluoromethanesulfonic acid to give 4-phenylpiperidine.[327]



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[317]Nishiyama, Y.; Kakushou, F.; Sonoda, N. *Bull. Chem. Soc. Jpn.* ***2000***, *73*, 2779.

[318]For example, see Calloway, N.O. *J. Am. Chem. Soc.* ***1937***, *59*, 1474; Brown, H.C.; Jungk, H. *J. Am. Chem. Soc.* ***1955***, *77*, 5584.

[319]Olah, G.A.; Kuhn, S.J. *J. Org. Chem.* ***1964***, *29*, 2317.

[320]For a review of selectivity in this reaction, see Olah, G.A., in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 1, Wiley, NY, ***1963***, pp. 881–905. This review also covers the case of alkylation versus acylation.

[321]It has proven possible in some cases. Thus, arenes ArH have been converted to $ArCCl_3$ with CCl_4 and excess $AlCl_3$: Raabe, D.; Hörhold, H. *J. Prakt. Chem.* ***1987***, *329*, 1131; Belen'kii, L.I.; Brokhovetsky, D.B.; Krayushkin, M.M. *Chem. Scr.*, ***1989***, *29*, 81.

[322]For the reaction of anisole using a $Yb(OTf)_3$ catalyst, see Sinha, S.; Mandal, B.; Chandrasekaran, S. *Tetrahedron Lett.* ***2000***, *41*, 9109.

[323]Ogoshi, S.; Nakashima, H.; Shimonaka, K.; Kurosawa, H. *J. Am. Chem. Soc.* ***2001***, *123*, 8626.

[324]Mukaiyama, T.; Nakano, M.; Kikuchi, W.; Matsuo, J.-i. *Chem. Lett.* ***2000***, 1010.

[325]In emim SbF_6, 1-ethyl-3-mthylimidazolium: Song, C.E.; Shim, W.H.; Roh, E.J.; Choi, J.H. *Chem. Commun.* ***2000***, 1695.

[326]For a $RuCl_3$/AgOTf catalyzed version, see Youn, S.W.; Pastine, S.J.; Sames, D. *Org. Lett.* ***2004***, *6*, 581.

[327]Klumpp, D.A.; Beauchamp, P.S.; Sanchez Jr., G.V.; Aguirre, S.; de Leon, S. *Tetrahedron Lett.* ***2001***, *42*, 5821.

When 4-methoxyphenol reacted with isobutylene (electrolysis with 3 *M* $LiClO_4$ in nitromethane and acetic acid, initial reaction with the phenolic oxygen generated an ether moiety and the resulting carbocation was attacked by the aromatic ring to form a benzofuran.[328] Acetylene reacts with 2 mol of aromatic compound to give 1,1-diarylethanes, and phenylacetylene reacted to give 1,1-diarylethenes with a $Sc(OTf)_3$ catalyst.[329] Variations are possible here as well. Phenol reacted with trimethylsilylethyne, in the presence of $SnCl_4$ and 50% BuLi, at 105°C, to give the 2-vinyl phenolic derivative.[330] A palladium-catalyzed reaction of ethyl propiolate and *p*-xylene, with trifluoroacetic acid, gave the 3-arylalkenyl ester.[331] A ruthenium catalyzed intramolecular reaction with a pendant alkyne unit led to a dihydronapthalene derivative.[332]

Alcohols are more active than alkyl halides, but if a Lewis acid catalyst is used more catalyst is required, since the catalyst complexes with the OH group. However, proton acids, such as H_2SO_4, are often used to catalyze alkylation with alcohols. An intramolecular cyclization was reported from an allylic alcohol, using P_2O_5, to give indene derivatives.[333] When carboxylic esters are the reagents, there is competition between alkylation and acylation (**11-17**). This competition can often be controlled by choice of catalyst, and alkylation is usually favored, but carboxylic esters are not often employed in Friedel–Crafts reactions. Other alkylating agents are ethers, thiols, sulfates, sulfonates, alkyl nitro compounds,[334] and even alkanes and cycloalkanes, under conditions where these are converted to carbocations. Notable here are ethylene oxide, which puts the CH_2CH_2OH group onto the ring,[335] and cyclopropyl[336] units. For all types of reagent the reactivity order is allylic $\sim$ benzylic $>$ tertiary $>$ secondary $>$ primary.

[328]Chiba, K.; Fukuda, M.; Kim, S.; Kitano, Y.; Toda, M. *J. Org. Chem.* ***1999***, *64*, 7654. For a variation using a seleno ether to form a fused six-membered ring, see Abe, H.; Koshiba, N.; Yamasaki, A.; Harayama, T. *Heterocycles* ***1999***, *51* 2301. See also, Shen, Y.; Atobe, M.; Fuchigami, T. *Org. Lett.* ***2004***, *6*, 2441.

[329]Tsuchimoto, T.; Maeda, T.; Shirakawa, E.; Kawakami, Y. *Chem. Commun.* ***2000***, 1573.

[330]Kobayasshi, K.; Yamaguchi, M. *Org. Lett.* ***2001***, *3*, 241.

[331]Jia, C.; Lu, W.; Oyamada, J.; Kitamura, T.; Katsuda, K.; Irie, M.; Fujiwara, Y. *J. Am. Chem. Soc.* ***2000***, *122*, 7252.

[332]Chatani, N.; Inoue, H.; Ikeda, T.; Murai, S. *J. Org. Chem.* ***2000***, *65*, 4913. For a $GaCl_3$ catalyzed version, see Inoue, H.; Chatani, N.; Murai, S. *J. Org. Chem.* ***2002***, *67*, 1414. For a mercuric salt catalyst, see Nishizawa, M.; Takao, H.; Yadav, V.K.; Imagawa, H.; Sugihara, T. *Org. Lett.* ***2003***, *5*, 4563. For a BF_3 catalyzed version that generates allenes, see Ishikawa, T.; Manabe, S.; Aikawa, T.; Kudo, T.; Saito, S. *Org. Lett.* ***2004***, *6*, 2361. See also, Fillion, E.; Carson, R.J.; Trépanier, V.E.; Goll, J.M.; Remorova, A.A. *J. Am. Chem. Soc.* ***2004***, *126*, 15354.

[333]Basavaiah, D.; Bakthadoss, M.; Reddy, G.J. *Synthesis* ***2001***, 919. For a variation involving a propargylic alcohols with a ruthenium catalyst and ammonium tetrafluoroborate, see Nishibayashi, Y.; Joshikawa, M.; Inada, Y.; Hidai, M.; Uemura, S. *J. Am. Chem. Soc.* ***2002***, *124*, 11846.

[334]Bonvino, V.; Casini, G.; Ferappi, M.; Cingolani, G.M.; Pietroni, B.R. *Tetrahedron* ***1981***, *37*, 615.

[335]Taylor, S.K.; Dickinson, M.G.; May, S.A.; Pickering, D.A.; Sadek, P.C. *Synthesis* ***1998***, 1133. See also, Brandänge, S.; Bäckvall, J.-E.; Leijonmarck, H. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 2051.

[336]Patra, P.K.; Patro, B.; Ila, H.; Junjappa, H. *Tetrahedron Lett.* ***1993***, *34*, 3951.

Regardless of which reagent is used, a catalyst is nearly always required.[337] Aluminum chloride and boron trifluoride are the most common, but many other Lewis acids have been used, and also proton acids, such as HF and H_2SO_4.[338] For active halides a trace of a less active catalyst, such as $ZnCl_2$, may be enough. For an unreactive halide, such as chloromethane, a more powerful catalyst, such as $AlCl_3$, is needed, and in larger amounts. In some cases, especially with alkenes, a Lewis acid catalyst causes reaction only if a small amount of proton-donating cocatalyst is present. Catalysts have been arranged in the following order of overall reactivity: $AlBr_3 > AlCl_3 > GaCl_3 > FeCl_3 > SbCl_5$[339]$> ZrCl_4, SnCl_4 > BCl_3, BF_3, SbCl_3$;[340] but the reactivity order in each case depends on the substrate, reagent, and conditions.

Alkyl mesylates undergo alkylation reaction with benzene rings in the presence of $Sc(OTf)_3$.[341] Allylic acetates undergo alkylation with $Mo(CO)_6$[342] and allylic chlorides react in the presence of $ZnCl_2/SiO_2$.[343] Montmorillonite clay (K10) is an effective medium for alkylation reactions.[344] Nafion-H, a super acidic perfluorinated resin sulfonic acid, is a very good catalyst for gas phase alkylations with alkyl halides, alcohols,[345] or alkenes.[346]

Friedel–Crafts alkylation is unusual among the principal aromatic substitutions in that the entering group is activating (the product is more reactive than the starting aromatic substrate), and di- and polyalkylation are frequently observed. However, the activating effect of simple alkyl groups (e.g., ethyl, isopropyl) is only ~1.5–3 times as fast as benzene for Friedel–Crafts alkylations,[347] so it is often possible to obtain high yields of monoalkyl product.[348] Actually, the fact that di- and polyalkyl derivatives are frequently obtained is not due to the small difference in reactivity, but to the circumstance that alkylbenzenes are preferentially soluble in the catalyst layer, where the reaction actually takes place.[349] This factor can be removed by the use of a suitable solvent, by high temperatures, or by high–speed stirring.

[337]There are a few exceptions. Certain alkyl and vinylic triflates alkylate aromatic rings without a catalyst, see Gramstad, T.; Haszeldine, R.N. *J. Chem. Soc.* ***1957***, 4069; Olah, G.A.; Nishimura, J. *J. Am. Chem. Soc.* ***1974***, *96*, 2214; Stang, P.J.; Anderson, A.G. *J. Am. Chem. Soc.* ***1978***, *100*, 1520.

[338]For a review of catalysts and solvents in Friedel–Crafts reactions, see Olah, G.A., in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 1, Wiley, NY, ***1963***, pp. 201–366, 853–881.

[339]For a review of $SbCl_5$ as a Friedel–Crafts catalyst, see Yakobson, G.G.; Furin, G.G. *Synthesis* ***1980***, 345.

[340]Russell, G.A. *J. Am. Chem. Soc.* ***1959***, *81*, 4834.

[341]Kotsuki, H.; Oshisi, T.; Inoue, M.; Kojima, T. *Synthesis* ***1999***, 603; Singh, R.P.; Kamble, R.M.; Chandra, K.L.; Saravanani, P.; Singh, V.K. *Tetrahedron* ***2001***, *57*, 241.

[342]Shimizu, I.; Sakamoto, T.; Kawaragi, S.; Maruyama, Y.; Yamamoto, A. *Chem. Lett.* ***1997***, 137.

[343]Kodomari, M.; Nawa, S.; Miyoshi, T. *J. Chem. Soc. Chem.Commun.* ***1995***, 1895.

[344]Sieskind, O.; Albrecht, P. *Tetrahedron Lett.* ***1993***, *34*, 1197.

[345]Aleksiuk, O.; Biali, S.E. *Tetrahedron Lett.* ***1993***, *34*, 4857.

[346]For a review of Nafion-H in organic synthesis, see Olah, G.A.; Iyer, P.S.; Prakash, G.K.S. *Synthesis* ***1986***, 513.

[347]Condon, F.E. *J. Am. Chem. Soc.* ***1948***, *70*, 2265; Olah, G.A.; Kuhn, S.J.; Flood, S.H. *J. Am. Chem. Soc.* ***1962***, *84*, 1688.

[348]See Davister, M.; Laszlo, P. *Tetrahedron Lett.* ***1993***, *34*, 533 for examples of paradoxical selectivity in Friedel–Crafts alkylation.

[349]Francis, A.W. *Chem. Rev.* ***1948***, *43*, 257.

It is important to note that the OH, OR, NH_2, and so on groups do not facilitate the reaction, since most Lewis acid catalysts coordinate with these basic groups. Although phenols give the usual Friedel–Crafts reactions, orienting ortho and para, the reaction is very poor for aniline derivatives. However, amines can undergo the reaction if alkenes are used as reagents and aluminum anilides as catalysts.[350] In this method, the catalyst is prepared by treating the amine to be alkylated with $\frac{1}{3}$ equivalent of $AlCl_3$. A similar reaction can be performed with phenols, though here the catalyst is $Al(OAr)_3$.[351] Primary aromatic amines (and phenols) can be methylated regioselectively in the ortho position by an indirect method (see **11-23**). For an indirect method for regioselective ortho methylation of phenols (see p. 1247).

Naphthalene and other fused ring compounds are so reactive that they react with the catalyst, and therefore tend to give poor yields in Friedel–Crafts alkylation. Heterocyclic rings are also tend to be poor substrates for the reaction. Although some furans and thiophenes have been alkylated, polymerization is quite common, and a true alkylation of a pyridine or a quinoline has never been described.[352] *N*-Methylpyrrole reacted with the C=C unit of methacrolein in the presence of a chiral catalyst (a chiral Friedel–Crafts catalyst) to give the 2-alkylated pyrrole, with good enantioselectivity.[353] Alkylation at C-5 of 2-trimethylsilylfuran was accomplished using the carbocation [$(p\text{-MeOC}_6H_4)_2CH^+$ OTf] and Proton Sponge (see p. 386).[354] Although mechanistically different, an intramolecular cyclization of an *N*-allylic pyrrole was accomplished using a rhodium catalyst with 100 atm of CO/H_2.[355] Note that alkylation of pyridine and other nitrogen heterocycles can be accomplished by a free radical[356] (**14-19**) and by a nucleophilic method (**13-17**). A variation generates an electrophilic species on the aromatic substrate. The reaction of isoquinoline with $ClCO_2Ph$ and AgOTf, followed by reaction with an allylic silane, led to a 2-allylic dihydroisoquinoline.[357]

In most cases, meta-directing groups make the ring too inactive for alkylation. Nitrobenzene cannot be alkylated, and there are only a few reports of successful Friedel–Crafts alkylations when electron-withdrawing groups are present.[358] This is not because the attacking species is not powerful enough; indeed we have

[350]For a review, see Stroh, R.; Ebersberger, J.; Haberland, H.; Hahn, W. *Newer Methods Prep. Org. Chem.* ***1963***, *2*, 227. This article also appeared in *Angew. Chem.* ***1957***, *69*, 124.

[351]Koshchii, V.A.; Kozlikovskii, Ya.B.; Matyusha, A.A. *J. Org. Chem. USSR* ***1988***, *24*, 1358; Laan, J.A.M.; Giesen, F.L.L.; Ward, J.P. *Chem. Ind. (London)* ***1989***, 354. For a review, see Stroh, R.; Seydel, R.; Hahn, W. *Newer Methods Prep. Org. Chem.* ***1963***, *2*, 337. This article also appeared in *Angew. Chem.* ***1957***, *69*, 669.

[352]Drahowzal, F.A., in Olah, G.A., *Friedel–Crafts and Related Reactions*, Vol. 2, Wiley, NY, ***1964***, p. 433.

[353]Paras, N.A.; MacMillan, D.W.C. *J. Am. Chem. Soc.* ***2001***, *123*, 4370.

[354]Herrlich, M.; Hampel, N.; Mayr, H. *Org. Lett.* ***2001***, *3*, 1629.

[355]Settambalo, R.; Caiazzo, A.; Lazzaroni, R. *Tetraehdron Lett.* ***2001***, *42*, 4045.

[356]For a silyl-mediated reaction with 2-bromopyridine and 2 equivalents of AIBN, see Núñez, A.; Sánchez, A.; Burgos, C.; Alvarez-Builla, J. *Tetrahedron* ***2004***, *60*, 6217.

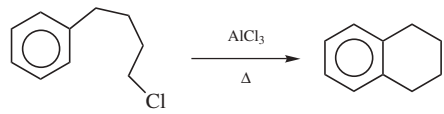
[357]Yamaguchi, R.; Nakayasu, T.; Hatano, B.; Nagura, T.; Kozima, S.; Fujita, K.-i. *Tetrahedron* ***2001***, *57*, 109.

[358]Campbell Jr., B.N.; Spaeth, E.C. *J. Am. Chem. Soc.* ***1959***, *81*, 5933; Yoneda, N.; Fukuhara, T.; Takahashi, Y.; Suzuki, A. *Chem. Lett.* ***1979***, 1003; Shen, Y.; Liu, H.; Chen,Y. *J. Org. Chem.* ***1990***, *55*, 3961.

seen (p. 681) that alkyl cations are among the most powerful of electrophiles. The difficulty is caused by the fact that, with inactive substrates, degradation and polymerization of the electrophile occurs before it can attack the ring. However, if an activating and a deactivating group are both present on a ring, Friedel–Crafts alkylation can be accomplished.[359] Aromatic nitro compounds can be methylated by a nucleophilic mechanism (**13-17**).

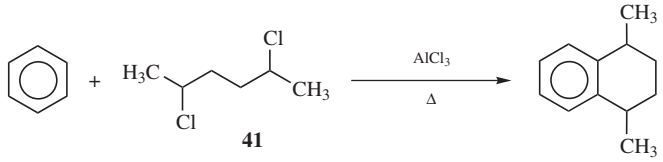
The intermediate for Friedel–Crafts alkylation is a carbocation, and rearrangement to a more stable cation can be quite facile. Therefore, rearrangement of the alkyl substrate occurs frequently and is an important synthetic limitation of Friedel–Crafts alkylation. For example, benzene treated with *n*-propyl bromide gives mostly isopropylbenzene (cumene) and much less *n*-propylbenzene. Rearrangement is usually in the order primary → secondary → tertiary and usually occurs by migration of the smaller group on the adjacent carbon. Therefore, in the absence of special electronic or resonance influences on the migrating group (such as phenyl), H migrates before methyl, which migrates before ethyl, and so on (see discussion of rearrangement mechanisms in Chapter 18). It is therefore not usually possible to put a primary alkyl group (other than methyl[360] and ethyl) onto an aromatic ring by Friedel–Crafts alkylation. Because of these rearrangements, *n*-alkylbenzenes are often prepared by *acylation* (**11-17**), followed by reduction (**19-61**).

An important use of the Friedel–Crafts alkylation reaction is to effect ring closure.[361] The most common method is to heat with aluminum chloride an aromatic compound having a halogen, hydroxy, or alkene group in the proper position, as, for example, in the preparation of tetralin, **40**.



40

Another way of effecting ring closure through Friedel–Crafts alkylation is to use a reagent containing two groups, such as **41**.



41

These reactions are most successful for the preparation of six-membered rings,[362] though five- and Seven-membered rings have also been closed in this

[359]Olah, G.A. in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 1, Wiley, NY, ***1963***, p. 34.
[360]For methylation using a specialized aluminum reagent, with a nickel catalyst, see Gelman, D.; Schumann, H.; Blum, J. *Tetrahedron Lett.* ***2000***, *41*, 7555.
[361]For a review, see Barclay, L.R.C., in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 2, Wiley, NY, ***1964***, pp. 785–977.
[362]See Khalaf, A.A.; Roberts, R.M. *J. Org. Chem.* ***1966***, *31*, 89.

manner. For other Friedel–Crafts ring-closure reactions, see **11-15**, **11-13**, and **11-17**. An interesting variation in this reaction showed that *N*-acyl aniline derivatives, upon treatment with $Et_2P(=O)H$ in water and a water soluble initiator (V-501) led to an intramolecular alkylation reaction to give an amide.[363]

As mentioned above, the electrophile in Friedel–Crafts alkylation is a carbocation, at least in most cases.[364] This is in accord with the knowledge that carbocations rearrange in the direction primary → secondary → tertiary (see Chapter 18). In each case the cation is formed from the attacking reagent and the catalyst. For the three most important types of reagent these reactions are

From alkyl halides: $RCl + AlCl_3 \longrightarrow R^+ + AlCl_4^-$

From alcohols[365] and Lewis acids: $ROH + AlCl_3 \longrightarrow ROAlCl_2 \longrightarrow R^+ + {}^-OAlCl_2$

From alcohols and proton acids: $ROH + H^+ \longrightarrow ROH_2^+ \longrightarrow R^+ + H_2O$

From alkenes (a supply of protons is usually required): $>C{=}C< + H^+ \longrightarrow H{-}\overset{|}{C}{-}C^{\oplus}$

There is direct evidence, from ir and nmr spectra, that the *tert*-butyl cation is quantitatively formed when *tert*-butyl chloride reacts with $AlCl_3$ in anhydrous liquid HCl.[366] In the case of alkenes, Markovnikov's rule (p. 1019) is followed. Carbocation formation is particularly easy from some reagents, because of the stability of the cations. Triphenylmethyl chloride[367] and 1-chloroadamantane[368] alkylate activated aromatic rings (e.g., phenols, amines) with no catalyst or solvent. Ions as stable as this are less reactive than other carbocations and often attack only active substrates. The tropylium ion, for example, alkylates anisole, but not benzene.[369] It was noted on p. 476 that relatively stable vinylic cations can be generated from certain vinylic compounds. These have been used to introduce vinylic groups into aryl substrates.[370] Lewis acids, such as BF_3[371] or $AlEt_3$,[372] can also be used to alkylation of aromatic rings with alkene units.

[363]Khan, T.A.; Tripoli, R.; Crawford, J.T.; Martin, C.G. Murphy, J.A. *Org. Lett.* ***2003***, *5*, 2971.

[364]For a discussion of the mechanism, see Taylor, R. *Electrophilic Aromatic Substitution*, *Electrophilic Aromatic Substitution*, Wiley, NY, ***1990***, pp. 188–213.

[365]See Bijoy, P.; Subba Rao, G.S.R. *Tetrahedron Lett.* ***1994***, *35*, 3341 for a double Friedle–Crafts alkylation involving a diol.

[366]Kalchschmid, F.; Mayer, E. *Angew. Chem. Int. Ed.* ***1976***, *15*, 773.

[367]See, for example, Hart, H.; Cassis, F.A. *J. Am. Chem. Soc.* ***1954***, *76*, 1634; Hickinbottom, W.J. *J. Chem. Soc.* ***1934***, 1700; Chuchani, G.; Zabicky, J. *J. Chem. Soc. C* ***1966***, 297.

[368]Takaku, M.; Taniguchi, M.; Inamoto, Y. *Synth. Commun.* ***1971***, *1*, 141.

[369]Bryce-Smith, D.; Perkins, N.A. *J. Chem. Soc.* ***1962***, 5295.

[370]Kitamura, T.; Kobayashi, S.; Taniguchi, H.; Rappoport, Z. *J. Org. Chem.* ***1982***, *47*, 5503.

[371]Majetich, G.; Liu, S.; Siesel, D. *Tetrahedron Lett.* ***1995***, *36*, 4749; Majetich, G.; Zhang, Y.; Feltman, T.L.; Belfoure, V. *Tetrahedron Lett.* ***1993***, *34*, 441; Majetich, G.; Zhang, Y.; Feltman, T.L.; Duncan Jr., S. *Tetrahedron Lett.* ***1993***, *34*, 445.

[372]Majetich, G.; Zhang, Y.; Liu, S. *Tetrahedron Lett.* ***1994***, *35*, 4887.

There is considerable evidence that many Friedel–Crafts alkylations, especially with primary reagents, do not go through a completely free carbocation. The ion may exist as a tight ion pair with, say, $AlCl_4^-$ as the counterion or as a complex. Among the evidence is that methylation of toluene by methyl bromide and methyl iodide gave different ortho/para/meta ratios,[373] although we would expect the same ratios if the same species attacked in each case. Other evidence is that, in some cases, the reaction kinetics are third order; first order each in aromatic substrate, attacking reagent, and catalyst.[374] In these instances a mechanism in which the carbocation is slowly formed and then rapidly attacked by the aromatic ring is ruled out since, in such a mechanism, the substrate would not appear in the rate expression. Since it is known that free carbocations, once formed, are rapidly attacked by the ring (acting as a nucleophile), there are no free carbocations here. Another possibility (with alkyl halides) is that some alkylations take place by an S_N2 mechanism (with respect to the halide), in which case no carbocations would be involved at all. However, a completely S_N2 mechanism requires inversion of configuration. Most investigations of Friedel–Crafts stereochemistry, even where an S_N2 mechanism might most be expected, have resulted in total racemization, or at best a few percent inversion. A few exceptions have been found,[375] most notably where the reagent was optically active propylene oxide, in which case 100% inversion was reported.[376]

Rearrangement is possible even with a non-carbocation mechanism. The rearrangement could occur *before* the attack on the ring takes place. It has been shown that treatment of $CH_3{}^{14}CH_2Br$ with $AlBr_3$ in the absence of any aromatic compound gave a mixture of the starting material and $^{14}CH_3CH_2Br$.[377] Similar results were obtained with $PhCH_2{}^{14}CH_2Br$, in which case the rearrangement was so fast that the rate could be measured only below $-70°C$.[378] Rearrangement could also occur *after* formation of the product, since alkylation is reversible (see **11-33**).[379]

See **14-17** and **14-19** for free-radical alkylation.

A variation of this reaction involves acylation of a β-keto ester, followed by Friedel–Crafts cyclization of the ketone moiety. The product is a coumarin **43**, in what is known as the *Pechmann condensation.*[380] Isolation of esters, such as **42**, is not

[373]Brown, H.C.; Jungk, H. *J. Am. Chem. Soc.* ***1956***, *78*, 2182.

[374]For examples see Choi, S.U.; Brown, H.C. *J. Am. Chem. Soc.* ***1963***, *85*, 2596.

[375]Some instances of retention of configuration have been reported; a neighboring-group mechanism is likely in these cases: see Masuda, S.; Nakajima, T.; Suga, S. *Bull. Chem. Soc. Jpn.* ***1983***, *56*, 1089; Effenberger, F.; Weber, T. *Angew. Chem. Int. Ed.* ***1987***, *26*, 142.

[376]Nakajima, T.; Suga, S.; Sugita, T.; Ichikawa, K. *Tetrahedron* ***1969***, *25*, 1807. For cases of almost complete inversion, with acyclic reagents, see Piccolo, O.; Azzena, U.; Melloni, G.; Delogu, G.; Valoti, E. *J. Org. Chem.* ***1991***, *56*, 183.

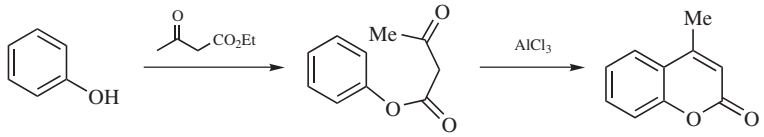
[377]Adema, E.H.; Sixma, F.L.J. *Recl. Trav. Chim. Pays-Bas* ***1962***, *81*, 323, 336.

[378]For a review of the use of isotopic labeling to study Friedel–Crafts reactions, see Roberts, R.M.; Gibson, T.L. *Isot. Org. Chem.* ***1980***, *5*, 103.

[379]For an example, see Lee, C.C.; Hamblin, M.C.; Uthe, J.F. *Can. J. Chem.* ***1964***, *42*, 1771.

[380] von Pechmann, H.; Duisberg, C. *Berchti* ***1883***, *16*, 2119; Sethna, S.; Shah, N.M. *Chem. Rev.* ***1945***, *36*, 1 (see p 10); Sethna, S.; Phadke, R. *Org. React.* ***1953***, *7*, 1.

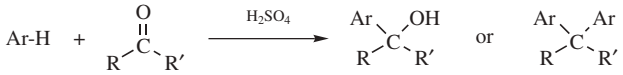
always necessary, and protonic acids can be used rather than Lewis acids. The Pechmann condensation is facilitated by the presence of hydroxyl (OH), dimethylamino (NMe_2) and alkyl groups meta to the hydroxyl of the phenol.[381] The reaction has been accomplished using microwave irradiation on graphite/Montmorillonite K10.[382] Pechmann condensation in an ionic liquid using ethyl acetate has also been reported.[383]



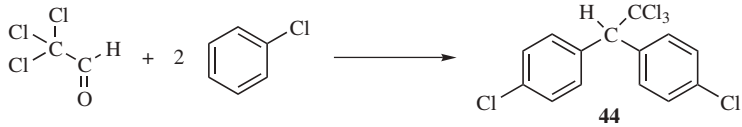
42 **43**

OS **I**, 95, 548; **II**, 151, 229, 232, 236, 248; **III**, 343, 347, 504, 842; **IV**, 47, 520, 620, 665, 702, 898, 960; **V**, 130, 654; **VI**, 109, 744.

11-12 Hydroxyalkylation or Hydroxyalkyl-de-hydrogenation



When an aldehyde, ketone, or other carbonyl-containing substrate is treated with a protonic or Lewis acid, an oxygen-stabilized cation is generated. In the presence of an aromatic ring, Friedel–Crafts type alkylation occurs. The condensation of aromatic rings with aldehydes or ketones is called *hydroxyalkylation*.[384] The reaction can be used to prepare alcohols,[385] though more often the alcohol initially produced reacts with another molecule of aromatic compound (**11-11**) to give diarylation. For this the reaction is quite useful, an example being the preparation of DDT, **44**:



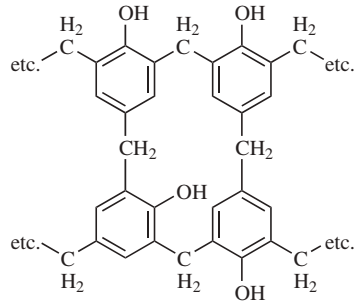
44

The diarylation reaction is especially common with phenols (the diaryl product here is called a bisphenol). The reaction is normally carried out in alkaline solution on

[381]Shah, M.M.; Shah, R.C. *Ber.* ***1938***, *71*, 2075; Miyano, M.; Dorn, C.R. *J. Org. Chem.* ***1972***, *37*, 259.
[382]Frère, S.; Thiéry, V.; Besson, T. *Tetrahedron Lett.* ***2001***, *42*, 2791.
[383]In [bmim]Cl·$2AlCl_3$, 1-butyl-3-methylimidazolium chloroaluminate: Potdar, M.K.; Mohile, S.S.; Salunkhe, M.M. *Tetrahedron Lett.* ***2001***, *42*, 9285.
[384]For a review, see Hofmann, J.E.; Schriesheim, A., in Olah, G.A., *Friedel–Crafts and Related Reactions*, Vol. 2, Wiley, NY, ***1963***, pp. 597–640.
[385]See, for example, Casiraghi, G.; Casnati, G.; Puglia, G.; Sartori, G. *Synthesis* ***1980***, 124.

the phenolate ion.[386] Another variation involved Friedel–Crafts coupling of an aldehyde to an activated aromatic compound (an aniline derivative) to give diaryl carbinols that exhibited atropisomerism (see 146).[387] When the reaction was done with a chiral aluminum complex, modest enantioselectivity was observed.

The hydroxymethylation of phenols with formaldehyde is called the *Lederer–Manasse reaction*. This reaction must be carefully controlled,[388] since it is possible for the para and both ortho positions to be substituted and for each of these to be rearylated, so that a polymeric structure **45** is produced. However, such polymers, which are of the Bakelite type (phenol–formaldehyde resins, **45**), are of considerable commercial importance.



45

The attacking species is the carbocation,

formed from the aldehyde or ketone and the acid catalyst, except when the reaction is carried out in basic solution.

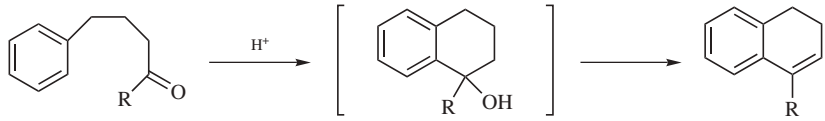
When an aromatic ring is treated with diethyl oxomalonate, $(EtOOC)_2C{=}O$, the product is an arylmalonic acid derivative $ArC(OH)(COOEt)_2$, which can be converted to an arylmalonic acid, $ArCH(COOEt)_2$.[389] This is therefore a way of applying the malonic ester synthesis (**10-67**) to an aryl group (see also, **13-14**). Of course, the opposite mechanism applies here: The aryl species is the nucleophile.

Two methods, both involving boron-containing reagents, have been devised for the regioselective ortho hydroxymethylation of phenols or aromatic amines.[390]

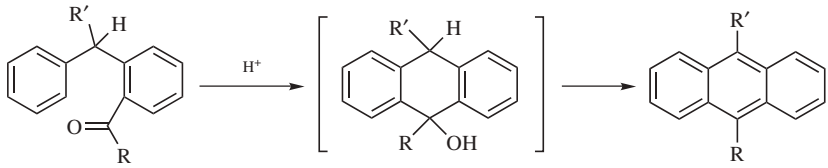
OS **III**, 326; **V**, 422; **VI**, 471, 856; **VIII**, 75, 77, 80. Also see, OS **I**, 214.

[386]For a review, see Schnell, H.; Krimm, H. *Angew. Chem. Int. Ed.* ***1963***, *2*, 373.
[387]Gothelf, A.S.; Hansen, T.; Jørgensen, K.A. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 854.
[388]See, for example, Casiraghi, G.; Casnati, G.; Pochini, A.; Puglia, G.; Ungaro, R.; Sartori, G. *Synthesis* ***1981***, 143.
[389]Ghosh, S.; Pardo, S.N.; Salomon, R.G. *J. Org. Chem.* ***1982***, *47*, 4692.
[390]Sugasawa, T.; Toyoda, T.; Adachi, M.; Sasakura, K. *J. Am. Chem. Soc.* ***1978***, *100*, 4842; Nagata, W.; Okada, K.; Aoki, T. *Synthesis* ***1979***, 365.

11-13 Cyclodehydration of Carbonyl-Containing Compounds



As described in the previous section (**11-12**), the reaction of carbonyl-containing functional groups with protonic or Lewis acids lead to oxygen-stabilized carbocations. When generated in the presence of an aromatic ring, Friedel–Crafts alkylation occurs to give an alcohol or an alkene, if dehydration occurs under the reaction conditions. When an aromatic compound contains an aldehyde or ketone function in a position suitable for closing a suitably sized ring, treatment with acid results in cyclodehydration. The reaction is a special case of **11-12**, but in this case dehydration almost always takes place to give a double bond conjugated with the aromatic ring.[391] The method is very general and is widely used to close both carbocyclic and heterocyclic rings.[392] Polyphosphoric acid is a common reagent, but other acids have also been used. In a variation known as the *Bradsher reaction*,[393] diarylmethanes containing a carbonyl group in the ortho position can be cyclized to anthracene derivatives, **46**. In this case, 1,4-dehydration takes place, at least formally.



46

An intramolecular cyclization of an aryl ether to the carbonyl of a pendant aryl ketone, on clay with microwave irradiation, led to a benzofuran via Friedel–Crafts cyclization and elimination of water.[394]

The carbonyl unit involved in the cyclization process is not restricted to aldehydes and ketones. The carbonyl of acid derivatives, such as amides can also be utilized. One of the more important cyclodehydration reactions is applied to the formation of heterocyclic systems via cyclization of β-aryl amides, in what is called the *Bischler–Napieralski reaction*.[395] In this reaction amides of the type **47** are

[391]For examples where the hydroxy compound was the principal product (with $R = CF_3$), see Fung, S.; Abraham, N.A.; Bellini, F.; Sestanj, K. *Can. J. Chem.* ***1983***, *61*, 368; Bonnet-Delpon, D.; Charpentier-Morize, M.; Jacquot, R. *J. Org. Chem.* ***1988***, *53*, 759.

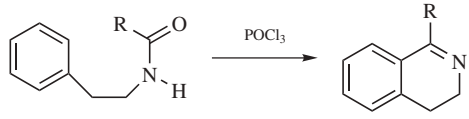
[392]For a review, see Bradsher, C.K. *Chem. Rev.* ***1987***, *87*, 1277.

[393]For examples, see Bradsher, C.K. *J. Am. Chem. Soc.* ***1940***, *62*, 486; Saraf, S.D.; Vingiello, F.A. *Synthesis* ***1970***, 655; Bradsher, C.K. Chem. Rev. ***1987***, *87*, 1277, see pp. 1287–1294.

[394]Meshram, H.M.; Sekhar, K.C.; Ganesh, Y.S.S.; Yadav, J.S. *Synlett* ***2000***, 1273.

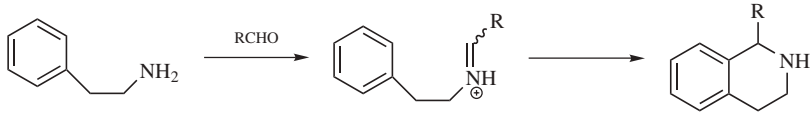
[395]For a review of the mechanism, see Fodor, G.; Nagubandi, S. *Tetrahedron* ***1980***, *36*, 1279.

cyclized with phosphorous oxychloride or other reagents, including polyphosphoric acid, sulfuric acid or phosphorus pentoxide, to give a dihydroisoquinoline, **48**. The Bischler–Napieralski reaction has been done in ionic liquids using $POCl_3$.[396] The reaction has also been done using solid-phase (see p. 416) techniques.[397]



47 **48**

If the starting compound contains a hydroxyl group in the α position, an additional dehydration takes place and the product is an isoquinoline.[398] Higher yields can be obtained if the amide is treated with PCl_5 to give an imino chloride $ArCH_2CH_2N{=}CR{-}Cl$, which is isolated and then cyclized by heating.[399] In this latter case, a nitrilium ion $ArCH_2CH_2{}^{\oplus}N{\equiv}CR$ is an intermediate.



49

Another useful variation is the *Pictet–Spengler isoquinoline synthesis*, also known as the *Pictet–Spengler reaction*.[400] The reactive intermediate is an iminium ion **49** rather than an oxygen-stabilized cation, but attack at the electrophilic carbon of the C=N unit (see **16-31**) leads to an isoquinoline derivative. When a β-arylamine reacts with an aldehyde, the product is an iminium salt, which cyclizes with an aromatic ring to complete the reaction and generate a tetrahydroisoquinoline.[401] A variety of aldehydes can be used, and substitution on the aromatic ring leads to many derivatives. When the reaction is done in the presence of a chiral thiourea catalyst, good enantioselectivity was observed.[402]

Another variation in this basic procedure leads to tetrahydroisoquinolines. When phenethylamine was treated with *N*-hydroxymethylbenzotriazole and then $AlCl_3$ in chloroform, cyclization occurred, and reduction with sodium borohydride gave the 1,2,3,4-tetrahydro-*N*-methylisoquinoline.[403]

[396]The reaction was done in bmim PF_6, 1-butyl-3-methylimidazolium hexafluorophosphate: Judeh, Z.M.A.; Ching, C.B.; Bu, J.; McCluskey, A. *Tetrahedron Lett.* ***2002***, *43*, 5089.
[397]Chern, M.-S.; Li, W.R. *Tetrahedron Lett.* ***2004***, *45*, 8323.
[398]Wang, X.-j.; Tan, J.; Grozinger, K. *Tetrahedron Lett.* ***1998***, *39*, 6609.
[399]Fodor, G.; Gal, G.; Phillips, B.A. *Angew. Chem. Int. Ed.* ***1972***, *11*, 919.
[400] Pictet, A.; Spengler, T. *Ber.* ***1911***, *44*, 2030; Cox, E.D.; Cook, J.M. *Chem. Rev.* ***1995***, *95*, 1797. See also Whaley, W.M.; Govindachari, T.R. *Org. React.* ***1951***, *6*, 74.
[401]Ong, H.H.; May, E.L. *J. Heterocyclic Chem.* ***1971***, *8*, 1007.
[402]Taylor, M.S.; Jacobsen, E.N. *J. Am. Chem. Soc.* ***2004***, *126*, 10558.
[403]Locher, C.; Peerzada, N. *J. Chem. Soc., Perkin Trans. 1* ***1999***, 179.

OS **I**, 360, 478; **II**, 62, 194; **III**, 281, 300, 329, 568, 580, 581; **IV**, 590; **V**, 550; **VI**, 1. Also see, OS **I**, 54.

11-14 Haloalkylation or Haloalkyl-de-hydrogenation

$$\mathrm{ArH + HCHO + HCl} \xrightarrow{\mathrm{ZnCl_2}} \mathrm{ArCH_2Cl}$$

When certain aromatic compounds are treated with formaldehyde and HCl, the CH_2Cl group is introduced into the ring in a reaction called *chloromethylation*. The reaction has also been carried out with other aldehydes and with HBr and HI. The more general term *haloalkylation* covers these cases.[404] The reaction is successful for benzene, and alkyl-, alkoxy-, and halobenzenes. It is greatly hindered by meta-directing groups, which reduce yields or completely prevent the reactions. Amines and phenols are too reactive and usually give polymers unless deactivating groups are also present, but phenolic ethers and esters successfully undergo the reaction. Compounds of lesser reactivity can often be chloromethylated with chloromethyl methyl ether ($ClCH_2OMe$), or methoxyacetyl chloride $MeOCH_2COCl$.[405] Zinc chloride is the most common catalyst, but other Friedel–Crafts catalysts are also employed. As with reaction **11-12** and for the same reason, an important side product is the diaryl compound Ar_2CH_2 (from formaldehyde).

Apparently, the initial step involves reaction of the aromatic compound with the aldehyde to form the hydroxyalkyl compound, exactly as in **11-12**, and then the HCl converts this to the chloroalkyl compound.[406] The acceleration of the reaction by $ZnCl_2$ has been attributed[407] to the raising of the acidity of the medium, causing an increase in the concentration of $HOCH_2^+$ ions.

OS **III**, 195, 197, 468, 557; **IV**, 980.

11-15 Friedel–Crafts Arylation: The Scholl Reaction

De-hydrogen-coupling

$$2\,\mathrm{ArH} \xrightarrow[\mathrm{H^+}]{\mathrm{AlCl_3}} \mathrm{Ar{-}Ar + H_2}$$

The coupling of two aromatic molecules by treatment with a Lewis acid and a proton acid is called the *Scholl reaction*.[408] Yields are low and the synthesis is seldom useful. High temperatures and strong-acid catalysts are required, and the reaction fails for substrates that are destroyed by these conditions. Because the reaction

[404]For reviews, see Belen'kii, L.I.; Vol'kenshtein, Yu.B.; Karmanova, I.B. *Russ. Chem. Rev.* ***1977***, *46*, 891; Olah, G.A.; Tolgyesi, W.S., in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 2, Wiley, NY, ***1963***, pp. 659–784.

[405]McKillop, A.; Madjdabadi, F.A.; Long, D.A. *Tetrahedron Lett.* ***1983***, *24*, 1933.

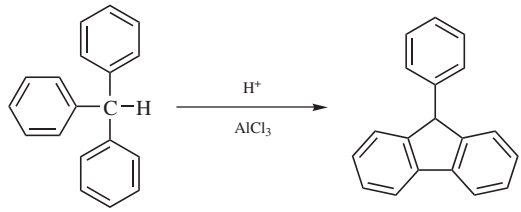
[406]Ziegler, E.; Hontschik, I.; Milowiz, L. *Monatsh. Chem.* ***1948***, *79*, 142; Ogata, Y.; Okano, M. *J. Am. Chem. Soc.* ***1956***, *78*, 5423. See also, Olah, G.A.; Yu, S.H. *J. Am. Chem. Soc.* ***1975***, *97*, 2293.

[407]Lyushin, M.M.; Mekhtiev, S.D.; Guseinova, S.N. *J. Org. Chem. USSR* ***1970***, *6*, 1445.

[408]For reviews, see Kovacic, P.; Jones, M.B. *Chem. Rev.* ***1987***, *87*, 357; Balaban, A.T.; Nenitzescu, C.D., in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 2, Wiley, NY, ***1964***, pp. 979–1047.

becomes important with large fused-ring systems, ordinary Friedel–Crafts reactions (**11-11**) on these systems are rare. For example, naphthalene gives binaphthyl under Friedel–Crafts conditions. Yields can be increased by the addition of a salt, such as $CuCl_2$ or $FeCl_3$, which acts as an oxidant.[409] Rhodium catalysts have also been used.[410]

Intramolecular Scholl reactions, such as formation of **50** from triphenylmethane,



50

are much more successful than the intermolecular reaction. The mechanism is not clear, but it may involve attack by a proton to give an arenium ion of the type **12** (p. 662), which would be the electrophile that attacks the other ring.[411] Sometimes arylations have been accomplished by treating aromatic substrates with particularly active aryl halides, especially fluorides. For free-radical arylations, see reactions **12-15**, **13-26**, **13-27**, **13-10**, **14-17**, and **14-18**.

OS **IV**, 482; **X**, 359. Also see, OS **V**, 102, 952.

11-16 Arylation of Aromatic Compounds By Metalated Aryls

$$\text{Ar-M} \xrightarrow{\text{Ar}'\text{-H}} \text{Ar—Ar}'$$

Many metalated aryl compounds are known to couple with aromatic compounds. Aniline derivatives react with $ArPb(OAc)_3$, for example, to give the 2-arylaniline.[412] Phenolic anions also react to form biaryls, with modest enantioselectivity in the presence of brucine.[413]

Phenylboronates [$ArB(OR)_2$] react with electron-deficient aromatic compounds, such as acetophenone, to give the biaryl.[414] Arylboronates also react with π-allyl palladium complexes to form the alkylated aromatic compound.[415]

[409]Kovacic, P.; Koch, Jr., F.W. *J. Org. Chem.* ***1965***, *30*, 3176; Kovacic, P.; Wu, C. *J. Org. Chem.* ***1961***, *26*, 759, 762. For examples with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 77–84; Sartori, G.; Maggi, R.; Bigi, F.; Grandi, M. *J. Org. Chem.* ***1993***, *58*, 7271

[410]Barrett, A.G.M.; Itoh, T.; Wallace, E.M. *Tetrahedron Lett.* ***1993***, *34*, 2233.

[411]For a discussion, see Clowes, G.A. *J. Chem. Soc., C* ***1968***, 2519.

[412]Saito, S.; Kano, T.; Ohyabu, Y.; Yamamoto, H. *Synlett* ***2000***, 1676.

[413]Kano, T.; Ohyabu, Y.; Saito, S.; Yamamoto, H. *J. Am. Chem. Soc.* ***2002***, *124*, 5365.

[414]Kakiuchi, F.; Kan, S.; Igi, K.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* ***2003***, *125*, 1698.

[415]Ortar, G. *Tetrahedron Lett.* ***2003***, *44*, 4311.

11-17 Friedel–Crafts Acylation

Acylation or Acyl-de-hydrogenation

$$\mathrm{ArH + RCOCl} \xrightarrow{\mathrm{AlCl_3}} \mathrm{ArCOR}$$

The most important method for the preparation of aryl ketones is known as *Friedel–Crafts acylation*.[416] The reaction is of wide scope. Reagents other than acyl halides can be used,[417] including carboxylic acids,[418] anhydrides, and ketenes. Oxalyl chloride has been used to give diaryl 1,2-diketones.[419] Carboxylic esters usually give alkylation as the predominant product (see **11-11**).[420] *N*-Carbamoyl β-lactams reacted with naphthalene in the presence of trifluoromethanesulfonic acid to give the keto-amide.[421]

The alkyl group (R in RCOCl) may be aryl as well as alkyl. The major disadvantages of Friedel–Crafts alkylation, polyalkylation, and rearrangement of the intermediate carbocation, are not a problem in Friedel–Crafts acylation. Rearrangement of the alkyl group (R in RCOCl) is never found because the intermediate is an acylium ion (an acyl cation, $RC{\equiv}O^+$, see below). Because the RCO group is deactivating, the reaction stops cleanly after one group is introduced. All four acyl halides can be used, though chlorides are most commonly employed. The order of activity is usually, but not always, I > Br > Cl > F.[422] Catalysts are Lewis acids,[423] similar to those in reaction **11-11**, but in acylation a little > than 1 equivalent of catalyst is required per mole of reagent, because the first mole coordinates

[416]For reviews of Friedel–Crafts acylation, see Olah, G.A. *Friedel–Crafts and Related Reactions*, Wiley, NY, ***1963–1964***, as follows: Vol. 1, Olah, G.A. pp. 91–115; Vol. 3, Gore, P.H. pp. 1–381; Peto, A.G. pp. 535–910; Sethna, S. pp. 911–1002; Jensen, F.R.; Goldman, G. pp. 1003–1032. For another review, see Gore, P.H. *Chem. Ind. (London)* ***1974***, 727.

[417]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1423–1426.

[418]Ranu, B.C.; Ghosh, K.; Jana, U. *J. Org. Chem.* ***1996***, *61*, 9546; Kawamura, M.; Cui, D.-M.; Hayashi, T.; Shimada, S. *Tetrahedron Lett.* ***2003***, *44*, 7715. For an example of acylation by heating with octanoic acid, without a catalyst, see Kaur, J.; Kozhevnikov, I.V. *Chem.Commun.* ***2002***, 2508.

[419]Mohr, B.; Enkelmann, V.; Wegner, G. *J. Org. Chem.* ***1994***, *59*, 635; Taber, D.F.; Sethuraman, M.R. *J. Org. Chem.* ***2000***, *65*, 254.

[420]For a reaction involving the Friedel–Crafts acylation using an ester, see Hwang, J.P.; Prakash, G.K.S.; Olah, G.A. *Tetrahedron* ***2000***, *56*, 7199.

[421]Anderson, K.W.; Tepe, J. *Org. Lett.* ***2002***, *4*, 459.

[422]Yamase, Y. *Bull. Chem. Soc. Jpn.* ***1961***, *34*, 480; Corriu, R. *Bull. Soc. Chim. Fr.* ***1965***, 821.

[423]The usual Lewis acids can be used, as described in **11–11**, and ferric chloride, iodine, zinc chloride, and iron are probably the most common catalysts. For a review, see Pearson, D.E.; Buehler, C.A. *Synthesis* ***1972***, 533. Recently employed catalysts include, $\mathbf{Ga(ONf)_3}$, where Nf = nonafluorobutanesulfonate: Matsu, J.-i.; Odashima, K.; Kobayashi, S. *Synlett* ***2000***, 403. $\mathbf{In(OTf)_3}$ with $LiClO_4$: Chapman, C.J.; Frost, C.G.; Hartley, J.P.; Whittle, A.J. *Tetrahedron Lett.* ***2001***, *42*, 773. $\mathbf{InCl_3}$: Choudhary, V.R.; Jana, S.K.; Patil, N.S. *Tetrahedron Lett.* ***2002***, *43*, 1105. $\mathbf{Sc(OTf)_3}$: Kawada, A.; Mitamura, S.; Matsuo, J-i.; Tsuchiya, T.; Kobayashi, S. *Bull. Chem. Soc. Jpn.* ***2000***, *73*, 2325. $\mathbf{Yb[C(SO_2C_4F_4)_3]_3}$: Barrett, A.G.M.; Bouloc, N.; Braddock, D.C.; Chadwick, D.; Henderson, D.A. *Synlett* ***2002***, 1653. $\mathbf{BiOCl_3}$: Répichet, S.; Le Roux, C.; Roques, N.; Dubac, J. *Tetrahedron Lett.* ***2003***, *44,* 2037. **ZnO**: Sarvari, M.H.; Sharghi, H. *J. Org. Chem.* ***2004***, *69*, 6953.

with the oxygen of the reagent [as in $R(Cl)C{=}O^{+}\ {}^{-}AlCl_3$].[424] A reusable catalyst [$Ln(OTf)_3$—$LiClO_4$] has been developed as well.[425] HY-Zeolite has also been used to facilitate the reaction with acetic anhydride.[426] A platinum catalyst was used with acetic anhydride,[427] $TiCl_4$ with acetyl chloride[428] or acetyl chloride and zinc powder with microwave irradiation.[429] Friedel–Crafts acylation using a carboxylic acid with a catalyst called Envirocat-EPIC (an acid-treated clay-based material was reported.[430] Friedel–Crafts acylation was reported in an ionic liquid.[431] An interesting acylation reaction was reported that coupled trichlorophenylmethane to benzene, giving benzophenone in the presence of the ionic liquid $AlCl_3$-*n*-BPC.[432] Acylation has been accomplished in carbon disulfide.[433]

Proton acids can be used as catalysts when the reagent is a carboxylic acid. The mixed carboxylic sulfonic anhydrides $RCOOSO_2CF_3$ are extremely reactive acylating agents and can smoothly acylate benzene without a catalyst.[434] With active substrates (e.g., aryl ethers, fused-ring systems, thiophenes), Friedel–Crafts acylation can be carried out with very small amounts of catalyst, often just a trace, or even sometimes with no catalyst at all.

The reaction is quite successful for many types of substrate, including fused ring systems, which give poor results in **11-11**. Compounds containing ortho–para-directing groups, including alkyl, hydroxy, alkoxy, halogen, and acetamido groups, are easily acylated and give mainly or exclusively the para products, because of the relatively large size of the acyl group. However, aromatic amines give poor results. With amines and phenols there may be competition from *N*- or *O*-acylation; however, *O*-acylated phenols can be converted to *C*-acylated phenols by the Fries rearrangement (**11-27**). Friedel–Crafts acylation is usually prevented by meta-directing groups. Indeed, nitrobenzene is often used as a solvent for the reaction. Many heterocyclic systems, including furans, thiophenes, pyrans, and pyrroles[435]

[424]The crystal structures of several of these complexes have been reported: Rasmussen, S.E.; Broch, N.C. *Acta Chem. Scand.* ***1966***, *20*, 1351; Chevrier, B.; Le Carpentier, J.; Weiss, R. *J. Am. Chem. Soc.* ***1972***, *94*, 5718. For a review of these complexes, see Chevrier, B.; Weiss, R. *Angew. Chem. Int. Ed.* ***1974***, *13*, 1.

[425]Kawada, A.; Mitamura, S.; Kobayashi, S. *Chem. Commun.* ***1996***, 183. See Kawada, A.; Mitamura, S.; Kobayashi, S. *SynLett*, ***1994***, 545 for the use of $Sc(OTf)_3$ with acetic anhydride and Hachiya, I.; Moriwaki, M.; Kobayashi, S. *Tetrahedron Lett.* ***1995***, *36*, 409 for the use of $Hf(OTf)_4$.

[426]Sreekumar, R.; Padmukumar, R. *Synth. Commun.* ***1997***, *27*, 777. See Paul, V.; Sudalai, A.; Daniel, T.; Srinivasan, K.V. *Tetrahedron Lett.* ***1994***, *35*, 2601 for the use of an acidic zeolite.

[427]Fürstner, A.; Voigtländer, D.; Schrader, W.; Giebel, D.; Reetz, M.T. *Org. Lett.* ***2001***, *3*, 417.

[428]Bensari, A.; Zaveri, N.T. *Synthesis* ***2003***, 267.

[429]Paul, S.; Nanda, P.; Gupta, R.; Loupy, A. *Synthesis* ***2003***, 2877.

[430]Bandgari, B.P.; Sadavarte, V.S. *Synth. Commun.* ***1999***, *29*, 2587.

[431]The reaction was catalyzed by Br_2O_3 in bmim NTf_2, 1-butyl-3-methylimidazolium triflimide: Gmouth, S.; Yang, H.; Vaultier, M. *Org. Lett.* ***2003***, *5*, 2219.

[432]This catalyst is *n*-butylpyridinium chloroaluminate, see Rebeiro, G.L.; Khadilkar, B.M. *Synth. Commun.* ***2000***, *30*, 1605.

[433]Georgakilas, V.; Perdikomatis, G.P.; Triantafyllou, A.S.; Siskos, M.G.; Zarkadis, A.K. *Tetrahedron* ***2002***, *58*, 2441.

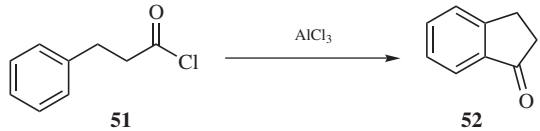
[434]Effenberger, F.; Sohn, E.; Epple, G. *Chem. Ber.* ***1983***, *116*, 1195. See also, Keumi, T.; Yoshimura, K.; Shimada, M.; Kitajima, H. *Bull. Chem. Soc. Jpn.* ***1988***, *44*, 455.

[435]Yadav, J.S.; Reddy, B.V.S.; Kondaji, G.; Rao, R.S.; Kumar, S.P. *Tetrahedron Lett.* ***2002***, *43*, 8133.

but not pyridines or quinolines, can be acylated in good yield. Initial reaction of indole with Et_2AlCl[436] or $SnCl_4$,[437] followed by acetyl chloride leads to 3-acetylindole. By comparison, the reaction of *N*-acetylindole with acetic anhydride and $AlCl_3$ gave *N*,6-diacetylindole.[438] Acetylation at C-3 was also accomplished with acetyl chloride in the ionic liquid emimcl-$AlCl_3$.[439] Gore, in Ref. 417 (pp. 36–100; with tables, pp. 105–321), presents an extensive summary of the substrates to which this reaction has been applied. Pyridines and quinolines can be also be acylated by a free-radical mechanism (reaction **14-19**).

When a mixed-anhydride RCOOCOR′ is the reagent, two products are possible: ArCOR and ArCOR′. Which product predominates depends on two factors. If R contains electron-withdrawing groups, then ArCOR′ is chiefly formed, but if this factor is approximately constant in R and R′, the ketone with the larger R group predominantly forms.[440] This means that *formylations* of the ring do not occur with mixed anhydrides of formic acid HCOOCOR.

An important use of the Friedel–Crafts acylation is to effect ring closure.[441] This can be done if an acyl halide, anhydride, or carboxylic acid[442] group is in the proper position. An example is the conversion of **51** to **52**.



51 **52**

The reaction is used mostly to close six-membered rings, but has also been done for five- and seven-membered rings, which close less readily. Even larger rings can be closed by high-dilution techniques.[443] Tricyclic and larger systems are often made by using substrates containing one of the acyl groups on a ring. Many fused-ring systems are made in this manner. If the bridging group is CO, the product is a quinone.[444] One of the most common catalysts for intramolecular Friedel–Crafts

[436]Okauchi, T.; Itonaga, M.; Minami, T.; Owa, T.; Kitoh, K.; Yoshino, H. *Org. Lett.* ***2000***, *2*, 1485; Zhang, Z; Yang, Z.; Wong, H.; Zhu, J.; Meanwell, N.A.; Kadow, J.F.; Wang, T. *J. Org. Chem.* ***2002***, *67*, 6226.

[437]Ottoni, O.; de V.F. Neder, A.; Dias, A.K.B.; Cruz, R.P.A.; Aquino, L.B. *Org. Lett.* ***2001***, *3*, 1005.

[438]Cruz, R.P.A.; Ottoni, O.; Abella, C.A.M.; Aquino, L.B. *Tetrahedron Lett.* ***2001***, *42*, 1467. 3-Methylindole was converted to 2-acetyl-3-methylindole with acetyl chloride and zinc(II) chloride: see Pal, M.; Dakarapu, R.; Padakanti, S. *J. Org. Chem.* ***2004***, *69*, 2913.

[439]The ionic liquid emimcl-$AlCl_3$ is 1-ethyl-3-methylimidazolium chloroaluminate, see Yeung, K.-S.; Farkas, M.E.; Qiu, Z.; Yang, Z. *Tetrahedron lett.* ***2002***, *43*, 5793.

[440]Edwards, Jr., W.R.; Sibelle, E.C. *J. Org. Chem.* ***1963***, *28*, 674.

[441]For a review, see Sethna, S., in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 3, Wiley, NY, ***1964***, pp. 911–1002;. For examples with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1427–1431.

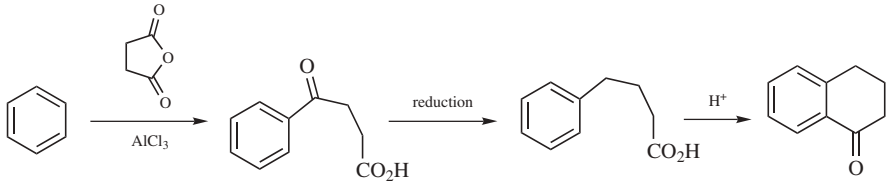
[442]For an example using $Tb(OTf)_3$, see Cui, D.-M.; Zhang, C.; Kawamura, M.; Shimada, S. *Tetrahedron Lett.* ***2004***, *45*, 1741.

[443]For example, see Schubert, W.M.; Sweeney, W.A.; Latourette, H.K. *J. Am. Chem. Soc.* ***1954***, *76*, 5462.

[444]For discussions, see Naruta, Y.; Maruyama, K., in Patai, S.; Rappoport, Z. *The Chemistry of the Quinonoid Compounds*, Vol. 2, pt. 1, Wiley, NY, ***1988***, pp. 325–332; Thomson, R.H., in Patai, S. *The Chemistry of the Quinonoid Compounds*, Vol. 1, pt. 1, Wiley, NY, ***1974***; pp. 136–139.

acylation is polyphosphoric acid[445] (because of its high potency), but $AlCl_3$, H_2SO_4, and other Lewis and proton acids are also used, though acylations with acyl halides are not generally catalyzed by proton acids.

Friedel–Crafts acylation can be carried out with cyclic anhydrides,[446] in which case the product contains a carboxyl group in the side chain (**53**). When succinic anhydride is used, the product is $ArCOCH_2CH_2COOH$. This can be reduced (**19-61**) to $ArCH_2CH_2CH_2COOH$, which can then be cyclized by an internal Friedel–Crafts acylation to give **54**. The total process is called the *Haworth reaction*:[447]

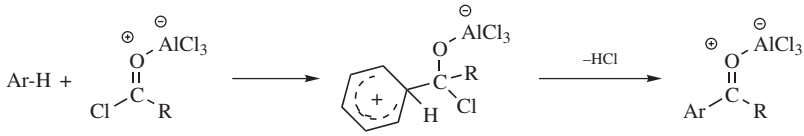


53 **54**

The mechanism of Friedel–Crafts acylation is not completely understood,[448] but at least two mechanisms probably operate, depending on conditions.[449] In most cases the attacking species is the acyl cation, either free or as an ion pair, formed by[450]

$$RCOCl + AlCl_3 \longrightarrow RCO^+ + AlCl_4^-$$

If R is tertiary, RCO^+ may lose CO to give R^+, so that the alkyl arene ArR is often a side product or even the main product. This kind of cleavage is much more likely with relatively unreactive substrates, where the acylium ion has time to break down. For example, pivaloyl chloride Me_3CCOCl gives the normal acyl product with anisole, but the alkyl product Me_3CPh with benzene. In the other mechanism, an acyl cation is not involved, but the 1:1 complex (**55**) attacks directly.[451]



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[445]For a review of polyphosphoric acid, see Rowlands, D.A., in Pizey, J.S. *Synthetic Reagents*, Vol. 6, Wiley, NY, ***1985***, pp. 156–414.

[446]For a review see Peto, A.G., in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 3, Wiley, NY, ***1964***, p. 535.

[447]See Agranat, I.; Shih, Y. *J. Chem. Educ.* ***1976***, *53*, 488.

[448]See Effenberger, F.; Eberhard, J.K.; Maier, A.H. *J. Am. Chem. Soc.* ***1996***, *118*, 12572 for first evidence of the reacting electrophile.

[449]For a review of the mechanism, see Taylor, R. *Electrophilic Aromatic Substitution*, Wiley, NY, ***1990***, pp. 222–237.

[450]After 2 min, exchange between PhCOCl and $Al(^{36}Cl)_3$ is complete: Oulevey, G.; Susz, P.B. *Helv. Chim. Acta* ***1964***, *47*, 1828.

[451]For example, see Corriu, R.; Dore, M.; Thomassin, R. *Tetrahedron* ***1971***, *27*, 5601, 5819; Tan, L.K.; Brownstein, S. *J. Org. Chem.* ***1983***, *48*, 302.

Free-ion attack is more likely for sterically hindered R.[452] The ion CH_3CO^+ has been detected (by IR spectroscopy) in the liquid complex between acetyl chloride and aluminum chloride, and in polar solvents, such as nitrobenzene; but in nonpolar solvents, such as chloroform, only the complex and not the free ion is present.[453] In any event, 1 equivalent of catalyst certainly remains complexed to the product at the end of the reaction. When the reaction is performed with $RCO^+SbF_6^-$, no catalyst is required and the free ion[454] (or ion pair) is undoubtedly the attacking entity.[455] The use of $LiClO_4$ on the metal triflate-catalyzed Friedel–Crafts acylation of methoxynaphthalene derivatives has been examined, and the presence of the lithium salt leads to acylation in the ring containing the methoxy unit, whereas reaction occurs in the other ring in the absence of lithium salts.[456] Note that lithium perchlorate forms a complex with acetic anhydride, which can be used for the Friedel–Crafts acetylation of activated aromatic compounds.[457]

OS **I**, 109, 353, 476, 517; **II**, 3, 8, 15, 81, 156, 169, 304, 520, 569; **III**, 6, 14, 23, 53, 109, 183, 248, 272, 593, 637, 761, 798; **IV**, 8, 34, 88, 898, 900; **V**, 111; **VI**, 34, 618, 625 **X**, 125.

Reaction **11-18** is a direct formylation of the ring.[458] Reaction **11-17** has not been used for formylation, since neither formic anhydride nor formyl chloride is stable at ordinary temperatures. Formyl chloride has been shown to be stable in chloroform solution for 1 h at −60°C,[459] but it is not useful for formylating aromatic rings under these conditions. Formic anhydride has been prepared in solution, but has not been isolated.[460] Mixed anhydrides of formic and other acids are known[461] and can be used to formylate amines (see **16-73**) and alcohols, but no formylation takes place when they are applied to aromatic rings. See **13-17** for a nucleophilic method for the formylation of aromatic rings.

A related reaction involves a biaryl, where one ring is a phenol. Treatment with BCl_3 and an $AlCl_3$ catalyst, followed by reaction with CO and $Pd(OAc)_2$, led to

[452]Yamase, Y. *Bull. Chem. Soc. Jpn.* ***1961***, *34*, 484; Gore, P.H. *Bull. Chem. Soc. Jpn.* ***1962***, *35*, 1627; Satchell, D.P.N. *J. Chem. Soc.* ***1961***, 5404.

[453]Cook, D. *Can. J. Chem.* ***1959***, *37*, 48; Cassimatis, D.; Bonnin, J.P.; Theophanides, T. *Can. J. Chem.* ***1970***, *48*, 3860.

[454]Crystal structures of solid $RCO^+ SbF_6^-$ salts have been reported: Boer, F.P. *J. Am. Chem. Soc.* ***1968***, *90*, 6706; Chevrier, B.; Le Carpentier, J.; Weiss, R. *Acta Crystallogr., Sect. B*, ***1972***, *28*, 2673; *J. Am. Chem. Soc.* ***1972***, *94*, 5718.

[455]Olah, G.A.; Lin, H.C.; Germain, A. *Synthesis* ***1974***, 895. For a review of acylium salts in organic synthesis, see Al-Talib, M.; Tashtoush, H. *Org. Prep. Proced. Int.* ***1990***, *22*, 1.

[456]Kobayashi, S.; Komoto, I. *Tetrahedron* ***2000***, *56*, 6463.

[457]Bartoli, G.; Bosco, M.; Marcantoni, E.; Massaccesi, M.; Rinalde, S.; Sambri, L. *Tetrahedron Lett.* ***2002***. *43*, 6331.

[458]For a review, see Olah, G.A.; Kuhn, S.J. Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 3, Wiley, NY, ***1964***, pp. 1153–1256. For a review of formylating agents, see Olah, G.A.; Ohannesian, L.; Arvanaghi, M. *Chem. Rev.* ***1987***, *87*, 671. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1423–1426.

[459]Staab, H.A.; Datta, A.P. *Angew. Chem. Int. Ed.* ***1964***, *3*, 132.

[460]Olah, G.A.; Vankar, Y.D.; Arvanaghi, M.; Sommer, J. *Angew. Chem. Int. Ed.* ***1979***, *18*, 614; Schijf, R.; Scheeren, J.W.; van Es, A.; Stevens, W. *Recl. Trav. Chim. Pays-Bas* ***1965***, *84*, 594.

[461]Stevens, W.; van Es, A. *Recl. Trav. Chim. Pays-Bas* ***1964***, *83*, 863.

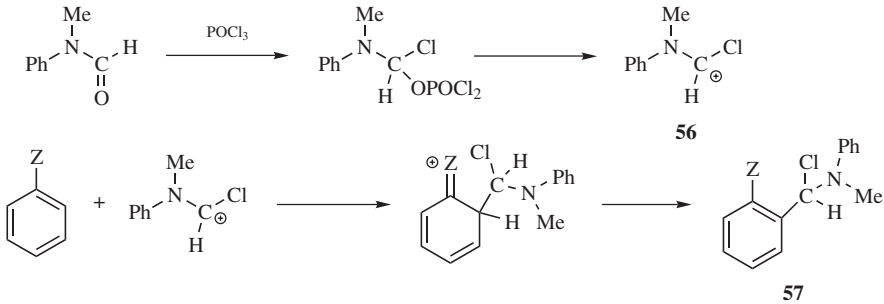
carbonylation and acylation to give the corresponding lactone.[462] Carbonylation of aromatic compounds can lead to aryl ketones. Heating an aromatic compound with $Ru(CO)_{12}$, ethylene and 20 atm of CO gave the corresponding aryl ethyl ketone.[463]

11-18 Formylation

Formylation or Formyl-de-hydrogenation

$$\text{Ar-H} \longrightarrow \text{Ar-CHO}$$

The reaction with disubstituted formamides $R_2N{-}CHO$ and phosphorus oxychloride, called the *Vilsmeier* or the *Vilsmeier–Haack reaction*,[464] is the most common method for the formylation of aromatic rings.[465] However, it is applicable only to active substrates, such as amines and phenols. An intramolecular version is also known.[466] Aromatic hydrocarbons and heterocycles can also be formylated, but only if they are much more active than benzene (e.g., azulenes, ferrocenes). Although *N*-phenyl-*N*-methylformamide is a common reagent, other arylalkyl amides and dialkyl amides are also used.[467] Phosgene ($COCl_2$) has been used in place of $POCl_3$. The reaction has also been carried out with other amides to give ketones (actually an example of **11-17**), but not often. The attacking species[468] is **56**,[469] and the mechanism is probably that shown to give **57**, which is unstable and easily hydrolyzes to the product. Either formation of **56** or the reaction of **56** with the substrate can be rate determining, depending on the reactivity of the substrate.[470]



[462]Zhou, Q.J.; Worm, K.; Dolle, R.E. *J.Org. Chem.* ***2004***, *69*, 5147.
[463]Ie, Y.; Chatani, N.; Ogo, T.; Marshall, D.R.; Fukuyama, T.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* ***2000***, *65*, 1475.
[464]See Blaser, D.; Calmes, M.; Daunis, J.; Natt, F.; Tardy-Delassus, A.; Jacquier, R. *Org. Prep. Proceed. Int.* ***1993***, *25*, 338 for improvements in this reaction.
[465]For a review, see Jutz, C. *Adv. Org. Chem.* ***1976***, *9*, pt. 1, 225.
[466]Meth-Cohn, O.; Goon, S. *J. Chem. Soc. Perkin Trans. 1* ***1997***, 85.
[467]For a review of dimethylformamide, see Pizey, J.S. *Synthetic Reagents*, Vol. 1, Wiley, NY, ***1974***, pp. 1–99.
[468]For a review of such species, see Kantlehner, W. *Adv. Org. Chem.* ***1979***, *9*, pt. 2, 5.
[469]See Arnold, Z.; Holy, A. *Collect. Czech. Chem. Commun.* ***1962***, *27*, 2886; Fritz, H.; Oehl, R. *Liebigs Ann. Chem.* ***1971***, *749*, 159; Jugie, G.; Smith, J.A.S.; Martin, G.J. *J. Chem. Soc. Perkin Trans. 2* ***1975***, 925.
[470]Alunni, S.; Linda, P.; Marino, G.; Santini, S.; Savelli, G. *J. Chem. Soc. Perkin Trans. 2* ***1972***, 2070.

When $(CF_3SO_2)_2O$ was used instead of $POCl_3$, the reaction was extended to some less-active compounds, including naphthalene and phenanthrene.[471]

In a related reaction, paraformaldehyde can be used, with $MgCl_2$—NEt_3, to convert phenol to phenol 2-carboxaldehyde.[472] Another variation treated acetanilide with $POCl_3$—DMF and generated 2-chloroquinoline-3-carboxaldehyde.[473] Used in conjunction with conjugated hydroxylamines, a tandem Vilsmeier–Beckman reaction (see **18-17** for the Beckman rearrangement) leads to pyridines (2-chloro-3-carboxaldehyde).[474] A chain-extension variation has been reported in which an aryl alkyl ketone is treated with $POCl_3$/DMF on silica with microwave irradiation to give a conjugated aldehyde, ArC(=O)R → ArC(Cl)=CHCHO.[475]

OS **I**, 217; **III**, 98, **IV**, 331, 539, 831, 915.

$$\mathrm{ArH + Zn(CN)_2 \xrightarrow{HCl} ArCH{=}NH_2^+\,Cl^- \xrightarrow{H_2O} ArCHO}$$

Formylation with $Zn(CN)_2$ and HCl is called the *Gatterman reaction*.[476] It can be applied to alkylbenzenes, phenols and their ethers, and many heterocyclic compounds. However, it cannot be applied to aromatic amines. In the original version of this reaction the substrate was treated with HCN, HCl, and $ZnCl_2$, but the use of $Zn(CN)_2$ and HCl (HCN and $ZnCl_2$ are generated *in situ*) makes the reaction more convenient to carry out and yields are not diminished. The mechanism of the Gatterman reaction has not been investigated very much, but it is known that an initially formed but not isolated nitrogen-containing product is hydrolyzed to aldehyde. This product is presumed to be $ArCH{=}NH_2^+Cl^-$, as shown. When benzene was treated with NaCN under superacid conditions (F_3CSO_2OH—SbF_5, see p. 236), a good yield of product was obtained, leading to the conclusion that the electrophile in this case was $^+C(H){=}N^+H_2$.[477] The Gatterman reaction may be regarded as a special case of **11-24**.

Another method, formylation with CO and HCl in the presence of $AlCl_3$ and CuCl[478] (the *Gatterman–Koch reaction*), is limited to benzene and alkylbenzenes.[479]

[471]Martínez, A.G.; Alvarez, R.M.; Barcina, J.O.; Cerero, S. de la M.; Vilar, E.T.; Fraile, A.G.; Hanack, M.; Subramanian, L.R. *J. Chem. Soc., Chem. Commun.* ***1990***, 1571.

[472]Hofsløkken, N.U.; Skattebøl, L. *Acta Chem. Scand.* ***1999***, *53*, 258.

[473]Ali, M.M.; Tasneem, Rajanna, K.C.; Prakash, P.K.S. *Synlett* ***2001***, 251. For another variation to generate 4-chloro-2-phenyl-*N*-formyldihydroquinoline derivatives, see Akila, S.; Selvi, S.; Balasubramanian, K. *Tetrahedron* ***2001***, *57*, 3465.

[474]Amaresh, R.R.; Perumal, P.T. *Synth. Commun.* ***2000***, *30*, 2269.

[475]Paul, S.; Gupta, M.; Gupta, R. *Synlett* ***2000***, 1115.

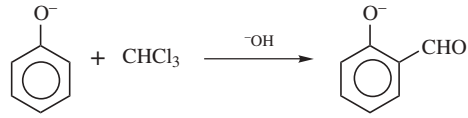
[476]For a review, see Truce, W.E. *Org. React.* ***1957***, *9*, 37. See Tanaka, M.; Fujiwara, M.; Ando, H. *J. Org. Chem.* ***1995***, *60*, 2106 for rate studies.

[477]Yato, M.; Ohwada, T.; Shudo, K. *J. Am. Chem. Soc.* ***1991***, *113*, 691.

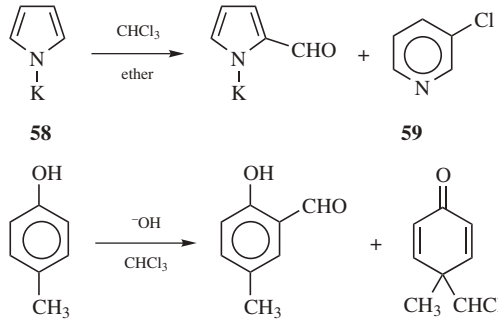
[478]The CuCl is not always necessary: see Toniolo, L.; Graziani, M. *J. Organomet. Chem.* ***1980***, *194*, 221.

[479]For a review, see Crounse, N.N. *Org. React.* ***1949***, *5*, 290.

OS **II**, 583; **III**, 549.



In the *Reimer–Tiemann reaction*, aromatic rings are formylated by reaction with chloroform and hydroxide ion.[480] The method is useful only for phenols and certain heterocyclic compounds such as pyrroles and indoles. Unlike the previous formylation methods (**11-18**), this one is conducted in basic solution. Yields are generally low, seldom rising above 50%.[481] The incoming group is directed ortho, unless both ortho positions are filled, in which case the attack is para.[482] Certain substrates have been shown to give abnormal products instead of or in addition to the normal ones. For example, **58** and **60** gave, respectively, **59** and **61** as well as the normal aldehyde products. From the nature of the reagents and



from the kind of abnormal products obtained, it is clear that the reactive entity in this reaction is dichlorocarbene CCl_2.[483] This is known to be produced by treatment of chloroform with bases (p. 521); it is an electrophilic reagent and is known to give ring expansion of aromatic rings (see **15-64**), accounting for products like **58**. The mechanism of the normal reaction is thus something like this.[484]

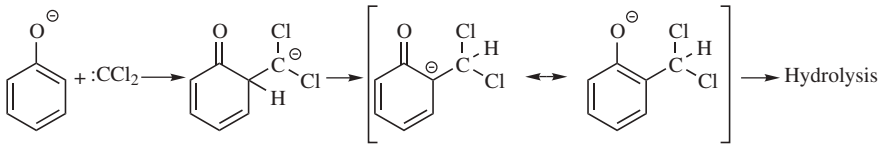
[480]For a review, see Wynberg, H.; Meijer, E.W. *Org. React.* ***1982***, *28*, 1.

[481]For improved procedures, see Thoer, A.; Denis, G.; Delmas, M.; Gaset, A. *Synth. Commun.* ***1988***, *18*, 2095; Cochran, J.C.; Melville, M.G. *Synth. Commun.* ***1990***, *20*, 609.

[482]Increased para selectivity has been achieved by the use of polyethylene glycol: Neumann, R.; Sasson, Y. *Synthesis* ***1986***, 569.

[483]For a review of carbene methods for introducing formyl and acyl groups into organic molecules see Kulinkovich, O.G. *Russ. Chem. Rev.* ***1989***, *58*, 711.

[484]Robinson, E.A. *J. Chem. Soc.* ***1961***, 1663; Hine, J.; van der Veen, J.M. *J. Am. Chem. Soc.* ***1959***, *81*, 6446. See also, Langlois, B.R. *Tetrahedron Lett.* ***1991***, *32*, 3691.



The formation of **61** in the case of **60** can be explained by attack of some of the CCl_2 ipso to the CH_3 group. Since this position does not contain a hydrogen, normal proton loss cannot take place and the reaction ends when the CCl_2^- moiety acquires a proton.

A method closely related to the Reimer–Tiemann reaction is the *Duff reaction*, in which hexamethylenetetramine $(CH_2)_6N_4$ is used instead of chloroform. This reaction can be applied only to phenols and amines; ortho substitution is generally observed and yields are low. A mechanism[485] has been proposed that involves initial aminoalkylation (**11-22**) to give $ArCH_2NH_2$, followed by dehydrogenation to ArCH=NH and hydrolysis of this to the aldehyde product. When $(CH_2)_6N_4$ is used in conjunction with F_3CCOOH, the reaction can be applied to simple alkylbenzenes; yields are much higher and a high degree of regioselectively para substitution is found.[486] In this case too an imine seems to be an intermediate.

OS **III**, 463; **IV**, 866

$$ArH + Cl_2CHOMe \xrightarrow{AlCl_3} ArCHO$$

Besides **11-18**, several other formylation methods are known.[487] In one of these, dichloromethyl methyl ether formylates aromatic rings with Friedel–Crafts catalysts.[488] The ArCHClOMe compound is probably an intermediate. Orthoformates have also been used.[489] In another method, aromatic rings are formylated with formyl fluoride HCOF and BF_3.[490] Unlike formyl chloride, formyl fluoride is stable enough for this purpose. This reaction was successful for benzene, alkylbenzenes, PhCl, PhBr, and naphthalene. Phenols can be regioselectively formylated in the ortho position in high yields by treatment with 2 equivalents of paraformaldehyde in aprotic solvents in the presence of $SnCl_4$ and a tertiary amine.[491] Phenols have also been formylated indirectly by conversion to the aryllithium reagent followed by treatment with *N*-formyl piperidine.[492] See also the indirect method mentioned at **11-23**.

[485]Ogata, Y.; Kawasaki, A.; Sugiura, F. *Tetrahedron* ***1968***, *24*, 5001.
[486]Smith, W.E. *J. Org. Chem.* ***1972***, *37*, 3972.
[487]For methods other than those described here, see Smith, R.A.J.; Manas, A.R.B. *Synthesis* ***1984***, 166; Olah, G.A.; Laali, K.; Farooq, O. *J. Org. Chem.* ***1985***, *50*, 1483; Nishino, H.; Tsunoda, K.; Kurosawa, K. *Bull. Chem. Soc. Jpn.* ***1989***, *62*, 545.
[488]Rieche, A.; Gross, H.; Höft, E. *Chem. Ber.* ***1960***, *93*, 88; Lewin, A.H.; Parker, S.R.; Fleming, N.B.; Carroll, F.I. *Org. Prep. Proceed. Int.* ***1978***, *10*, 201.
[489]Gross, H.; Rieche, A.; Matthey, G. *Chem. Ber.* ***1963***, *96*, 308.
[490]Olah, G.A.; Kuhn, S.J. *J. Am. Chem. Soc.* ***1960***, *82*, 2380.
[491]Casiraghi, G.; Casnati, G.; Puglia, G.; Sartori, G.; Terenghi, G. *J. Chem. Soc. Perkin Trans. 1* ***1980***, 1862.
[492]Hardcastle, I.R.; Quayle, P.; Ward, E.L.M. *Tetrahedron Lett.* ***1994***, *35*, 1747.

OS **V**, 49; **VII**, 162.

Reactions **11-19** and **11-20** are direct carboxylations[493] of aromatic rings.[494]

11-19 Carboxylation With Carbonyl Halides

Carboxylation or **Carboxy-de-hydrogenation**

$$ArH + COCl_2 \xrightarrow{AlCl_3} ArCOOH$$

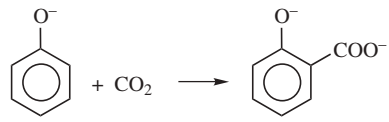
Phosgene, in the presence of Friedel–Crafts catalysts, can carboxylate the ring. This process is analogous to **11-17**, but the ArCOCl initially produced hydrolyzes to the carboxylic acid. However, in most cases the reaction does not take this course, but instead the ArCOCl attacks another ring to give a ketone ArCOAr. A number of other reagents have been used to get around this difficulty, among them oxalyl chloride, urea hydrochloride, chloral Cl_3CCHO,[495] carbamoyl chloride H_2NCOCl, and *N*,*N*-diethylcarbamoyl chloride.[496] With carbamoyl chloride the reaction is called the *Gatterman amide synthesis* and the product is an amide. Among compounds carboxylated by one or another of these reagents are benzene, alkylbenzenes, and fused ring systems.[497]

Although mechanistically different, other methods are available to convert aromatic compounds to aromatic carboxylic acids. The palladium-catalyzed reaction of aromatic compounds and formic acid leads to benzoic acid derivatives.[498] Diphenyliodonium tetrafluoroborate, $Ph_2I^+BF_4^-$ reacts with CO and In in DMF, with a palladium catalyst, to give benzophenone.[499]

OS **V**, 706; **VII**, 420.

11-20 Carboxylation With Carbon Dioxide: The Kolbe–Schmitt Reaction

Carboxylation or **Carboxy-de-hydrogenation**



[493]For other carboxylation methods, one of which leads to the anhydride, see Sakakibara, T.; Odaira, M. *J. Org. Chem.* ***1976***, *41*, 2049; Fujiwara, Y.; Kawata, I.; Kawauchi, T.; Taniguchi, H. *J. Chem. Soc., Chem. Commun.* ***1982***, 132.

[494]For a review, see Olah, G.A.; Olah, J.A., in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 3, Wiley, NY, ***1964***, pp. 1257–1273.

[495]Menegheli, P.; Rezende, M.C.; Zucco, C. *Synth. Commun.* ***1987***, *17*, 457.

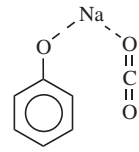
[496]Naumov, Yu.A.; Isakova, A.P.; Kost, A.N.; Zakharov, V.P.; Zvolinskii, V.P.; Moiseikina, N.F.; Nikeryasova, S.V. *J. Org. Chem. USSR* ***1975***, *11*, 362.

[497]For the use of phosgene to carboxylate phenols, see Sartori, G.; Casnati, G.; Bigi, F.; Bonini, G. *Synthesis* ***1988***, 763.

[498]Shibahara, F.; Kinoshita, S.; Nozaki, K. *Org. Lett.* ***2004***, *6*, 2437.

[499]Zhou, T.; Chen, Z.-C. *Synth. Commun.* ***2002***, *32*, 3431.

Sodium phenoxides can be carboxylated, mostly in the ortho position, by carbon dioxide (the *Kolbe–Schmitt reaction*). The mechanism is not clearly understood, but apparently some kind of a complex is formed between the reactants,[500] making the carbon of the CO_2 more positive and putting it in a good



position to attack the ring. Potassium phenoxide, which is less likely to form such a complex,[501] is chiefly attacked in the para position.[502] Carbon tetrachloride can be used instead of CO_2 under Reimer–Tiemann (**11-18**) conditions.

Sodium or potassium phenoxide can be carboxylated regioselectively in the para position in high yield by treatment with sodium or potassium carbonate and carbon monoxide.[503] ^{14}C Labeling showed that it is the carbonate carbon that appears in the *p*-hydroxybenzoic acid product.[504] The CO is converted to sodium or potassium formate. Carbon monoxide has also been used to carboxylate aromatic rings with palladium compounds as catalysts.[505] In addition, a palladium-catalyzed reaction has been used directly to prepare acyl fluorides ArH → ArCOF.[506]

An enzymatic carboxylation was reported, in supercritical CO_2 (see p. $$$), in which exposure of pyrrole to *Bacillus megaterium* PYR2910 and $KHCO_3$ gave the potassium salt of pyrrole-2-carboxylic acid.[507]

OS **II**, 557.

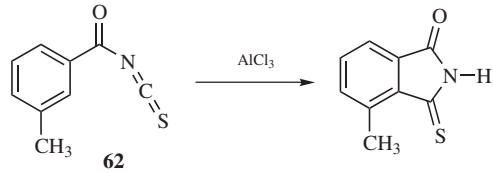
11-21 Amidation

N-Alkylcarbamoyl-de-hydrogenation

$$\mathrm{ArH + RNCO} \xrightarrow{\mathrm{AlCl_3}} \mathrm{ArCONHR}$$

[500]Hales J.L.; Jones, J.I.; Lindsey, A.S. *J. Chem. Soc.* ***1954***, 3145.
[501]There is evidence that, in the complex formed from potassium salts, the bonding is between the aromatic compound and the carbon atom of CO_2: Hirao, I.; Kito, T. *Bull. Chem. Soc. Jpn.* ***1973***, *46*, 3470.
[502]Actually, the reaction seems to be more complicated than this. At least part of the potassium *p*-hydroxybenzoate that forms comes from a rearrangement of initially formed potassium salicylate. Sodium salicylate does not rearrange. See Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1967***, pp. 344–348. See also, Ota, K. *Bull. Chem. Soc. Jpn.* ***1974***, *47*, 2343.
[503]Yasuhara, Y.; Nogi, T. *J. Org. Chem.* ***1968***, *33*, 4512, *Chem. Ind. (London)* ***1969***, 77.
[504]Yasuhara, Y.; Nogi, T.; Saishō *Bull. Chem. Soc. Jpn.* ***1969***, *42*, 2070.
[505]See Sakakibara, T.; Odaira, Y. *J. Org. Chem.* ***1976***, *41*, 2049; Jintoku, T.; Taniguchi, H.; Fujiwara, Y. *Chem. Lett.* ***1987***, 1159; Ugo, R.; Chiesa, A. *J. Chem. Soc. Perkin Trans. 1* ***1987***, 2625.
[506]Sakakura, T.; Chaisupakitsin, M.; Hayashi, T.; Tanaka, M. *J. Organomet. Chem.* ***1987***, *334*, 205.
[507]Matsuda, T.; Ohashi, Y.; Harada, T.; Yanagihara, R.; Nagasawa, T.; Nakamura, K. *Chem. Commun.* ***2001***, 2194.

N-Substituted amides can be prepared by direct attack of isocyanates on aromatic rings.[508] The R group may be alkyl or aryl, but if the latter, dimers and trimers are also obtained. Isothiocyanates similarly give thioamides.[509] The reaction has been carried out intramolecularly both with aralkyl isothiocyanates and acyl isothiocyanates.[510] In the latter case, the product is easily hydrolyzable to a dicarboxylic acid; this is a way



62

of putting a carboxyl group on a ring ortho to one already there (**62** is prepared by treatment of the acyl halide with lead thiocyanate). The reaction gives better yields with substrates of the type $ArCH_2CONCS$, where six-membered rings are formed.

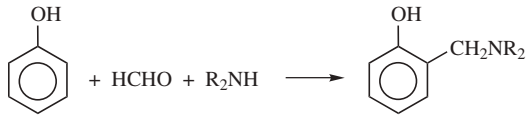
There are interesting transition metal-catalyzed-reactions that lead to aryl amides. The use of $POCl_3$ and DMF, with a palladium catalyst, converts aryl iodides to benzamides.[511] A palladium-catalyzed reaction of aryl halides and formamide leads to benzamide derivatives.[512] Carbonylation is another method that generates amides. When an aryl iodide was treated with a secondary amine and $Mo(CO)_6$, in the presence of 3 equivalents of DBU, 10% $Pd(OAc)_2$, with microwave irradiation at 100°C, the corresponding benzamide was obtained.[513]

OS **V**, 1051; **VI**, 465.

Reactions **11-12–11-23** involve the introduction of a CH_2Z group, where Z is halogen, hydroxyl, amino, or alkylthio. They are all Friedel–Crafts reactions of aldehydes and ketones and, with respect to the carbonyl compound, additions to the C=O double bond. They follow mechanisms discussed in Chapter 16.

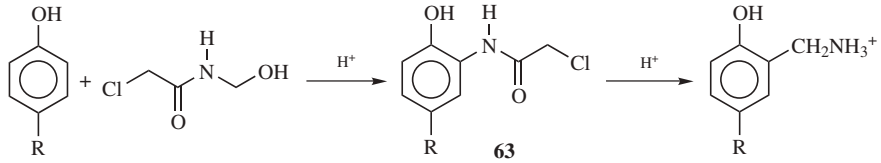
11-22 Aminoalkylation and Amidoalkylation

Dialkylaminoalkylation or **Dialkylamino-de-hydrogenation**



[508]Effenberger, F.; Gleiter, R.; Heider, L.; Niess, R. *Chem. Ber.* ***1968***, *101*, 502; Piccolo, O.; Filippini, L.; Tinucci, L.; Valoti, E.; Citterio, A. *Tetrahedron* ***1986***, *42*, 885.
[509]Jagodziński, T. *Synthesis* ***1988***, 717.
[510]Smith, P.A.S.; Kan, R.O. *J. Org. Chem.* ***1964***, *29*, 2261.
[511]Hosoi, K.; Nozaki, K.; Hiyama, T. *Org. Lett.* ***2002***, *4*, 2849.
[512]Schnyder, A.; Beller, M.; Mehltretter, G.; Nsenda, T.; Studer, M.; Indolese, A.F. *J. Org. Chem.* ***2001***, *66*, 4311. See also, Schnyder, A.; Indolese, A.F. *J. Org. Chem.* ***2002***, *67*, 594.
[513]Wannberg, J.; Larhed, M. *J. Org. Chem.* ***2003***, *68*, 5750.

Phenols, secondary and tertiary aromatic amines,[514] pyrroles, and indoles can be aminomethylated by treatment with formaldehyde and a secondary amine. Other aldehydes have sometimes been employed. Aminoalkylation is a special case of the Mannich reaction (**16-19**). When phenols and other activated aromatic compounds are treated with *N*-hydroxymethylchloroacetamide, *amidomethylation* takes place[515] to

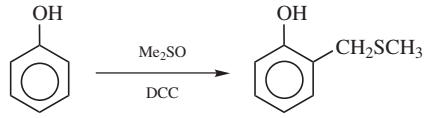


give **63**, which is often hydrolyzed *in situ* to the aminoalkylated product. Other *N*-hydroxyalkyl and *N*-chlorinated compounds have also been used.[374]

OS **I**, 381; **IV**, 626; **V**, 434; **VI**, 965; **VII**, 162.

11-23 Thioalkylation

Alkylthioalkylation or **Alkylthioalkyl-de-hydrogenation**



A methylthiomethyl group can be inserted into the ortho position of phenols by heating with dimethyl sulfoxide and dicyclohexylcarbodiimide (DCC).[516] Other reagents can be used instead of DCC, among them $SOCl_2$,[517] and acetic anhydride.[518] Alternatively, the phenol can be treated with dimethyl sulfide and *N*-chlorosuccinimide, followed by triethylamine.[519] The reaction can be applied to amines (to give *o*-$NH_2C_6H_4CH_2SMe$) by treatment with *t*-BuOCl, Me_2S, and NaOMe in CH_2Cl_2.[520] Aromatic hydrocarbons have been thioalkylated with ethyl α-(chloromethylthio)-acetate $ClCH_2SCH_2COOEt$ (to give $ArCH_2SCH_2CO$-OEt)[521] and with methyl methylsulfinylmethyl sulfide $MeSCH_2SOMe$ or methylthiomethyl *p*-tolyl sulfone $MeSCH_2$-$SO_2C_6H_4Me$ (to give $ArCH_2SMe$),[522] in each case with a Lewis acid catalyst.

OS **VI**, 581, 601.

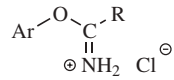
[514]Miocque, M.; Vierfond, J. *Bull. Soc. Chim. Fr.* ***1970***, 1896, 1901, 1907.
[515]For a review, see Zaugg, H.E. *Synthesis* ***1984***, 85.
[516]Burdon, M.G.; Moffatt, J.G. *J. Am. Chem. Soc.* ***1966***, *88*, 5855, ***1967***, *89*, 4725; Olofson, R.A.; Marino, J.P. *Tetrahedron* ***1971***, *27*, 4195.
[517]Sato, K.; Inoue, S.; Ozawa, K.; Tazaki, M. *J. Chem. Soc. Perkin Trans. 1* ***1984***, 2715.
[518]Hayashi, Y.; Oda, R. *J. Org. Chem.* ***1967***, *32*, 457; Pettit, G.H.; Brown, T.H. *Can. J. Chem.* ***1967***, *45*, 1306; Claus, P. *Monatsh. Chem.* ***1968***, *99*, 1034.
[519]Gassman, P.G.; Amick, D.R. *J. Am. Chem. Soc.* ***1978***, *100*, 7611.
[520]Gassman, P.G.; Gruetzmacher, G. *J. Am. Chem. Soc.* ***1973***, *95*, 588; Gassman, P.G.; van Bergen, T.J. *J. Am. Chem. Soc.* ***1973***, *95*, 590, 591.
[521]Tamura, Y.; Tsugoshi, T.; Annoura, H.; Ishibashi, H. *Synthesis* ***1984***, 326.
[522]Torisawa, Y.; Satoh, A.; Ikegami, S. *Tetrahedron Lett. 1988, 29*, 1729.

11-24 Acylation with Nitriles: The Hoesch Reaction

Acylation or **Acyl-de-hydrogenation**

$$ArH + RCN \xrightarrow[ZnCl_2]{HCl} ArCOR$$

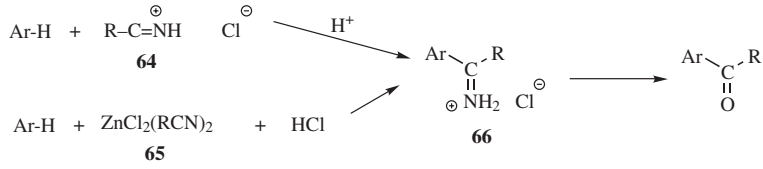
Friedel–Crafts acylation with nitriles and HCl is called the *Hoesch* or the *Houben–Hoesch reaction*.[523] In most cases, a Lewis acid is necessary; zinc chloride is the most common. The reaction is generally useful only with phenols, phenolic ethers, and some reactive heterocyclic compounds such as pyrrole, but it can be extended to aromatic amines by the use of BCl_3.[524] Acylation in the case of aniline derivatives is regioselectively ortho. Monohydric phenols, however, generally do not give ketones[525] but are attacked at the oxygen to



An imino ester

produce imino esters. Many nitriles have been used. Even aryl nitriles give good yields if they are first treated with HCl and $ZnCl_2$ and then the substrate added at 0°C.[526] In fact, this procedure increases yields with any nitrile. If thiocyanates RSCN are used, thiol esters ArCOSR can be obtained. The Gatterman reaction (**11-18**) is a special case of the Hoesch synthesis.

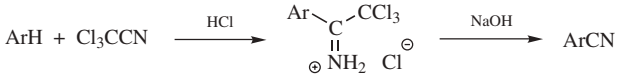
The reaction mechanism is complex and not completely settled.[527] The first stage consists of an attack on the substrate by a species containing the nitrile and HCl (and the Lewis acid, if present) to give an imine salt (**66**). Among the possible attacking species are **64** and **65**. In the second stage, the salts are hydrolyzed to the products, first the iminium salt, and then the ketone. Ketones can also be obtained by treating phenols or phenolic ethers with a nitrile in the presence of F_3CSO_2OH.[528] The mechanism in this case is different.



OS **II**, 522.

[523]For a review, see Ruske, W., in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 3, Wiley, NY, ***1964***, pp. 383–497.
[524]Sugasawa, T.; Toyoda, T.; Adachi, M.; Sasakura, K. *J. Am. Chem. Soc.* ***1978***, *100*, 4842; Sugasawa, T.; Adachi, M.; Sasakura, K.; Kitagawa, A. *J. Org. Chem.* ***1979***, *44*, 578.
[525]For an exception, see Toyoda, T.; Sasakura, K.; Sugasawa, T. *J. Org. Chem.* ***1981***, *46*, 189.
[526]Zil'berman, E.N.; Rybakova, N.A. *J. Gen. Chem. USSR* ***1960***, *30*, 1972.
[527]For discussions, see Ruske, W., in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 3, Wiley, NY, ***1964***, p. 383; Jeffery, E.A.; Satchell, D.P.N. *J. Chem. Soc. B* ***1966***, 579.
[528]Amer, M.I.; Booth, B.L.; Noori, G.F.M.; Proença, M.F.J.R.P. *J. Chem. Soc. Perkin Trans. 1* ***1983***, 1075.

11-25 Cyanation or Cyano-de-hydrogenation



Aromatic hydrocarbons (including benzene), phenols, and phenolic ethers can be cyanated with trichloroacetonitrile, BrCN, or mercury fulminate $Hg(ONC)_2$.[529] In the case of Cl_3CCN, the actual attacking entity is probably $Cl_3C-\overset{\oplus}{C}=NH$, formed by addition of a proton to the cyano nitrogen. Secondary aromatic amines ArNHR, as well as phenols, can be cyanated in the ortho position with Cl_3CCN and BCl_3.[530]

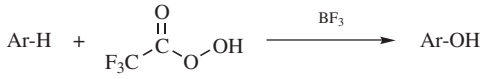
It is noted that aryl triflates are converted to the aryl nitrile by treatment with $Zn(CN)_2$ and a palladium catalyst.[531]

OS **III**, 293.

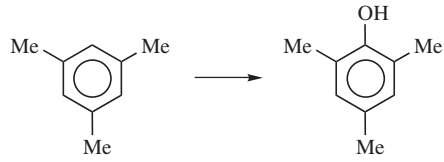
F. Oxygen Electrophiles

Oxygen electrophiles are very uncommon, since oxygen does not bear a positive charge very well. However, there is one reaction that can be mentioned.

11-26 Hydroxylation or Hydroxy-de-hydrogenation



There have been only a few reports of direct hydroxylation[532] by an electrophilic process (see, however, **14-5**).[533] In general, poor results are obtained, partly because the introduction of an OH group activates the ring to further attack. Quinone formation is common. However, alkyl-substituted benzenes, such as mesitylene or durene can be hydroxylated in good yield with trifluoroperacetic acid and boron trifluoride.[534] In the case of mesitylene, the product (**67**) is not subject to further attack.



67

[529]Olah, G.A., in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 1, Wiley, NY, ***1963***, pp. 119–120.
[530]Adachi, M.; Sugasawa, T. *Synth. Commun.* ***1990***, *20*, 71.
[531]Kubota, H.; Rice, K.C. *Tetrahedron Lett.* ***1998***, *39*, 2907.
[532]For a list of hydroxylation reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 977–978.
[533]For reviews of electrophilic hydroxylation, see Jacquesy, J.; Gesson, J.; Jouannetaud, M. *Rev. Chem. Intermed.* ***1988***, *9*, 1, see pp. 5–10; Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Academic Press, NY, ***1985***, pp. 173–176, 347–350.
[534]Hart, H.; Buehler, C.A. *J. Org. Chem.* ***1964***, *29*, 2397. See also, Hart, H. *Acc. Chem. Res.* ***1971***, *4*, 337.

In a related procedure, even benzene and substituted benzenes (e.g., PhMe, PhCl, xylenes) can be converted to phenols in good yields with sodium perborate–F_3CSO_2OH.[535] Aromatic amines, *N*-acyl amines, and phenols were hydroxylated with H_2O_2 in SbF_5—HF.[536] Pyridine and quinoline were converted to their 2-acetoxy derivatives in high yields with acetyl hypofluorite AcOF at $-75°C$.[537]

Another hydroxylation reaction is the *Elbs reaction*.[538] In this method phenols can be oxidized to *p*-diphenols with $K_2S_2O_8$ in alkaline solution.[539] Primary, secondary, or tertiary aromatic amines give predominant or exclusive ortho substitution unless both ortho positions are blocked, in which case para substitution is found. The reaction with amines is called the *Boyland–Sims oxidation*. Yields are low with either phenols or amines, generally $<50\%$. The mechanisms are not clear,[540] but for the Boyland–Sims oxidation there is evidence that the $S_2O_8^{2-}$ ion attacks at the ipso position, and then a migration follows.[541]

Electrolysis of benzene, in the presence of trifluoroacetic acid and triethylamine, leads to a 73% yield of phenol.[542]

G. Metal Electrophiles

Reactions in which a metal replaces the hydrogen of an aromatic ring are considered along with their aliphatic counterparts in Chapter 12 (**12-22** and **12-23**).

HYDROGEN AS THE LEAVING GROUP IN REARRANGEMENT REACTIONS

In these reactions, a group is detached from a *side chain* and then attacks the ring, but in other aspects they resemble the reactions already treated in this chapter.[543] Since a group moves from one position to another in a molecule, these are rearrangements. In all these reactions, the question arises as to whether the group that cleaves from a given molecule attacks the same molecule or another one, that is is the reaction intramolecular or intermolecular? For intermolecular reactions the mechanism is the same as ordinary aromatic substitution, but for intramolecular

[535]Prakash, G.K.S.; Krass, N.; Wang, Q.; Olah, G.A. *Synlett* ***1991***, 39.

[536]Berrier, C.; Carreyre, H.; Jacquesy, J.; Joannetaud, M. *New J. Chem.* ***1990***, *14*, 283, and cited references.

[537]Rozen, S.; Hebel, D.; Zamir, D. *J. Am. Chem. Soc.* ***1987***, *109*, 3789.

[538]For a review of the Elbs and Boyland–Sims reactions, see Behrman, E.J. *Org. React.* ***1988***, *35*, 421.

[539]For a method for the ortho hydroxylation of phenols, see Capdevielle, P.; Maumy, M. *Tetrahedron Lett.* ***1982***, *23*, 1573, 1577.

[540]Behrman, E.J. *J. Am. Chem. Soc.* ***1967***, *89*, 2424; Ogata, Y.; Akada, T. *Tetrahedron* ***1970***, *26*, 5945; Walling, C.; Camaioni, D.M.; Kim, S.S. *J. Am. Chem. Soc.* ***1978***, *100*, 4814.

[541]Srinivasan, C.; Perumal, S.; Arumugam, N. *J. Chem. Soc. Perkin Trans. 2* ***1985***, 1855.

[542]Fujimoto, K.; Tokuda, Y.; Maekawa, H.; Matsubara, Y.; Mizuno, T.; Nishiguchi, I. *Tetrahedron* ***1996***, *52*, 3889; Fujimoto, K.; Maekawa, H.; Tokuda, Y.; Matsubara, Y.; Mizuno, T.; Nishiguchi, I. *SynLett*, ***1995***, 661.

[543]For a monograph, see Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1967***. For reviews, see Williams, D.L.H.; Buncel, I.M. *Isot. Org. Chem.* ***1980***, *5*, 147; Williams, D.L.H., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, ***1972***, pp. 433–486.

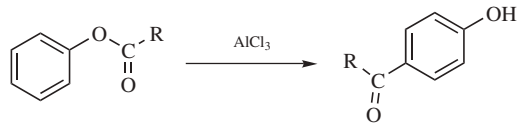
cases the migrating group could never be completely free, or else it would be able to attack another molecule. Since the migrating species in intramolecular rearrangements is thus likely to remain near the atom from which it cleaved, it has been suggested that intramolecular reactions are more likely to lead to ortho products than are the intermolecular type. This characteristic has been used, among others, to help decide whether a given rearrangement is inter- or intramolecular, though there is evidence that at least in some cases, an intermolecular mechanism can still result in a high degree of ortho migration.[544]

The Claisen (**18-33**) and benzidine (**18-36**) rearrangements, which superficially resemble those in this section, have different mechanisms and are treated in Chapter 18.

A. Groups Cleaving from Oxygen

11-27 The Fries Rearrangement

1/*C*-Hydro,5/*O*-acyl-interchange[545]



Phenolic esters can be rearranged by heating with Friedel–Crafts catalysts in a synthetically useful reaction known as the *Fries rearrangement*.[546] Both *o*- and *p*-acylphenols can be produced, and it is often possible to select conditions so that either one predominates. The ortho/para ratio is dependent on the temperature, solvent, and amount of catalyst used. Exceptions are known, but low temperatures generally favor the para product and high temperatures the ortho product. The R group may be aliphatic or aromatic. Any meta-directing substituent on the ring interferes with the reactions, as might be expected for a Friedel–Crafts process. In the case of aryl benzoates treated with F_3CSO_2OH, the Fries rearrangement was shown to be reversible and an equilibrium was established.[547] Transition-metal-catalyzed Fries rearrangements have been reported.[548]

[544]See Dawson, I.M.; Hart, L.S.; Littler, J.S. *J. Chem. Soc. Perkin Trans. 2* ***1985***, 1601.

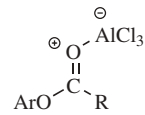
[545]This is the name for the para migration. For the ortho migration, the name is 1/*C*-hydro,3/*O*-acyl-interchange.

[546]For reviews, see Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1967***, pp. 72–82, 365–368; Gerecs, A., in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 3, Wiley, NY, ***1964***, pp. 499–533. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, p. 1310.

[547]Effenberger, F.; Gutmann, R. *Chem. Ber.* ***1982***, *115*, 1089.

[548]With **$Sc(OTf)_3$**, see Kobayashi, S.; Moriwaki, M.; Hachiya, I. *Tetrahedron Lett.* ***1996***, *37*, 4183; with $ZrCl_4$ see Harrowven, D.C.; Dainty, R.F. *Tetrahedron Lett.* ***1996***, *37*, 7659; with **$Hf(OTf)_4$** see Kobayashi, S.; Moriwaki, M.; Hachiya, I. *Tetrahedron Lett.* ***1996***, *37*, 2053. Also see Kobayashi, S.; Moriwaki, M.; Hachiya, I. *J. Chem. Soc., Chem. Commun.* ***1995***, 1527.

The exact mechanism has still not been completely worked out.[549] Opinions have been expressed that it is completely intermolecular,[550] completely intramolecular,[551] and partially inter- and intramolecular.[552] One way to decide between inter- and intramolecular processes is to run the reaction of the phenolic ester in the presence of another aromatic compound, say, toluene. If some of the toluene is acylated, the reaction must be, at least in part, intermolecular. If the toluene is not acylated, the presumption is that the reaction is intramolecular, though this is not certain, for it may be that the toluene is not attacked because it is less active than the other. A number of such experiments (called *crossover experiments*) have been carried out; sometimes crossover products have been found and sometimes not. As in **11-17**, an initial complex (**68**) is formed between the substrate and the catalyst, so that a catalyst/substrate molar ratio of at least 1:1 is required. In the presence of aluminum chloride, the Fries rearrangement can be induced with microwave irradiation.[553] Simply heating phenyl acetate with microwave irradiation gives the Fries rearrangement.[554] The Fries rearrangement has been carried out in ionic melts.[555]



68

The Fries rearrangement can also be carried out with UV light, in the absence of a catalyst.[556] This reaction, called the *photo-Fries rearrangement*,[557] is predominantly an intramolecular free-radical process. Both ortho and para migration are observed.[558] Unlike the Lewis acid-catalyzed Fries rearrangement, the photo-Fries reaction can be accomplished, though often in low yields, when meta-directing groups are on the ring. The available evidence strongly suggests the following

[549]For the mechanism in polyphosphoric acid, see Sharghi, H.; Eshghi, H. *Bull. Chem. Soc. Jpn.* ***1993***, *66*, 135.

[550]Martin, R.; Gavard, J.; Delfly, M.; Demerseman, P.; Tromelin, A. *Bull. Soc. Chim. Fr.* ***1986***, 659 and cited references.

[551]Ogata, Y.; Tabuchi, H. *Tetrahedron* ***1964***, *20*, 1661.

[552]Munavilli, S. *Chem. Ind. (London)* ***1972***, 293; Warshawsky, A.; Kalir, R.; Patchornik, A. *J. Am. Chem. Soc.* ***1978***, *100*, 4544; Dawson, I.M.; Hart, L.S.; Littler, J.S. *J. Chem. Soc. Perkin Trans. 2* ***1985***, 1601.

[553]Khadilkar, B.M.; Madyar, V.R. *Synth. Commun.* ***1999***, *29*, 1195.

[554]Paul, S.; Gupta, M. *Synthesis* ***2004***, 1789.

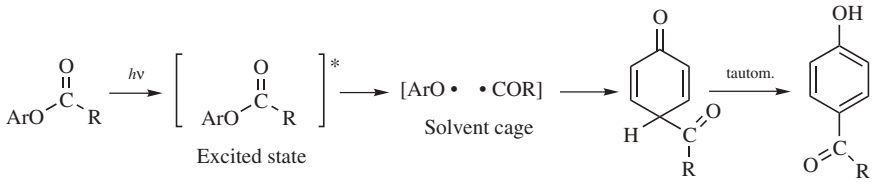
[555]Harjani, J.R.; Nara, S.J.; Salunkhe, M.M. *Tetrahedron Lett.* ***2001***, *42*, 1979.

[556]Kobsa, H. *J. Org. Chem.* ***1962***, *27*, 2293; Anderson, J.C.; Reese, C.B. *J. Chem. Soc.* ***1963***, 1781; Finnegan, R.A.; Matice, J.J. *Tetrahedron* ***1965***, *21*, 1015.

[557]For reviews, see Belluš, D. *Adv. Photochem.* ***1971***, *8*, 109; Belluš, D.; Hrdlovič, P. *Chem. Rev.* ***1967***, *67*, 599; Stenberg, V.I. *Org. Photochem.* ***1967***, *1*, 127. See Cui, C.; Wang, X.; Weiss, R.G. *J. Org. Chem.* ***1996***, *61*, 1962.

[558]The migration can be made almost entirely ortho by cyclodextrin encapsulation (see p. 129): Syamala, M.S.; Rao, B.N.; Ramamurthy, V. *Tetrahedron* ***1988***, *44*, 7234. See also, Veglia, A.V.; Sanchez, A.M.; de Rossi, R.H. *J. Org. Chem.* ***1990***, *55*, 4083.

mechanism involving formation of the excited state ester followed by dissociation to a radical pair[559] for the photo-Fries rearrangement[560] (illustrated for para attack).



The phenol ArOH is always a side product, resulting from some ArO• that leaks from the solvent cage and abstracts a hydrogen atom from a neighboring molecule. When the reaction was performed on phenyl acetate in the gas phase, where there are no solvent molecules to form a cage (but in the presence of isobutane as a source of abstractable hydrogens), phenol was the chief product and virtually no *o*- or *p*-hydroxyacetophenone was found.[561] Other evidence[562] for the mechanism is that CIDNP has been observed during the course of the reaction[563] and that the ArO•radical has been detected by flash photolysis[564] and by nanosecond time-resolved Raman spectroscopy.[565]

Treatment of *O*-arylsulfonate esters with $AlCl_3$—$ZnCl_2$, on silica with microwave irradiation, leads to 2-sulfonyl phenols in a thia-Fries rearrangement.[566] A similar reaction was reported with *O*-arylsulfonamides.[567]

OS **II**, 543; **III**, 280, 282.

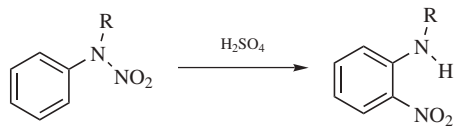
B. Groups Cleaving from Nitrogen[568]

It has been shown that $PhNH_2D$ rearranges to *o*- and *p*-deuterioaniline.[569] The migration of OH, formally similar to reactions **11-28–11-32**, is a nucleophilic substitution and is treated in Chapter 13 (**13-32**).

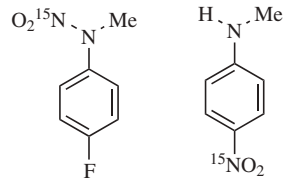
[559]Proposed by Kobsa, H. *J. Org. Chem.* ***1962***, *27*, 2293.
[560]It has been suggested that a second mechanism, involving a four-center transition state, is also possible: Bellus, D.; Schaffner, K.; Hoigné, J. *Helv. Chim. Acta* ***1968***, *51*, 1980; Sander, M.R.; Hedaya, E.; Trecker, D.J. *J. Am. Chem. Soc.* ***1968***, *90*, 7249; Belluš, D. *Adv. Photochem.* ***1971***, *8*, 109.
[561]Meyer, J.W.; Hammond, G.S. *J. Am. Chem. Soc.* ***1972***, *94*, 2219.
[562]For evidence from isotope effect studies, see Shine, H.J.; Subotkowski, W. *J. Org. Chem.* ***1987***, *52*, 3815.
[563]Adam, W.; Arce de Sanabia, J.; Fischer, H. *J. Org. Chem.* ***1973***, *38*, 2571; Adam, W. *J. Chem. Soc., Chem. Commun.* ***1974***, 289.
[564]Kalmus, C.E.; Hercules D.M. *J. Am. Chem. Soc.* ***1974***, *96*, 449.
[565]Beck, S.M.; Brus, L.E. *J. Am. Chem. Soc.* ***1982***, *104*, 1805.
[566]Moghaddam, F.M.; Dakamin, M.G. *Tetrahedron Lett.* ***2000***, *41*, 3479.
[567]Benson, G.A.; Maughan, P.J.; Shelly, D.P.; Spillane, W.J. *Tetrahedron Lett.* ***2001***, *42*, 8729.
[568]For a review, see Stevens, T.S.; Watts, W.E. *Selected Molecular Rearrangements*, Van Nostrand-Reinhold, Princeton, NJ ***1973***, pp. 192–199.
[569]Okazaki, N.; Okumura, A. *Bull. Chem. Soc. Jpn.* ***1961***, *34*, 989.

11-28 Migration of the Nitro Group

1/*C*-Hydro,3/*N*-nitro-interchange



N-Nitro aromatic amines rearrange on treatment with acids to *o*- and *p*-nitroamines with the ortho compounds predominating.[570] Aside from this indication of an intramolecular process, there is also the fact that virtually no meta isomer is produced in this reaction,[571] although direct nitration of an aromatic amine generally gives a fair amount of meta product. Thus a mechanism in which NO_2^+ is dissociated from the ring, and then attacks another molecule must be ruled out. Further results indicating an intramolecular process include the observation that rearrangement of several substrates in the presence of $K^{15}NO_3$ gave products containing no ^{15}N,[572] and that rearrangement of a mixture of $PhNH^{15}NO_2$ and unlabeled *p*-$MeC_6H_4NHNO_2$ gave 2-nitro-4-methylaniline containing no ^{15}N.[573] On the other hand, rearrangement of **69** in the presence of



69 **70**

unlabeled $PhNMeNO_2$ gave labeled **70**, which did not arise by displacement of F.[574] The R group may be hydrogen or alkyl. Two principal mechanisms have been suggested, one involving cyclic attack by the oxygen of the nitro group at the ortho position before the group cleaves,[575] and the other involving a cleavage into a

[570]For reviews, see Williams, D.L.H., in Patai, S. *The Chemistry of Functional Groups, Supplement F*, pt. 1, Wiley, NY, ***1982***, pp. 127–153; White, W.N. *Mech. Mol. Migr.* ***1971***, *3*, 109–143; Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1967***, pp. 235–249.

[571]Hughes, E.D.; Jones, G.T. *J. Chem. Soc.* ***1950***, 2678.

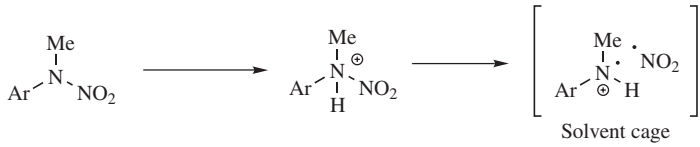
[572]Brownstein, S.; Bunton, C.A.; Hughes, E.D. *J. Chem. Soc.* ***1958***, 4354; Banthorpe, D.V.; Thomas, J.A.; Williams, D.L.H. *J. Chem. Soc.* ***1965***, 6135.

[573]Geller, B.A.; Dubrova, L.N. *J. Gen. Chem. USSR* ***1960***, *30*, 2627.

[574]White, W.N.; Golden, J.T. *J. Org. Chem.* ***1970***, *35*, 2759.

[575]Banthorpe, D.V.; Thomas, J.A. *J. Chem. Soc.* ***1965***, 7149, 7158. Also see, Brownstein, S.; Bunton, C.A.; Hughes, E.D. *J. Chem. Soc.* ***1958***, 4354; Banthorpe, D.V.; Thomas, J.A.; Williams, D.L.H. *J. Chem. Soc.* ***1965***, 6135.

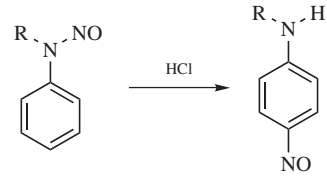
radical and a radical ion held together in a solvent cage.[576] Among the evidence for the latter view[577] are



the effects of substituents on the rate of the reaction,[578] ^{15}N and ^{14}C kinetic isotope effects that show non-concertedness,[579] and the fact that both *N*-methylaniline and nitrous acid are produced in sizable and comparable amounts in addition to the normal products *o*- and *p*-nitro-*N*-methylaniline.[580] These side products are formed when the radicals escape from the solvent cage.

11-29 Migration of the Nitroso Group: The Fischer–Hepp Rearrangement

1/*C*-Hydro-5/*N*-nitroso-interchange



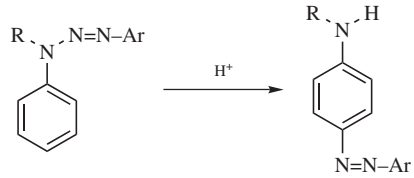
The migration of a nitroso group, formally similar to **11-28**, is important because *p*-nitroso secondary aromatic amines cannot generally be prepared by direct *C*-nitrosation of secondary aromatic amines (see **12-50**). The reaction, known as the *Fischer–Hepp rearrangement*,[581] is brought about by treatment of *N*-nitroso secondary aromatic amines with HCl. Other acids give poor or no results. In benzene systems the para product is usually formed exclusively.[582] The mechanism of the rearrangement is not completely understood. The fact that the reaction takes place in a large excess of urea[583] shows that it is intramolecular[584] since, if NO^+, NOCl,

[576]White, W.N.; White, H.S.; Fentiman, A. *J. Org. Chem.* ***1976***, *41*, 3166.
[577]For additional evidence, see White, W.N.; Klink, J.R. *J. Org. Chem.* ***1977***, *42*, 166; Ridd, J.H.; Sandall, J.P.B. *J. Chem. Soc., Chem. Commun.* ***1982***, 261.
[578]White, W.N.; Klink, J.R. *J. Org. Chem.* ***1970***, *35*, 965.
[579]Shine, H.J.; Zygmunt, J.; Brownawell, M.L.; San Filippo, Jr., J. *J. Am. Chem. Soc.* ***1984***, *106*, 3610.
[580]White, W.N.; White, H.S. *J. Org. Chem.* ***1970***, *35*, 1803.
[581]For reviews, see Williams, D.L.H. *Nitrosation*, Cambridge University Press, Cambridge, ***1988***, pp. 113–128; Williams, D.L.H., in Patai, S. *The Chemistry of Functional Groups, Supplement F*, pt. 1, Wiley, NY, ***1982***, Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1967***, pp. 231–235.
[582]For a report of formation of 15% ortho product in the case of *N,N*-diaryl-*N*-nitroso amides, see Titova, S.P.; Arinich, A.K.; Gorelik, M.V. *J. Org. Chem. USSR* ***1986***, *22*, 1407.
[583]Aslapovskaya, T.I.; Belyaev, E.Yu.; Kumarev, V.P.; Porai-Koshits, B.A. *Org. React. USSR* ***1968***, *5*, 189; Morgan, T.D.B.; Williams, D.L.H. *J. Chem. Soc. Perkin Trans. 2* ***1972***, 74.
[584]See also, Belyaev, E.Yu.; Nikulicheva, T.I. *Org. React. USSR* ***1971***, *7*, 165; Williams, D.L.H. *Tetrahedron* ***1975***, *31*, 1343; *J. Chem. Soc. Perkin Trans. 2* ***1982***, 801.

or some similar species were free in the solution, it would be captured by the urea, preventing the rearrangement.

11-30 Migration of an Arylazo Group

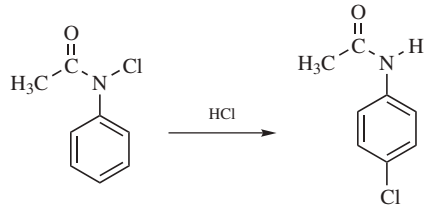
1/*C*-Hydro-5/*N*-arylazo-interchange



Rearrangement of aryl triazenes can be used to prepare azo derivatives of primary and secondary aromatic amines.[585] These are first diazotized at the amino group (see **11-4**) to give triazenes, which are then rearranged by treatment with acid. The rearrangement always gives the para isomer, unless that position is occupied.

11-31 Migration of Halogen: The Orton Rearrangement

1/*C*-Hydro-5/*N*-halo-interchange



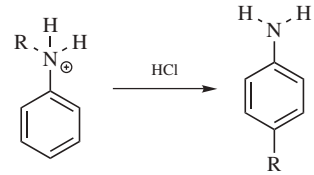
Migration of a halogen from a nitrogen side chain to the ring by treatment with HCl is called the *Orton rearrangement*.[586] The main product is the para isomer, though some ortho product may also be formed. The reaction has been carried out with *N*-chloro- and *N*-bromoamines and less often with *N*-iodo compounds. The amine must be acylated, except that $PhNCl_2$ gives 2,4-dichloroaniline. The reaction is usually performed in water or acetic acid. There is considerable evidence (cross-halogenation, labeling, etc.) that this is an intermolecular process.[587] First, the HCl reacts with the starting material to give $ArNHCOCH_3$ and Cl_2; then the chlorine halogenates the ring as in **11-10**. Among the evidence is that chlorine has been isolated from the reaction mixture. The Orton rearrangement can also

[585]For a review, see Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1967***, pp. 212–221.
[586]For reviews, see Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1967***, pp. 221–230, 362–364: Bieron, J.F.; Dinan, F.J., in Zabicky, J. *The Chemistry of Amides*, Wiley, NY, ***1970***, pp. 263–269.
[587]The reaction has been found to be intramolecular in aprotic solvents: Golding, P.D.; Reddy, S.; Scott, J.M.W.; White, V.A.; Winter, J.G. *Can. J. Chem.* ***1981***, *59*, 839.

be brought about photochemically[588] and by heating in the presence of benzoyl peroxide.[589] These are free-radical processes.

11-32 Migration of an Alkyl Group[590]

1/*C*-Hydro-5/*N*-alkyl-interchange



When HCl salts of arylalkylamines are heated at ~200–300°C, migration occurs in what is called the *Hofmann–Martius reaction*. It is an intermolecular reaction, since crossing is found. For example, methylanilinium bromide gave not only the normal products *o*- and *p*-toluidine but also aniline and di- and trimethylanilines.[591] As would be expected for an intermolecular process, there is isomerization when R is primary.

With primary R, the reaction probably goes through the alkyl halide formed initially in an S_N2 reaction:

$$\overset{\oplus}{R}NH_2Ar + Cl^- \longrightarrow RCl + ArNH_2$$

Evidence for this view is that alkyl halides have been isolated from the reaction mixture and that Br^-, Cl^-, and I^- gave different ortho/para ratios, which indicates that the halogen is involved in the reaction.[591] Further evidence is that the alkyl halides isolated are not rearranged (as would be expected if they are formed by an S_N2 mechanism), even though the alkyl groups in the ring are rearranged. Once the alkyl halide is formed, it reacts with the substrate by a normal Friedel–Crafts alkylation process (**11-11**), accounting for the rearrangement. When R is secondary or tertiary, carbocations may be directly formed so that the reaction does not go through the alkyl halides.[592]

It is also possible to carry out the reaction by heating the amine (not the salt) at a temperature between 200 and 350°C with a metal halide, such as $CoCl_2$, $CdCl_2$, or $ZnCl_2$. When this is done, the reaction is called the *Reilly–Hickinbottom rearrangement*. Primary R groups larger than ethyl give both rearranged and unrearranged products.[593] The reaction is not generally useful for secondary and tertiary R groups, which are usually cleaved to alkenes under these conditions.

[588]For example, see Hodges, F.W. *J. Chem. Soc.* ***1933***, 240.
[589]For example, Ayad, K.N.; Beard, C.; Garwood, R.F.; Hickinbottom, W.J. *J. Chem. Soc.* ***1957***, 2981; Coulson, J.; Williams, G.H.; Johnston, K.M. *J. Chem. Soc. B* ***1967***, 174.
[590]For reviews, see Grillot, G.F. *Mech. Mol. Migr.* ***1971***, *3* 237; Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1967***, pp. 249–257.
[591]Ogata, Y.; Tabuchi, H.; Yoshida, K. *Tetrahedron* ***1964***, *20*, 2717.
[592]Hart, H.; Kosak, J.R. *J. Org. Chem.* ***1962***, *27*, 116.
[593]For example, see Birchal, J.M.; Clark, M.T.; Goldwhite, H.; Thorpe, D.H. *J. Chem. Soc. Perkin Trans. 1* ***1972***, 2579.

When acylated arylamines are photolyzed, migration of an acyl group takes place[594] in a process that resembles the photo-Fries reaction (**11-27**).

OTHER LEAVING GROUPS

Three types of reactions are considered in this section.

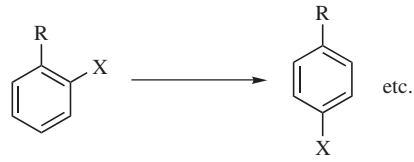
1. Reactions in which hydrogen replaces another leaving group:

$$ArX + H^+ \longrightarrow ArH$$

2. Reactions in which an electrophile other than hydrogen replaces another leaving group:

$$ArX + Y^+ \longrightarrow ArY$$

3. Reactions in which a group (other than hydrogen) migrates from one position in a ring to another. Such migrations can be either inter- or intramolecular:



The three types are not treated separately, but reactions are classified by leaving group.

A. Carbon Leaving Groups

11-33 Reversal of Friedel–Crafts Alkylation

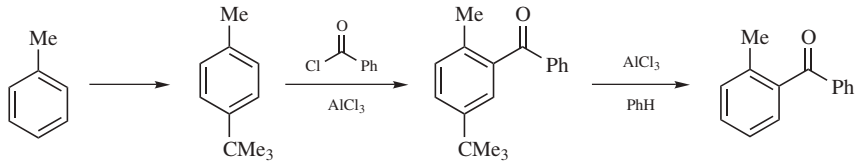
Hydro-de-alkylation or **Dealkylation**

$$ArR + H^+ \xrightarrow{AlCl_3} ArH$$

Alkyl groups can be cleaved from aromatic rings by treatment with proton and/or Lewis acids. Tertiary R groups are the most easily cleaved; because this is true, the *tert*-butyl group is occasionally introduced into a ring, used to direct another

[594]For examples see Elad, D.; Rao, D.V.; Stenberg, V.I. *J. Org. Chem.* ***1965***, *30*, 3252; Shizuka, H.; Tanaka, I. *Bull. Chem. Soc. Jpn.* ***1968***, *41*, 2343; ***1969***, *42*, 909; Fischer, M. *Tetrahedron Lett.* ***1968***, 4295; Hageman, H.J. *Recl. Trav. Chim. Pays-Bas* ***1972***, *91*, 1447; Chênevert, R.; Plante, R. *Can. J. Chem.* ***1983***, *61*, 1092; Abdel-Malik, M.M.; de Mayo, P. *Can. J. Chem.* ***1984***, *62*, 1275; Nassetta, M.; de Rossi, R.H.; Cosa, J.J. *Can. J. Chem.* ***1988***, *66*, 2794.

group, and then removed.[595] For example, 4-*tert*-butyltoluene (**71**) reacted with benzoyl chloride and $AlCl_3$ to give the acylated product, and subsequent treatment with $AlCl_3$ led to loss of the *tert*-butyl group to give **72**.[596]

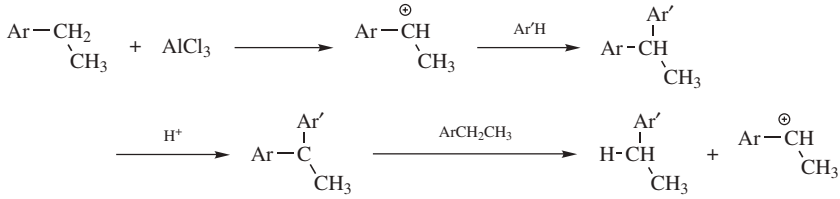


71 **72**

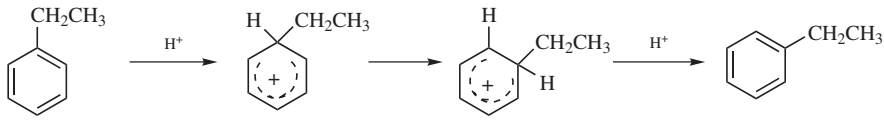
Secondary R groups are harder to cleave, and primary R harder still. Because of this reaction, care must be taken when using Friedel–Crafts catalysts (Lewis or proton acids) on aromatic compounds containing alkyl groups. True cleavage, in which the R becomes an alkene, occurs only at high temperatures, >400°C.[597] At ordinary temperatures, the R group attacks another ring, so that the bulk of the product may be dealkylated, but there is a residue of heavily alkylated material. The isomerization reaction, in which a group migrates from one position in a ring to another or to a different ring, is therefore more important than true cleavage. In these reactions, the meta isomer is generally the most favored product among the dialkylbenzenes; and the 1,3,5 product the most favored among the trialkylbenzenes, because they have the highest thermodynamic stabilities. Alkyl migrations can be inter- or intramolecular, depending on the conditions and on the R group. The following experiments can be cited: Ethylbenzene treated with HF and BF_3 gave, almost completely, benzene and diethylbenzenes[598] (entirely intermolecular); propylbenzene labeled in the β position gave benzene, propylbenzene, and di- and tripropylbenzenes, but the propylbenzene recovered was partly labeled in the a position and not at all in the γ position[599] (both intra- and intermolecular); *o*-xylene treated with HBr and $AlBr_3$ gave a mixture of *o*- and *m*-, but no *p*-xylene, while *p*-xylene gave *p*- and *m*-, but no *o*-xylene, and no trimethyl compounds could be isolated in these experiments[600] (exclusively intramolecular rearrangement). Apparently, methyl groups migrate only intramolecularly, while other groups may follow either path.[601]

[595]For reviews of such reactions, where the blocking group is *tert*-butyl, benzyl, or a halogen, see Tashiro, M. *Synthesis* ***1979***, 921; Tashiro, M.; Fukata, G. *Org. Prep. Proced. Int.* ***1976***, *8*, 51.
[596]Hofman, P.S.; Reiding, D.J.; Nauta, W.T. *Recl. Trav. Chim. Pays-Bas* ***1960***, *79*, 790.
[597]Olah, G.A., in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 1, Wiley, NY, ***1963***, pp. 36–38.
[598]McCaulay, D.A.; Lien, A.P. *J. Am. Chem. Soc.* ***1953***, *75*, 2407. For similar results, see Roberts, R.M.; Roengsumran, S. *J. Org. Chem.* ***1981***, *46*, 3689; Bakoss, H.J.; Roberts, R.M.G.; Sadri, A.R. *J. Org. Chem.* ***1982***, *47*, 4053.
[599]Roberts, R.M.G.; Douglass, J.E. *J. Org. Chem.* ***1963***, *28*, 1225.
[600]Brown, H.C.; Jungk, H. *J. Am. Chem. Soc.* ***1955***, *77*, 5579; Allen, R.H.; Yats, L.D. *J. Am. Chem. Soc.* ***1959***, *81*, 5289.
[601]Allen, R.H. *J. Am. Chem. Soc.* ***1960***, *82*, 4856.

The mechanism[602] of intermolecular rearrangement can involve free alkyl cations, but there is much evidence to show that this is not necessarily the case. For example, many of them occur without rearrangement within the alkyl group. The following mechanism has been proposed for intermolecular rearrangement without the involvement of carbocations that are separated from the ring.[603]



Evidence for this mechanism is that optically active $PhCHDCH_3$ labeled in the ring with ^{14}C and treated with $GaBr_3$ in the presence of benzene gave ethylbenzene containing no deuterium and two deuterium atoms and that the rate of loss of radioactivity was about equal to the rate of loss of optical activity.[603] The mechanism of intramolecular rearrangement is not very clear. 1,2-shifts of this kind have been proposed:[604]



There is evidence from ^{14}C labeling that intramolecular migration occurs only through 1,2-shifts.[605] Any 1,3 or 1,4 migration takes place by a series of two or more 1,2-shifts.

Phenyl groups have also been found to migrate. Thus *o*-terphenyl, heated with $AlCl_3$—H_2O, gave a mixture containing 7% *o*-, 70% *m*-, and 23% *p*-terphenyl.[606] Alkyl groups have also been replaced by groups other than hydrogen (e.g., nitro groups).

Unlike alkylation, *Friedel–Crafts acylation* has been generally considered to be irreversible, but a number of instances of electrofugal acyl groups have been reported,[607] especially where there are two ortho substituents, for example the

[602]For a review of the mechanism of this and closely related reactions, see Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1967***, pp. 1–55.

[603]Streitwieser, Jr., A.; Reif, L. *J. Am. Chem. Soc.* ***1964***, *86*, 1988.

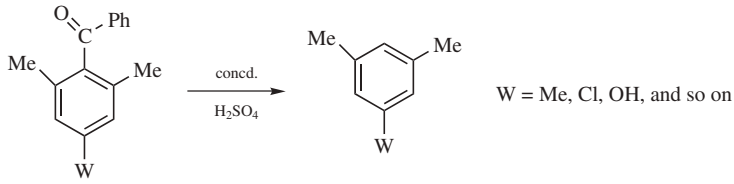
[604]Olah, G.A.; Meyer, M.W.; Overchuk, N.A. *J. Org. Chem.* ***1964***, *29*, 2313.

[605]See, for example, Steinberg, H.; Sixma, F.L.J. *Recl. Trav. Chim. Pays-Bas* ***1962***, *81*, 185; Koptyug, V.A.; Isaev, I.S.; Vorozhtsov, Jr., N.N. *Doklad. Akad. Nauk SSSR*, ***1963***, *149*, 100.

[606]Olah, G.A.; Meyer, M.W. *J. Org. Chem.* ***1962***, *27*, 3682.

[607]For some other examples see Agranat, I.; Bentor, Y.; Shih, Y. *J. Am. Chem. Soc.* ***1977***, *99*, 7068; Bokova, A.I.; Buchina, I.K. *J. Org. Chem. USSR* ***1984***, *20*, 1199; Benedikt, G.M.; Traynor, L. *Tetrahedron Lett.* ***1987***, *28*, 763; Gore, P.H.; Moonga, B.S.; Short, E.L. *J. Chem. Soc. Perkin Trans. 2* ***1988***, 485; Keumi, T.; Morita, T.; Ozawa, Y.; Kitajima, H. *Bull. Chem. Soc. Jpn.* ***1989***, *62*, 599; Giordano, C.; Villa, M.; Annunziata, R. *Synth. Commun.* ***1990***, *20*, 383.

hydro-de-benzoylation of **73**.[608]



73

OS **V**, 332. Also see OS **III**, 282, 653; **V**, 598.

11-34 Decarbonylation of Aromatic Aldehydes

Hydro-de-formylation or **Deformylation**

$$\mathrm{ArCHO} \xrightarrow{\mathrm{H_2SO_4}} \mathrm{ArH + CO}$$

The decarbonylation of aromatic aldehydes with sulfuric acid[609] is the reverse of the *Gatterman–Koch reaction* (**11-18**). It has been carried out with trialkyl- and trialkoxybenzaldehydes. The reaction takes place by the ordinary arenium ion mechanism: the attacking species is H^+ and the leaving group is HCO^+, which can lose a proton to give CO or combine with OH^- from the water solvent to give formic acid.[610] Aromatic aldehydes have also been decarbonylated with basic catalysts.[611] When basic catalysts are used, the mechanism is probably similar to the S_E1 process of **11-35** (see also **14-32**).

11-35 Decarboxylation of Aromatic Acids

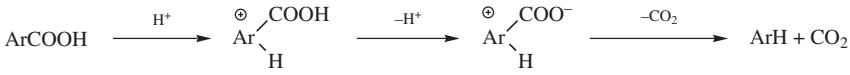
Hydro-de-carboxylation or **Decarboxylation**

$$\mathrm{ArCOOH} \xrightarrow[\text{quinoline}]{\mathrm{Cu}} \mathrm{ArH + CO_2}$$

The decarboxylation of aromatic acids is most often carried out by heating with copper and quinoline. However, two other methods can be used with certain substrates. In one method the salt of the acid ($ArCOO^-$) is heated, and in the other the carboxylic acid is heated with a strong acid, often sulfuric. The latter method is accelerated by the presence of electron-donating groups in ortho and para positions

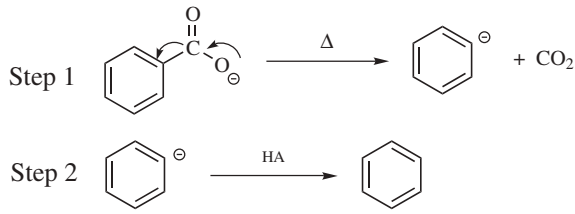
[608]Al-Ka'bi, J.; Farooqi, J.A.; Gore, P.H.; Moonga, B.S.; Waters, D.N. *J. Chem. Res. (S)* ***1989***, 80.
[609]For reviews of the mechanism, see Taylor, R. in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, ***1972***, pp. 316–323; Schubert, W.M.; Kintner, R.R., in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***, pp. 695–760.
[610]Burkett, H.; Schubert, W.M.; Schultz, F.; Murphy, R.B.; Talbott, R. *J. Am. Chem. Soc.* ***1959***, *81*, 3923.
[611]Bunnett, J.F.; Miles J.H.; Nahabedian, K.V. *J. Am. Chem. Soc.* ***1961***, *83*, 2512; Forbes, E.J.; Gregory, M.J. *J. Chem. Soc. B* ***1968***, 205.

and by the steric effect of groups in the ortho positions; in benzene systems it is generally limited to substrates that contain such groups. In this method, decarboxylation takes place by the arenium ion mechanism,[612] with



H^+ as the electrophile and CO_2 as the leaving group.[613] Evidently, the order of electrofugal ability is $CO_2 > H^+ > COOH^+$, so that it is necessary, at least in most cases, for the COOH to lose a proton before it can cleave.

When carboxylate *ions* are decarboxylated, the mechanism is entirely different, being of the S_E1 type. Evidence for this mechanism is that the reaction is first order and that electron-withdrawing groups, which would stabilize a carbanion, facilitate the reaction.[614]



Despite its synthetic importance, the mechanism of the copper–quinoline method has been studied very little, but it has been shown that the actual catalyst is cuprous ion.[615] In fact, the reaction proceeds much faster if the acid is heated in quinoline with cuprous oxide instead of copper, provided that atmospheric oxygen is rigorously excluded. A mechanism has been suggested in which it is the cuprous salt of the acid that actually undergoes the decarboxylation.[615] It has been shown that cuprous salts of aromatic acids are easily decarboxylated by heating in quinoline[616] and that arylcopper compounds are intermediates that can be isolated in some cases.[617] Metallic silver has been used in place of copper, with higher yields.[618]

[612]For a review, see Taylor, R., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, ***1972***, pp. 303–316. For a review of isotope effect studies of this reaction, see Willi, A.V. *Isot. Org. Chem.* ***1977***, *3*, 257.

[613]See, for example, Los, J.M.; Rekker, R.F.; Tonsbeeck, C.H.T. *Recl. Trav. Chim. Pays-Bas* ***1967***, *86*, 622; Huang, H.H.; Long, F.A. *J. Am. Chem. Soc.* ***1969***, *91*, 2872; Willi, A.V.; Cho, M.H.; Won, C.M. *Helv. Chim. Acta* ***1970***, *53*, 663.

[614]See, for example, Segura, P.; Bunnett, J.F.; Villanova, L. *J. Org. Chem.* ***1985***, *50*, 1041.

[615]Cohen, T.; Schambach, R.A. *J. Am. Chem. Soc.* ***1970***, *92*, 3189. See also, Aalten, H.L.; van Koten, G.; Tromp, J.; Stam, C.H.; Goubitz, K.; Mak, A.N.S. *Recl. Trav. Chim. Pays-Bas* ***1989***, *108*, 295.

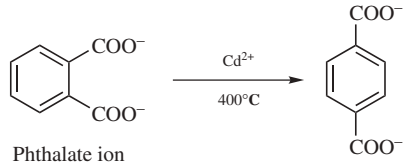
[616]Cairncross, A.; Roland, J.R.; Henderson, R.M.; Sheppard, W.A. *J. Am. Chem. Soc.* ***1970***, *92*, 3187; Cohen, T.; Berninger, R.W.; Wood, J.T. *J. Org. Chem.* ***1978***, *43*, 37.

[617]For example, see Ibne-Rasa, K.M. *J. Am. Chem. Soc.* ***1962***, *84*, 4962; Tedder, J.M.; Theaker, G. *J. Chem. Soc.* ***1959***, 257.

[618]Chodowska-Palicka, J.; Nilsson, M. *Acta Chem. Scand.* ***1970***, *24*, 3353.

In certain cases, the carboxyl group can be replaced by electrophiles other than hydrogen, for example NO,[618] I,[619] Br,[620] or Hg.[621]

Rearrangements are also known to take place. For example, when the phthalate ion is heated with a catalytic amount of cadmium, the terphthalate ion (**74**) is produced:[622]



Phthalate ion

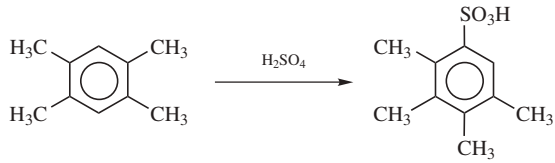
74

In a similar process, potassium benzoate heated with cadmium salts disproportionates to benzene and **74**. The term *Henkel reaction* (named for the company that patented the process) is used for these rearrangements.[623] An S_E1 mechanism has been suggested.[624] The terphthalate is the main product because it crystallizes from the reaction mixture, driving the equilibrium in that direction.[625]

For aliphatic decarboxylation, see **12-40**.

OS **I**, 274, 455, 541; **II**, 100, 214, 217, 341; **III**, 267, 272, 471, 637; **IV**, 590, 628; **V**, 635, 813, 982, 985. Also see, OS **I**, 56.

11-36 The Jacobsen Reaction



When polyalkyl- or polyhalobenzenes are treated with sulfuric acid, the ring is sulfonated, but rearrangement also takes place. The reaction, known as the *Jacobsen reaction*, is limited to benzene rings that have at least four substituents, which can be any combination of alkyl and halogen groups, where the alkyl groups can be

[619]Singh, R.; Just, G. *Synth. Commun.* ***1988***, *18*, 1327.

[620]For example, see Grovenstein, Jr., E.; Ropp, G.A. *J. Am. Chem. Soc.* ***1956***, *78*, 2560.

[621]For a review, see Larock, R.C. *Organomercury Compounds in Organic Synthesis*, Springer, NY, ***1985***, pp. 101–105.

[622]Raecke, B. *Angew. Chem.* ***1958***, *70*, 1; Riedel, O.; Kienitz, H. *Angew. Chem.* ***1960***, *72*, 738; McNelis, E. *J. Org. Chem.* ***1965***, *30*, 1209; Ogata, Y.; Nakajima, K. *Tetrahedron* ***1965***, *21*, 2393; Ratusky, J.; Sorm, F. *Chem. Ind. (London)*, ***1966***, 1798.

[623]For a review, see Ratusky, J., in Patai, S. *The Chemistry of Acid Derivatives*, pt. 1, Wiley, NY, ***1979***, pp. 915–944.

[624]See Ratusky, J. *Collect. Czech. Chem. Commun.* ***1973***, *38*, 74, 87, and references cited therein.

[625]Ratusky, J. *Collect. Czech. Chem. Commun.* ***1968***, *33*, 2346.

ethyl or methyl and the halogen iodo, chloro, or bromo. When isopropyl or *tert*-butyl groups are on the ring, these groups are cleaved to give alkenes. Since a sulfo group can later be removed (**11-38**), the Jacobsen reaction can be used as a means of rearranging polyalkylbenzenes. The rearrangement always brings the alkyl or halo groups closer together than they were originally. Side products in the case illustrated above are pentamethylbenzenesulfonic acid, 2,4,5-trimethylbenzenesulfonic acid, and so on, indicating an intermolecular process, at least partially.

The mechanism of the Jacobsen reaction is not established,[626] but there is evidence, at least for polymethylbenzenes, that the rearrangement is intermolecular, and that the species to which the methyl group migrates is a polymethylbenzene, not a sulfonic acid. Sulfonation takes place after the migration.[627] It has been shown by labeling that ethyl groups migrate without internal rearrangement.[628]

Isomerization of alkyl groups in substituted biphenyls has been observed[629] when the medium is a superacid (see p. 236).

B. Oxygen Leaving Groups

11-37 Deoxygenation

$$\mathrm{ArOR} \longrightarrow \mathrm{ArH}$$

In a few cases, it is possible to remove an oxygen substituent directly from the aromatic ring. Treatment of an aryl mesylate (ArOMs) with a nickel catalyst in DMF, for example, leads to the deoxygenated product, Ar—H.[630]

C. Sulfur Leaving Groups

11-38 Desulfonation or Hydro-de-sulfonation

$$\mathrm{ArSO_3H} \xrightarrow[\text{dil. } \mathrm{H_2SO_4}]{135-200^\circ\mathrm{C}} \mathrm{ArH} + \mathrm{H_2SO_4}$$

The cleavage of sulfo groups from aromatic rings is the reverse of **11-7**.[631] By the principle of microscopic reversibility, the mechanism is also the reverse.[632] Dilute H_2SO_4 is generally used, as the reversibility of sulfonation decreases with

[626]For discussions, see Suzuki, H. *Bull. Chem. Soc. Jpn.* ***1963***, *36*, 1642; Koeberg-Telder, A.; Cerfontain, H. *J. Chem. Soc. Perkin Trans. 2* ***1977***, 717; Cerfontain, H. *Mechanistic Aspects in Aromatic Sulfonation and Desulfonation*, Wiley, NY, ***1968***, pp. 214–226; Taylor, R., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, ***1972***, pp. 22–32, 48–55.

[627]Koeberg-Telder, A.; Cerfontain, H. *Recl. Trav. Chim. Pays-Bas* ***1987***, *106*, 85; Cerfontain, H.; Koeberg-Telder, A. *Can. J. Chem.* ***1988***, *66*, 162.

[628]Marvell, E.N.; Webb, D. *J. Org. Chem.* ***1962***, *27*, 4408.

[629]Sherman, S. C.; Iretskii, A. V.; White, M. G.; Gumienny, C.; Tolbert, L. M.; Schiraldi, D. A. *J. Org. Chem.* ***2002***, *67*, 2034.

[630]Sasaki, K.; Kubo, T.; Sakai, M.; Kuroda, Y. *Chem. Lett*, ***1997***, 617.

[631]For reviews, see Cerfontain, H. *Mechanistic Aspects in Aromatic Sulfonation and Desulfonation*, Wiley, NY, ***1968***, pp. 185–214; Taylor, R., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, ***1972***, pp. 349–355; Gilbert, E.E. *Sulfonation and Related Reactions*, Wiley,NY, ***1965***, pp. 427–442. See also, Krylov, E.N. *J. Org. Chem. USSR* ***1988***, *24*, 709.

[632]For a discussion, see Kozlov, V.A.; Bagrovskaya, N.A. *J. Org. Chem. USSR* ***1989***, *25*, 1152.

increasing H_2SO_4 concentration. The reaction permits the sulfo group to be used as a blocking group to direct meta and then to be removed. The sulfo group has also been replaced by nitro and halogen groups. Sulfo groups have also been removed from the ring by heating with an alkaline solution of Raney nickel.[633] In another catalytic process, aromatic sulfonyl bromides or chlorides are converted to aryl bromides or chlorides, respectively, on heating with chlorotris(triphenylphosphine) rhodium(I).[634] This reaction is similar to the decarbonylation of aromatic acyl halides mentioned in **14-32**.

$$ArSO_2Br \xrightarrow{RhCl(PPh_3)_3} ArBr$$

OS **I**, 388; **II**, 97; **III**, 262; **IV**, 364. Also see OS **I**, 519; **II**, 128; **V**, 1070.

D. Halogen Leaving groups

11-39 Dehalogenation or Hydro-de-halogenation

$$ArX \xrightarrow{AlCl_3} ArH$$

Aryl halides can be dehalogenated by Friedel–Crafts catalysts. Iodine is the most easily cleaved. Dechlorination is seldom performed and defluorination apparently never. The reaction is most successful when a reducing agent, say, Br^- or I^- is present to combine with the I^+ or Br^+ coming off.[635] Except for deiodination, the reaction is seldom used for preparative purposes. Migration of halogen is also found,[636] both intramolecular[637] and intermolecular.[638] The mechanism is probably the reverse of that of **11-10**.[639] Debromination of aromatic rings having two attached amino groups was accomplished by refluxing in aniline containing acetic acid/HBr.[640]

Rearrangement of polyhalobenzenes can also be catalyzed by very strong bases; for example 1,2,4-tribromobenzene is converted to 1,3,5-tribromobenzene by treatment with PhNHK.[641] This reaction, which involves aryl carbanion intermediates (S_E1 mechanism), has been called the *halogen dance*.[642]

[633]Feigl, F. *Angew. Chem.* ***1961***, *73*, 113.
[634]Blum, J.; Scharf, G. *J. Org. Chem.* ***1970***, *35*, 1895.
[635]Pettit, G.R.; Piatak, D.M. *J. Org. Chem.* ***1960***, *25*, 721.
[636]Olah, G.A.; Tolgyesi, W.S.; Dear, R.E.A. *J. Org. Chem.* ***1962***, *27*, 3441, 3449, 3455; De Valois, P.J.; Van Albada, M.P.; Veenland, J.U. *Tetrahedron* ***1968***, *24*, 1835; Olah, G.A.; Meidar, D.; Olah, J.A. *Nouv. J. Chim.*, ***1979***, *3*, 275.
[637]Koptyug, V.A.; Isaev, I.S.; Gershtein, N.A.; Berezovskii, G.A. *J. Gen. Chem. USSR* ***1964***, *34*, 3830; Erykalov, Yu.G.; Becker, H.; Belokurova, A.P. *J. Org. Chem. USSR* ***1968***, *4*, 2054; Jacquesy, J.; Jouannetaud, M. *Tetrahedron Lett.* ***1982***, *23*, 1673.
[638]Augustijn, G.J.P.; Kooyman, E.C.; Louw, R. *Recl. Trav. Chim. Pays-Bas* ***1963***, *82*, 965.
[639]Choguill, H.S.; Ridd, J.H. *J. Chem. Soc.* ***1961***, 822; Shine, H.J. *Aromatic Rearrangements, Elsevier, NY,* ***1967***, p. 1; Ref. 636.
[640]Choi, H.; Chi, D.Y. *J. Am. Chem. Soc.* ***2001***, *123*, 9202.
[641]Moyer, Jr., C.E.; Bunnett, J.F. *J. Am. Chem. Soc.* ***1963***, *85*, 1891.
[642]Bunnett, J.F. *Acc. Chem. Res.* ***1972***, *5*, 139; Mach, M.H.; Bunnett, J.F. *J. Org. Chem.* ***1980***, *45*, 4660; Sauter, F.; Fröhlich, H.; Kalt, W. *Synthesis* ***1989***, 771.

Removal of halogen from aromatic rings can also be accomplished by various reducing agents, among them Bu_3SnH,[643] catalytic hydrogenolysis,[644] catalytic transfer hydrogenolysis,[645] $Fe(CO)_5$,[646] Na—Hg in liquid NH_3,[647] $LiAlH_4$,[648] $LiAlH_4$ and a $NbCl_5$ catalyst,[649] $NaBH_4$ and a catalyst,[650] Ni/C with $Me_2NH{\cdot}BH_3$,[651] NaH,[652] HCOOH[653] or aqueous $HCOO^-$[654] with Pd/C, and Raney nickel in alkaline solution,[655] the last method being effective for fluorine, as well as for the other halogens. Carbon monoxide, with potassium tetracarbonylhydridoferrate $KHFe(CO)_4$ as a catalyst, specifically reduces aryl iodides.[656] Polymethylhydrosiloxane (PHMS) and KF, with a palladium catalyst, also reduces aryl iodides.[657] Not all these reagents operate by electrophilic substitution mechanisms. Some are nucleophilic substitutions and some are free-radical processes. Photochemical[658] and electrochemical[659] reduction are also known. Halogen can also be removed from aromatic rings indirectly by conversion to Grignard reagents (**12-38**) followed by hydrolysis (**11-41**).

OS **III**, 132, 475, 519; **V**, 149, 346, 998; **VI**, 82, 821.

11-40 Formation of Organometallic Compounds

$$\mathrm{ArBr} + \mathrm{M} \longrightarrow \mathrm{ArM}$$
$$\mathrm{ArBr} + \mathrm{RM} \longrightarrow \mathrm{ArM} + \mathrm{RBr}$$

[643]Maitra, U.; Sarma, K.D. *Tetrahedron Lett.* ***1994***, *35*, 7861.
[644]For example, see Subba Rao, Y.V.; Mukkanti, K.; Choudary, B.M. *J. Organomet. Chem.* ***1989***, *367*, C29. See also, Sajiki, H.; Kume, A.; Hattori, K.; Hirota, K. *Tetrahedron Lett.* ***2002***, *43*, 7247.
[645]Anwer, M.K.; Spatola, A.F. *Tetrahedron Lett.* ***1985***, *26*, 1381.
[646]Brunet, J.-J.; El Zaizi, A. *Bull. Soc. Chim. Fr.* ***1996***, *133*, 75.
[647]Austin, E.; Alonso, R.A.; Rossi, R.A. *J. Chem. Res. (S)* ***1990***, 190.
[648]Karabatsos, G.J.; Shone, R.L. *J. Org. Chem.* ***1968***, *33*, 619; Brown, H.C.; Chung, S.; Chung, F. *Tetrahedron Lett.* ***1979***, 2473. Evidence for a free-radical mechanism has been found in this reaction; see Chung, F.; Filmore, K.L. *J. Chem. Soc., Chem. Commun.* ***1983***, 358; Beckwith, A.L.J.; Goh, S.H. *J. Chem. Soc., Chem. Commun.* ***1983***, 905. See also, Beckwith, A.L.J.; Goh, S.H. *J. Chem. Soc., Chem. Commun.* ***1983***, 907; Han, B.H.; Baudjouk, P. *Tetrahedron Lett.* ***1982***, *23*, 1643.
[649]Fuchibe, K.; Akiyama, T. *Synlett* ***2004***, 1282.
[650]Egli, R.A. *Helv. Chim. Acta* ***1968***, *51*, 2090; Lin, S.; Roth, J.A. *J. Org. Chem.* ***1979***, *44*, 309; Narisada, M.; Horibe, I.; Watanabe, F.; Takeda, K. *J. Org. Chem.* ***1989***, *54*, 5308.
[651]Lipshutz, B.H.; Tomioka, T.; Sato, K. *Synlett* ***2001***, 970; Lipshutz, B.H.; Tomioka, T.; Pfeiffer, S.S. *Tetrahedron Lett.* ***2001***, *42*, 7737.
[652]Nelson, R.B.; Gribble, G.W. *J. Org. Chem.* ***1974***, *39*, 1425.
[653]Barren, J.P.; Baghel, S.S.; McCloskey, P.J. *Synth. Commun.* ***1993***, *23*, 1601.
[654]Arcadi, A.; Cerichelli, G.; Chiarini, M.; Vico, R.; Zorzan, D. *Eur. J. Org. Chem.* ***2004***, 3404.
[655]Buu-Hoï, N.P.; Xuong, N.D.; van Bac, N. *Bull. Soc. Chim. Fr.* ***1963***, 2442; de Koning, A.J. *Org. Prep. Proced. Int.* ***1975***, *7*, 31.
[656]Brunet, J.; Taillefer, M. *J. Organomet. Chem.* ***1988***, *348*, C5.
[657]Maleczka, Jr., R.E.; Rahaim, Jr., R.J.; Teixeira, R.R. *Tetrahedron Lett.* ***2002***, *43*, 7087.
[658]See, for example, Pinhey, J.T.; Rigby, R.D.G. *Tetrahedron Lett.* ***1969***, 1267, 1271; Barltrop, J.A.; Bradbury, D. *J. Am. Chem. Soc.* ***1973***, *95*, 5085.
[659]See Fry, A.J. *Synthetic Organic Electrochemistry*, 2nd ed., Wiley, NY, ***1989***, pp. 142–143. Also see, Bhuvaneswari, N.; Venkatachalam, C.S.; Balasubramanian, K.K. *Tetrahedron Lett.* ***1992***, *33*, 1499.

These reactions are considered along with their aliphatic counterparts at reactions **12-38** and **12-39**.

E. Metal Leaving Groups

11-41 Hydrolysis of Organometallic Compounds

Hydro-de-metallation or **Demetallation**

$$ArM + H^+ \longrightarrow ArH + M^+$$

Organometallic compounds can be hydrolyzed by acid treatment. For active metals, such as Mg, Li, and so on water is sufficiently acidic. The most important example of this reaction is hydrolysis of Grignard reagents, but M may be many other metals or metalloids. Examples are SiR_3, HgR, Na, and $B(OH)_2$. Since aryl Grignard and aryllithium compounds are fairly easy to prepare, they are often used to prepare salts of weak acids, such as alkynes.

$$PhMgBr + H{-}C{\equiv}C{-}H \longrightarrow H{-}C{\equiv}C{:}^- \ ^+MgBr + PhH$$

Where the bond between the metal and the ring is covalent, the usual arenium ion mechanism operates.[660] Where the bonding is essentially ionic, this is a simple acid–base reaction. For the aliphatic counterpart of this reaction, see reaction **12-24**.

Other reactions of aryl organometallic compounds are treated with their aliphatic analog: reactions **12-25–12-27** and **12-30–12-37**.

[660]For a discussion of the mechanism, see Taylor, R., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13, Elsevier, NY, ***1972***, pp. 278–303, 324–349.

CHAPTER 12

Aliphatic, Alkenyl, and Alkynyl Substitution, Electrophilic and Organometallic

In Chapter 11, it was pointed out that the most important leaving groups in electrophilic substitution are those that can best exist with an outer shell that is deficient in a pair of electrons. For aromatic systems, the most common leaving group is the proton. The proton is also a leaving group in aliphatic systems, but the reactivity depends on the acidity. Protons in saturated alkanes are very unreactive, but electrophilic substitutions are often easily carried out at more acidic positions, for example, α to a carbonyl group, or at an alkynyl position (RC≡CH). Since metallic ions are easily able to bear positive charges, we might expect that organometallic compounds would be especially susceptible to electrophilic substitution, and this is indeed the case.[1] Another important type of electrophilic substitution, known as *anionic cleavage*, involves the breaking of C–C bonds; in these reactions there are carbon leaving groups (**12-40–12-46**). A number of electrophilic substitutions at a nitrogen atom are treated at the end of the chapter.

Since a carbanion is what remains when a positive species is removed from a carbon atom, the subject of carbanion structure and stability (Chapter 5) is inevitably related to the material in this chapter. So is the subject of very weak acids and very strong bases (Chapter 8), because the weakest acids are those in which the hydrogen is bonded to carbon.

[1]For books on the preparation and reactions of organometallic compounds, see Hartley, F.R.; Patai, S. *The Chemistry of the Metal-Carbon Bond*, 5 vols., Wiley, NY, ***1984–1990***; Haiduc, I.; Zuckerman, J.J. *Basic Organometallic Chemistry*, Walter de Gruyter, NY, ***1985***; Negishi, E. *Organometallics in Organic Synthesis*, Wiley, NY, ***1980***; Aylett, B.J. *Organometallic Compounds*, 4th ed., Vol. 1, pt. 2, Chapman and Hall, NY, ***1979***; Coates, G.E.; Green, M.L.H.; Wade, K. *Organometallic Compounds*, 3rd ed., 2 vols., Methuen, London, ***1967–1968***; Eisch, J.J. *The Chemistry of Organometallic Compounds*, Macmillan, NY, ***1967***. For reviews, see Maslowsky, Jr., E. *Chem. Soc. Rev.* ***1980***, *9*, 25, and in Tsutsui, M. *Characterization of Organometallic Compounds*, Wiley, NY, ***1969–1971***, the articles by Cartledge, F.K.; Gilman, H. pt. 1, pp. 1–33, and by Reichle, W.T. pt. 2, pp. 653–826.

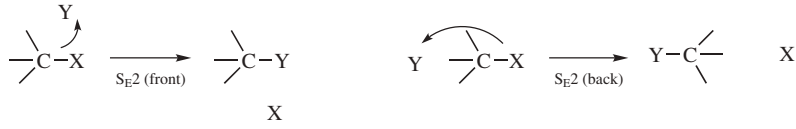
March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Sixth Edition, by Michael B. Smith and Jerry March

MECHANISMS

For aliphatic electrophilic substitution, we can distinguish at least four possible major mechanisms,[2] which we call S_E1, S_E2 (front), S_E2 (back), and S_Ei. The S_E1 is unimolecular; the other three are bimolecular. It is noted that the term "S_EAr" has been proposed to represent electrophilic aromatic substitution, so that the term "S_E2" refers exclusively to electrophilic substitutions where a steric course is possible.[3] To describe the steric course of an aliphatic substitution reaction, the suffixes "ret" and "inv" were proposed, referring to retention and inversion of configuration, respectively.

BIMOLECULAR MECHANISMS. S_E2 AND S_Ei

The bimolecular mechanisms for electrophilic aliphatic substitution are analogous to the S_N2 mechanism in that the new bond forms as the old one breaks. However, in the S_N2 mechanism the incoming group brings with it a pair of electrons, and this orbital can overlap with the central carbon only to the extent that the leaving group takes away its electrons; otherwise the carbon would have more than eight electrons at once in its outer shell. Since electron clouds repel, this means also that the incoming group attacks backside, at a position 180° from the leaving group, resulting in inversion of configuration. When the nucleophilic species attacks (donates electrons to) an electrophile, which brings to the substrate only a vacant orbital, predicting the direction the attack is not as straightforward. We can imagine two main possibilities: delivery of the electrophile to the front, which we call S_E2 (front), and delivery of the electrophile to the rear, which we call S_E2 (back). The possibilities can be pictured (charges not shown):

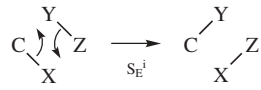


Both the S_E2 (front) and S_E2 (back) mechanisms are designated D_EA_E in the IUPAC system. With substrates in which we can distinguish the possibility, the former

[2]For monographs, see Abraham, M.H. *Comprehensive Chemical Kinetics*, Bamford, C.H.; Tipper, C.F.H. Eds., Vol. 12, Elsevier, NY, ***1973***; Jensen, F.R.; Rickborn, B. *Electrophilic Substitution of Organomercurials*, McGraw-Hill, NY, ***1968***; Reutov, O.A.; Beletskaya, I.P. *Reaction Mechanisms of Organometallic Compounds*, North-Holland Publishing Company, Amsterdam, The Netherlands, ***1968***. For reviews, see Abraham, M.H.; Grellier, P.L., in Hartley, F.R.; Patai, S. *The Chemistry of the Metal-Carbon Bond*, Vol. 2, Wiley, NY, pp. 25–149; Beletskaya, I.P. *Sov. Sci. Rev. Sect. B* ***1979***, *1*, 119; Reutov, O.A. *Pure Appl. Chem.* ***1978***, *50*, 717; ***1968***, *17*, 79; *Tetrahedron* ***1978***, *34*, 2827; *J. Organomet. Chem.* ***1975***, *100*, 219; *Russ. Chem. Rev.* ***1967***, *36*, 163; *Fortschr. Chem. Forsch.* ***1967***, *8*, 61; Matteson, D.S. *Organomet. Chem. Rev. Sect. A* ***1969***, *4*, 263; Dessy, R.E.; Kitching, W. *Adv. Organomet. Chem.* ***1966***, *4*, 267.

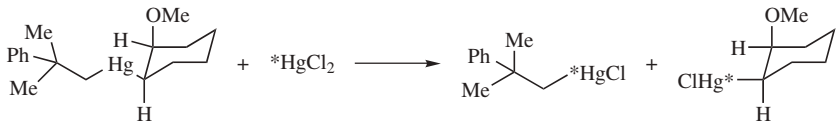
[3]Gawley, R.E. *Tetrahedron Lett*. ***1999***, *40*, 4297.

mechanism should result in retention of configuration and the latter in inversion. The reaction of allylsilanes with adamantyl chloride and $TiCl_4$, for example, gives primarily the antiproduct via a S_E2' reaction.[4] When the electrophile reacts from the front, there is a third possibility. A portion of the electrophile may assist in the removal of the leaving group, forming a bond with it at the same time that the new C–Y bond is formed:



This mechanism, which we call the S_Ei mechanism[5] (IUPAC designation: *cyclo*-$D_EA_ED_nA_n$), also results in retention of configuration.[6] Plainly, where a second-order mechanism involves this kind of internal assistance, backside attack is impossible.

It is evident that these three mechanisms are not easy to distinguish. All three give second-order kinetics, and two result in retention of configuration.[7] In fact, although much work has been done on this question, there are few cases in which we can unequivocally say that one of these three and not another is actually



1 **2**

taking place. Clearly, a study of the stereochemistry can distinguish between S_E2 (back) on the one hand and S_E2 (front) or S_Ei on the other. Many such investigations have been made. In the overwhelming majority of second-order electrophilic substitutions, the result has been retention of configuration or some other indication of frontside attack, indicating an S_E2 (front) or S_Ei mechanism. For example, when *cis*-**1** was treated with labeled mercuric chloride, the **2** produced was 100% cis. The bond between the mercury and the ring must have been broken (as well as the other Hg–C bond), since each of the products contained about half of the labeled mercury.[8] Another indication of frontside attack is that second-order

[4]Buckle, M.J.C.; Fleming, I.; Gil, S. *Tetrahedron Lett*. ***1992***, *33*, 4479.

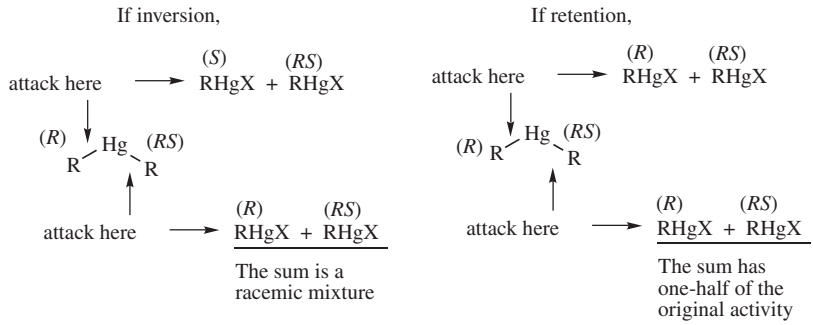
[5]The names for these mechanisms vary throughout the literature. For example, the S_Ei mechanism has also been called the S_F2, the S_E2 (closed), and the S_E2 (cyclic) mechanism. The original designations, S_E1, S_E2, and so on, were devised by the Hughes–Ingold school.

[6]It has been contended that the S_Ei mechanism violates the principle of conservation of orbital symmetry (p. 1208), and that the S_E2 (back) mechanism partially violates it: Slack, D.A.; Baird, M.C. *J. Am. Chem. Soc*. ***1976***, *98*, 5539.

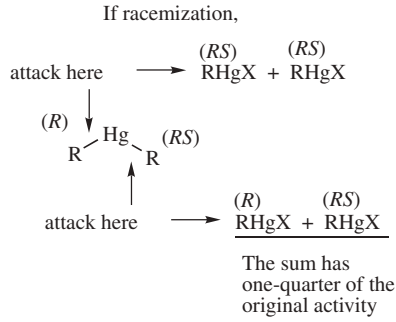
[7]For a review of the stereochemistry of reactions in which a carbon-transition-metal σ bond is formed or broken, see Flood, T.C. *Top. Stereochem*. ***1981***, *12*, 37. See also Jensen, F.R.; Davis, D.D. *J. Am. Chem. Soc*. ***1971***, *93*, 4048.

[8]Winstein, S.; Traylor, T.G.; Garner, C.S. *J. Am. Chem. Soc*. ***1955***, *77*, 3741.

electrophilic substitutions proceed very easily at *bridgehead* carbons (see p. 429).[9] Still another indication is the behavior of neopentyl as a substrate. S_N2 reactions at neopentyl are extremely slow (p. 479), because attack from the rear is blocked and the transition state for the reaction lies very high in energy. The fact that neopentyl systems undergo electrophilic substitution only slightly more slowly than ethyl[10] is further evidence for frontside attack. One final elegant experiment may be noted.



The compound di-*sec*-butylmercury was prepared with one *sec*-butyl group optically active and the other racemic.[11] This was accomplished by treatment of optically active *sec*-butylmercuric bromide with racemic *sec*-butylmagnesium bromide. The di-*sec*-butyl compound was then treated with mercuric bromide to give 2 eqiuivalents of *sec*-butylmercuric bromide. The steric course of the reaction could then be predicted by the following analysis, assuming that the bonds between the mercury and each carbon have a 50% chance of breaking. The original activity referred to is the activity of the optically active *sec*-butylmercuric bromide used to make the dialkyl compound. The actual result was that, under several different sets of conditions, the product had one-half of the original activity, demonstrating retention of configuration.



[9]Winstein, S.; Traylor, T.G. *J. Am. Chem. Soc*. ***1956***, *78*, 2597; Schöllkopf, U. *Angew. Chem*. ***1960***, *72*, 147. For a discussion, see Fort Jr., R.C.; Schleyer, P.v.R. *Adv. Alicyclic Chem*. ***1966***, *1*, 283, pp. 353–370.
[10]Hughes, E.D.; Volger, H.C. *J. Chem. Soc*. ***1961***, 2359.
[11]Jensen, F.R. *J. Am. Chem. Soc*. ***1960***, *82*, 2469; Ingold, C.K. *Helv. Chim. Acta* ***1964***, *47*, 1191.

However, inversion of configuration has been found in certain cases, demonstrating that the S_E2 (back) mechanism can take place. For example, the reaction of optically active *sec*-butyltrineopentyltin with bromine (**12-40**) gives inverted *sec*-butyl bromide.[12] A number of other organometallic compounds have also been shown to give inversion when treated with halogens,[13] although others do not.[14] So far, no inversion has been found with an organomercury substrate. It may be that still other examples of backside

$$\textit{sec}\text{-BuSnR}_3 + \text{Br}_2 \longrightarrow \textit{sec}\text{-BuBr} \qquad \text{R = neopentyl}$$

attack exist,[15] but have escaped detection because of the difficulty in preparing compounds with a configurationally stable carbon–metal bond. Compounds that are chiral because of a stereogenic carbon at which a carbon–metal bond is located[16] are often difficult to resolve and once resolved are often easily racemized. The resolution has been accomplished most often with organomercury compounds,[17] and most stereochemical investigations have therefore been made with these substrates. Only a few optically active Grignard reagents have been prepared[18] (i.e., in which the only stereogenic center is the carbon bonded to the magnesium). Because of this, the steric course of electrophilic substitutions at the C–Mg bond has not often been determined. However, in one such case, the reaction of both the exo and endo isomers of the 2-norbornyl Grignard reagent with $HgBr_2$ (to give 2-norbornylmercuric bromide) has been shown to proceed with retention of configuration.[19] It is likely that inversion takes place only when steric hindrance

[12]Jensen, F.R.; Davis, D.D. *J. Am. Chem. Soc.* ***1971***, *93*, 4048. For a review of the stereochemistry of S_E2 reactions with organotin substrates, see Fukuto, J.M.; Jensen, F.R. *Acc. Chem. Res.* ***1983***, *16*, 177.

[13]For example, See Applequist, D.E.; Chmurny, G.N. *J. Am. Chem. Soc.* ***1967***, *89*, 875; Glaze, W.H.; Selman, C.M.; Ball Jr., A.L.; Bray, L.E. *J. Org. Chem.* ***1969***, *34*, 641; Brown, H.C.; Lane, C.F. *Chem. Commun.* ***1971***, 521; Jensen, F.R.; Madan, V.; Buchanan, D.H. *J. Am. Chem. Soc.* ***1971***, *93*, 5283; Espenson, J.H.; Williams, D.A. *J. Am. Chem. Soc.* ***1974***, *96*, 1008; Bock, P.L.; Boschetto, D.J.; Rasmussen, J.R.; Demers, J.P.; Whitesides, G.M. *J. Am. Chem. Soc.* ***1974***, *96*, 2814; Magnuso, R.H.; Halpern, J.; Levitin, I.Ya.; Vol'pin, M.E. *J. Chem. Soc. Chem. Commun.* ***1978***, 44.

[14]See, for example, Rahm, A.; Pereyre, M. *J. Am. Chem. Soc.* ***1977***, *99*, 1672; McGahey, L.F.; Jensen, F.R. *J. Am. Chem. Soc.* ***1979***, *101*, 4397. Electrophilic bromination of certain organotin compounds was found to proceed with inversion favored for equatorial and retention for axial C–Sn bonds: Olszowy, H.A.; Kitching, W. *Organometallics* ***1984***, *3*, 1676. For a similar result, see Rahm, A.; Grimeau, J.; Pereyre, M. *J. Organomet. Chem.* ***1985***, *286*, 305.

[15]Cases of inversion involving replacement of a metal by a metal have been reported. See Tada, M.; Ogawa, H. *Tetrahedron Lett.* ***1973***, 2639; Fritz, H.L.; Espenson, J.H.; Williams, D.A.; Molander, G.A. *J. Am. Chem. Soc.* ***1974***, *96*, 2378; Gielen, M.; Fosty, R. *Bull. Soc. Chim. Belg.* ***1974***, *83*, 333; Bergbreiter, D.E.; Rainville, D.P. *J. Organomet. Chem.* ***1976***, *121*, 19.

[16]For a monograph, see Sokolov, V.I. *Chirality and Optical Activity in Organometallic Compounds*, Gordon and Breach, NY, ***1990***.

[17]Organomercury compounds were first resolved by three groups: Jensen, F.R.; Whipple, L.D.; Wedegaertner, D.K.; Landgrebe, J.A. *J. Am. Chem. Soc.* ***1959***, *81*, 1262; Charman, H.B.; Hughes, E.D.; Ingold, C.K. *J. Chem. Soc.* ***1959***, 2523, 2530; Reutov, O.A.; Uglova, E.V. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1959***, 735.

[18]This was done first by Walborsky, H.M.; Young, A.E. *J. Am. Chem. Soc.* ***1964***, *86*, 3288.

[19]Jensen, F.R.; Nakamaye, K.L. *J. Am. Chem. Soc.* ***1966***, *88*, 3437.

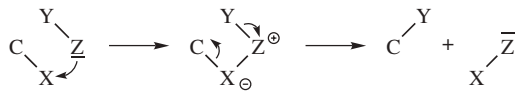
prevents reaction on the frontside and when the electrophile does not carry a Z group (p. 754).

The S_E2 (back) mechanism can therefore be identified in certain cases (if inversion of configuration is found), but it is plain that stereochemical investigations cannot distinguish between the S_E2 (front) and the S_Ei mechanisms and that, in the many cases where configurationally stable substrates cannot be prepared, such investigations are of no help at all in distinguishing among all three of the second-order mechanisms. Unfortunately, there are not many other methods that lead to unequivocal conclusions. One method that has been used in an attempt to distinguish between the S_Ei mechanism on the one hand and the S_E2 pathways on the other involves the study of salt effects on the rate. It may be recalled (p. 501) that reactions in which neutral starting molecules acquire charges in the transition state are aided by an increasing concentration of added ions. Thus the S_Ei mechanism would be less influenced by salt effects than would either of the S_E2 mechanisms. On this basis, Abraham and co-workers[20] concluded that the reactions $R_4Sn + HgX_2 \rightarrow RHgX + R_3SnX$ (X = Cl or I) take place by S_E2 and not by S_Ei mechanisms. Similar investigations involve changes in solvent polarity (see also, p. 765).[21] In the case of the reaction

$$sec\text{-}BuSnR_2R' + Br_2 \longrightarrow sec\text{-}BuBr$$

(where R = R′ = *i*Pr and R = *i*Pr, R′ = neopentyl), the use of polar solvents gave predominant inversion, while nonpolar solvents gave predominant retention.[22]

On the basis of evidence from reactivity studies, it has been suggested[23] that a variation of the S_Ei mechanism is possible in which the group Z becomes attached to X before the latter becomes detached:



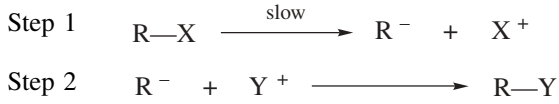
This process has been called the S_EC[22] or S_E2 (co-ord)[24] mechanism (IUPAC designation $A_n + cyclo\text{-}D_EA_ED_n$).

It has been shown that in certain cases (e.g., $Me_4Sn + I_2$) the reactants in an S_E2 reaction, when mixed, give rise to an immediate charge-transfer spectrum (p. 115), showing that an electron donor–acceptor (EDA) complex has been formed.[25] In these cases it is likely that the EDA complex is an intermediate in the reaction.

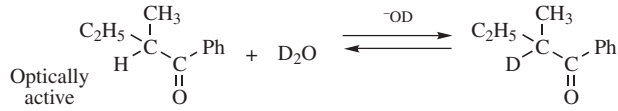
[20]Abraham, M.H.; Johnston, G.F. *J. Chem. Soc. A*, ***1970***, 188.
[21]See, for example, Abraham, M.H.; Dorrell, F.J. *J. Chem. Soc. Perkin Trans. 2* ***1973***, 444.
[22]Fukuto, J.M.; Newman, D.A.; Jensen, F.R. *Organometallics* ***1987***, *6*, 415.
[23]Abraham, M.H.; Hill, J.A. *J. Organomet. Chem.* ***1967***, *7*, 11.
[24]Abraham, M.H. *Comprehensive Chemical Kinetics*, Bamford, C.H.; Tipper, C.F.H. Eds., Vol. 12, Elsevier, NY, ***1973***, p. 15.
[25]Fukuzumi, S.; Kochi, J.K. *J. Am. Chem. Soc.* ***1980***, *102*, 2141, 7290.

THE S_E1 MECHANISM

The S_E1 mechanism is analogous to the S_N1. It involves two steps: a slow ionization and a fast combination.



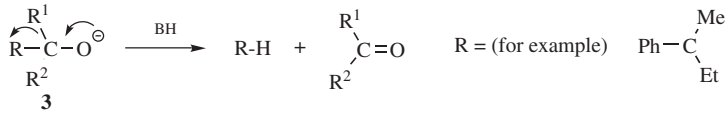
The IUPAC designation is $D_E + A_E$. First-order kinetics are predicted and many such examples have been found. Other evidence for the S_E1 mechanism was obtained in a study of base-catalyzed tautomerization. In the reaction



the rate of deuterium exchange was the same as the rate of racemization[26] and there was an isotope effect.[27]

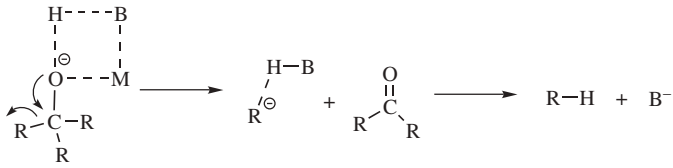
The S_N1 reactions do not proceed at strained bridgehead carbons (e.g., in [2.2.1] bicyclic systems, p. 435) because planar carbocations cannot form at these carbons. However, carbanions not stabilized by resonance are probably not planar, and S_E1 reactions readily occur with this type of substrate. Indeed, the question of carbanion structure is intimately tied into the problem of the stereochemistry of the S_E1 reaction. If a carbanion is planar, racemization should occur. If it is pyramidal and *can hold its structure*, the result should be retention of configuration. On the other hand, even a pyramidal carbanion will give racemization if it cannot hold its structure, that is, if there is pyramidal inversion as with amines (p. 142). Unfortunately, the only carbanions that can be studied easily are those stabilized by resonance, which makes them planar, as expected (p. 258). For simple alkyl carbanions, the main approach to determining structure has been to study the stereochemistry of S_E1 reactions rather than the other way around. Racemization is almost always observed, but whether this is caused by planar carbanions or by oscillating pyramidal carbanions is not known. In either, case racemization occurs whenever a carbanion is completely free or is symmetrically solvated.

However, even planar carbanions need not give racemization. Cram found that retention and even inversion can occur in the alkoxide (see **3**) cleavage reaction (**12-41**):

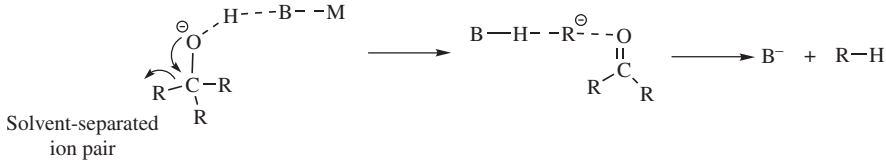


[26]Hsu, S.K.; Ingold, C.K.; Wilson, C.L. *J. Chem. Soc.* ***1938***, 78.
[27]Wilson, C.L. *J. Chem. Soc.* ***1936***, 1550.

which is a first-order S_E1 reaction involving resonance-stabilized planar carbanions (here designated R^-).[28] By changing the solvent Cram was able to produce products ranging from 99% retention to 60% inversion and including complete racemization. These results are explained by a carbanion that is not completely free but is solvated. In nondissociating, nonpolar solvents, such as benzene or dioxane, the alkoxide ion exists as an ion pair, solvated by the solvent BH:

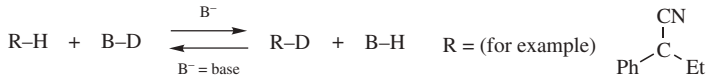


In the course of the cleavage, the proton of the solvent moves in to solvate the newly forming carbanion. As is easily seen, this solvation is asymmetrical since the solvent molecule is already on the front side of the carbanion. When the carbanion actually bonds with the proton, the result is retention of the original configuration. In protic solvents, such as diethylene glycol, a good deal of inversion is found. In these solvents, the *leaving group* solvates the carbanion, so the solvent can solvate it only from the opposite side:



When C–H bond formation occurs, the result is inversion. Racemization results in polar aprotic solvents, such as DMSO. In these solvents, the carbanions are relatively long lived (because the solvent has no proton to donate) and symmetrically solvated.

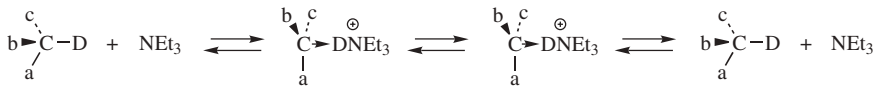
Similar behavior was found for carbanions generated by base-catalyzed hydrogen exchange (reaction **12-1**):[29]



[28]See Cram, D.J.; Langemann, A.; Allinger, J.; Kopecky, K.R. *J. Am. Chem. Soc*. ***1959***, *81*, 5740; Hoffman, T.D.; Cram, D.J. *J. Am. Chem. Soc*. ***1969***, *91*, 1009. For a discussion, see Cram, D.J. *Fundamentals of Carbanion Chemistry*, Academic Press, NY, ***1965***, pp. 138–158.

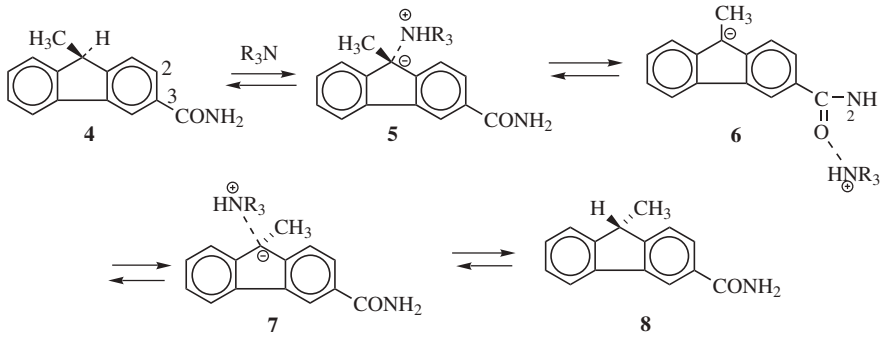
[29]See Roitman, J.N.; Cram, D.J. *J. Am. Chem. Soc*. ***1971***, *93*, 2225, 2231 and references cited therein; Cram, J.M.; Cram, D.J. *Intra-Sci. Chem. Rep*. ***1973***, *7(3)*, 1. For a discussion, see Cram, D.J. *Fundamentals of Carbanion Chemistry*, Academic Press, NY, ***1965***, pp. 85–105.

In this case, information was obtained from measurement of the ratio of k_e (rate constant for isotopic exchange) to k_a (rate constant for racemization). A k_e/k_a ratio substantially >1 means retention of configuration, since many individual isotopic exchanges are not producing a change in configuration. A k_e/k_a ratio of ~1 indicates racemization and a ratio of $\frac{1}{2}$ corresponds to inversion (see p. 430). All three types of steric behavior were found, depending on R, the base, and the solvent. As with the alkoxide cleavage reaction, retention was generally found in solvents of low dielectric constant, racemization in polar aprotic solvents, and inversion in protic solvents. However, in the proton-exchange reactions, a fourth type of behavior was encountered. In aprotic solvents, with aprotic bases like tertiary amines, the k_e/k_a ratio was found to be *less* than 0.5, indicating that racemization took place *faster* than isotopic exchange (this process is known as *isoracemization*). Under these conditions, the conjugate acid of the amine remains associated with the carbanion as an ion pair. Occasionally, the ion pair dissociates long enough for the carbanion to turn over and recapture the proton:



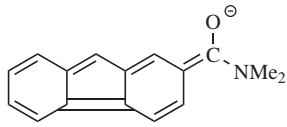
Thus, inversion (and hence racemization, which is produced by repeated acts of inversion) occurs without exchange. A single act of inversion without exchange is called *isoinversion*.

The isoinversion process can take place by a pathway in which a positive species migrates in a stepwise fashion around a molecule from one nucleophilic position to another. For example, in the exchange reaction of 3-carboxamido-9-methylfluorene (**4**) with Pr_3N in *t*-BuOH, it has been proposed that the amine removes

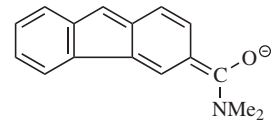


a proton from the 9 position of **4** and conducts the proton out to the C=O oxygen (**6**), around the molecule, and back to C-9 on the opposite face of the anion. Collapse of **7** gives the inverted product **8**. Of course, **6** could also go back to **4**, but a molecule that undergoes the total process **4** → **5** → **6** → **7** → **8** has experienced an inversion without an exchange. Evidence for this pathway, called the *conducted*

tour mechanism,[30] is that the 12-carboxamido isomer of **4** does not give isoracemization. In this case, the negative charge on the oxygen atom in the anion corresponding to **6** is less, because a canonical form in which oxygen acquires a full negative charge (**9**) results in disruption of the aromatic sextet in both



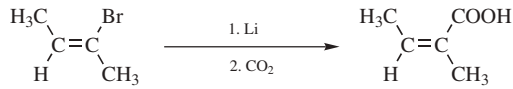
9



10

benzene rings (cf. **10** where one benzene ring is intact). Whether the isoracemization process takes place by the conducted tour mechanism or a simple nonstructured contact ion-pair mechanism depends on the nature of the substrate (e.g., a proper functional group is necessary for the conducted tour mechanism) and of the base.[31]

It is known that vinylic carbanions *can* maintain configuration, so that S_E1 mechanisms should produce retention there. This has been found to be the case. For example, *trans*-2-bromo-2-butene was converted to 64–74% angelic acid:[32]



Only ~5% of the cis isomer, tiglic acid, was produced. In addition, certain carbanions in which the negative charge is stabilized by *d*-orbital overlap can maintain configuration (p. 258) and S_E1 reactions involving them proceed with retention of configuration.

Electrophilic Substitution Accompanied by Double-Bond Shifts

11 **12**

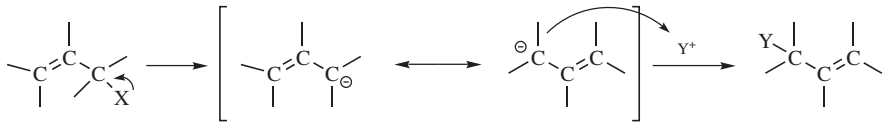
When electrophilic substitution is carried out at an allylic substrate, the product may be rearranged (**11** → **12**). This type of process is analogous to the nucleophilic

[30]Cram, D.J.; Ford, W.T.; Gosser, L. *J. Am. Chem. Soc.* ***1968***, *90*, 2598; Ford, W.T.; Cram, D.J. *J. Am. Chem. Soc.* ***1968***, *90*, 2606, 2612. See also Wong, S.M.; Fischer, H.P.; Cram, D.J. *J. Am. Chem. Soc.* ***1971***, *93*, 2235; Buchholz, S.; Harms, K.; Massa, W.; Boche, G. *Angew. Chem. Int. Ed.* ***1989***, *28*, 73.

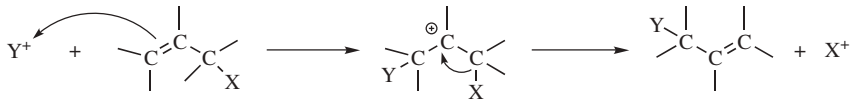
[31]Almy, J.; Hoffman, D.H.; Chu, K.C.; Cram, D.J. *J. Am. Chem. Soc.* ***1973***, *95*, 1185.

[32]Dreiding, A.S.; Pratt, R.J. *J. Am. Chem. Soc.* ***1954***, *76*, 1902. See also Walborsky, H.M.; Turner, L.M. *J. Am. Chem. Soc.* ***1972***, *94*, 2273.

allylic rearrangements discussed in Chapter 10 (p. 468). There are two principal pathways. The first of these is analogous to the S_E1 mechanism in that the leaving group is first removed, giving a resonance-stabilized allylic carbanion, which then attacks the electrophile.

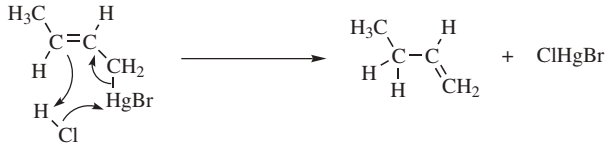


In the other pathway, the Y group is first attacked by the π-bond, giving a carbocation, which then loses X with formation of the alkene unit.

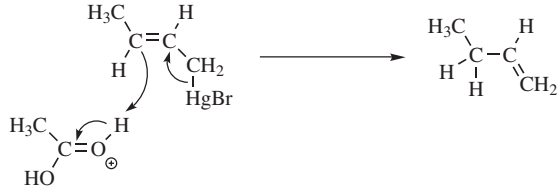


These mechanisms are more fully discussed under reaction **12-2**.

Most electrophilic allylic rearrangements involve loss of hydrogen, but they have also been observed with metallic leaving groups.[33] Sleezer, Winstein, and Young found that crotylmercuric bromide reacted with HCl $\sim 10^7$ times faster than *n*-butylmercuric bromide and the product was >99% 1-butene.[34] These facts point to an S_Ei' mechanism (IUPAC designation *cyclo*-1/3/$D_EA_ED_nA_n$):



The reaction of the same compound with acetic acid-perchloric acid seems to proceed by an S_E2' mechanism (IUPAC designation 1/3/D_EA_E):[34]



[33]For a review of reactions of allylic organometallic compounds, see Courtois, G.; Miginiac, L. *J. Organomet. Chem.* ***1974***, *69*, 1.

[34]Sleezer, P.D.; Winstein, S.; Young, W.G. *J. Am. Chem. Soc.* ***1963***, *85*, 1890. See also, Cunningham, I.M.; Overton, K.H. *J. Chem. Soc. Perkin Trans. 1* ***1975***, 2140; Kashin, A.N.; Bakunin, V.N.; Khutoryanskii, V.A.; Beletskaya, I.P.; Reutov, O.A. *J. Org. Chem. USSR* ***1979***, *15*, 12; *J. Organomet. Chem.* ***1979***, *171*, 309.

The geometry of electrophilic allylic rearrangement has not been studied very much (cf. the nucleophilic case, p. 471), but in most cases the rearrangement takes place with anti stereoselectivity,[35] although syn stereoselectivity has also been demonstrated.[36] In one case, use of the electrophile H^+ and the leaving group $SnMe_3$ gave both syn and anti stereoselectivity, depending on whether the substrate was cis or trans.[37]

Other Mechanisms

Addition–elimination (**12-16**) and cyclic mechanisms (**12-40**) are also known.

Much less work has been done on electrophilic aliphatic substitution mechanisms than on nucleophilic substitutions, and the exact mechanisms of many of the reactions in this chapter are in doubt. For many of them, not enough work has been done to permit us to decide which of the mechanisms described in this chapter is operating, if indeed any is. There may be other electrophilic substitution mechanisms, and some of the reactions in this chapter may not even be electrophilic substitutions at all.

REACTIVITY

Only a small amount of work has been done in this area, compared to the vast amount done for aliphatic nucleophilic substitution and aromatic electrophilic substitution. Only a few conclusions, most of them sketchy or tentative, can be drawn.[38]

1. *Effect of Substrate*. For S_E1 reactions electron-donating groups decrease rates and electron-withdrawing groups increase them. This is as would be expected from a reaction in which the rate-determining step is analogous to the cleavage of a proton from an acid. For the S_E2 (back) mechanism, Jensen and Davis[12] showed that the reactivity of alkyl groups is similar to that for the S_N2 mechanism (i.e., Me > Et > Pr > *i*Pr > neopentyl), as would be expected, since both involve backside attack and both are equally affected by steric hindrance. In fact, this pattern of reactivity can be regarded as evidence for the occurrence of the S_E2 (back) mechanism in cases where

[35]Hayashi, T.; Ito, H.; Kumada, M. *Tetrahedron Lett.* ***1982***, *23*, 4605; Wetter, H.; Scherer, P. *Helv. Chim. Acta* ***1983***, *66*, 118; Wickham, G.; Kitching, W. *J. Org. Chem.* ***1983***, *48*, 612; Fleming, I.; Kindon, N.D.; Sarkar, A.K. *Tetrahedron Lett.* ***1987***, *28*, 5921; Hayashi, T.; Matsumoto, Y.; Ito, Y. *Chem. Lett.* ***1987***, 2037, *Organometallics* ***1987***, *6*, 885; Matassa, V.G.; Jenkins, P.R.; Kümin, A.; Damm, L.; Schreiber, J.; Felix, D.; Zass, E.; Eschenmoser, A. *Isr. J. Chem.* ***1989***, *29*, 321.

[36]Wetter, H.; Scherer, P.; Schweizer, W.B. *Helv. Chim. Acta* ***1979***, *62*, 1985; Young, D.; Kitching, W. *J. Org. Chem.* ***1983***, *48*, 614; *Tetrahedron Lett.* ***1983***, *24*, 5793.

[37]Kashin, A.N.; Bakunin, V.N.; Beletskaya, I.P.; Reutov, O.A. *J. Org. Chem. USSR* ***1982***, *18*, 1973. See also, Wickham, G.; Young, D.; Kitching, W. *Organometallics* ***1988***, *7*, 1187.

[38]For a discussion, see Abraham, M.H. *Comprehensive Chemical Kinetics*, Bamford, C.H.; Tipper, C.F.H., Eds., Vol. 12; Elsevier, NY, ***1973***, pp. 211–241.

TABLE 12.1. Relative Rates of the Reaction of RHgBr with Br_2 and Br^- [41]

R	Relative Rate	R	Relative Rate
Me	1	Et	10.8
Et	10.8	*i*Bu	1.24
*i*Pr	780	Neopentyl	0.173
t-Bu	3370		

stereochemical investigation is not feasible.[39] For S_E2 reactions that proceed with retention, several studies have been made with varying results, depending on the reaction.[40] One such study, which examined the reaction $RHgBr + Br_2 \rightarrow RBr$ catalyzed by Br^-, gave the results shown in Table 12.1.[41] As can be seen, a branching increased the rates, while β branching decreased them. Sayre and Jensen attributed the decreased rates to steric hindrance, although attack here was definitely frontside, and the increased rates to the electron-donating effect of the alkyl groups, which stabilized the electron-deficient transition state.[42] Of course, steric hindrance should also be present with the a branched groups, so these workers concluded that if it were not, the rates would be even greater. The Br electrophile is a rather large one and it is likely that smaller steric effects are present with smaller electrophiles. The rates of certain second-order substitutions of organotin compounds have been found to increase with increasing electron withdrawal by substituents. This behavior has been ascribed[43] to an S_E2 mechanism involving ion pairs, analogous to Sneen's ion-pair mechanism for nucleophilic substitution (p. 441). Solvolysis of 2-bromo-1,1,1-trifluoro-2-(*p*-methoxyphenyl)ethane in water proceeds via a free carbocation intermediate, but ion pairing influences the reaction in the presence of bromide ion.[44]

2. *Effect of Leaving Group.* For both S_E1 and second-order mechanisms, the more polar the C–X bond, the easier it is for the electrofuge to cleave. For metallic leaving groups in which the metal has a valence >1, the nature of the other group or groups attached to the metal thus has an effect on the reaction.

[39]Another method involves measurement of the susceptibility of the rate to increased pressure: See Isaacs, N.S.; Javaid, K. *Tetrahedron Lett*. ***1977***, 3073; Isaacs, N.S.; Laila, A.H. *Tetrahedron Lett*. ***1984***, *25*, 2407.
[40]For some of these, see Abraham, M.H.; Grellier, P.L. *J. Chem. Soc. Perkin Trans. 2* ***1973***, 1132; Dessy, R.E.; Reynolds, G.F.; Kim, J. *J. Am. Chem. Soc*. ***1959***, *81*, 2683; Minato, H.; Ware, J.C.; Traylor, T.G. *J. Am. Chem. Soc*. ***1963***, *85*, 3024; Boué, S.; Gielen, M.; Nasielski, J. *J. Organomet. Chem*. ***1967***, *9*, 443; Abraham, M.H.; Broadhurst, A.T.; Clark, I.D.; Koenigsberger, R.U.; Dadjour, D.F. *J. Organomet. Chem*. ***1981***, *209*, 37.
[41]Sayre, L.M.; Jensen, F.R. *J. Am. Chem. Soc*. ***1979***, *101*, 6001.
[42]A similar conclusion, that steric and electronic effects are both present, was reached for a different system by Nugent, W.A.; Kochi, J.K. *J. Am. Chem. Soc*. ***1976***, *98*, 5979.
[43]Reutov, O.A. *J. Organomet. Chem*. ***1983***, *250*, 145. See also, Butin, K.P.; Magdesieva, T.V. *J. Organomet. Chem*. ***1985***, *292*, 47; Beletskaya, I.P. *Sov. Sci. Rev. Sect. B* ***1979***, *1*, 119.
[44]Richard, J.P. *J. Org. Chem*. ***1992***, *57*, 625.

For example, consider a series of organomercurials RHgW. Because a more electronegative W decreases the polarity of the C–Hg bond and furthermore results in a less stable HgW^+, the electrofugal ability of HgW decreases with increasing electronegativity of W. Thus, HgR′ (from RHgR′) is a better leaving group than HgCl (from RHgCl). Also in accord with this is the leaving-group order Hg-*t*-Bu > Hg-*i*Pr > HgEt > HgMe, reported for acetolysis of R_2Hg,[42] since the more highly branched alkyl groups better help to spread the positive charge. It might be expected that, when metals are the leaving groups, S_E1 mechanisms would be favored, while with carbon leaving groups, second-order mechanisms would be found. However, the results so far reported have been just about the reverse of this. For carbon leaving groups the mechanism is usually S_E1, while for metallic leaving groups the mechanism is almost always S_E2 or S_Ei. A number of reports of S_E1 reactions with metallic leaving groups have appeared,[45] but the mechanism is not easy to prove and many of these reports have been challenged.[46] Reutov and co-workers[45] have expressed the view that in such reactions a nucleophile (which may be the solvent) must assist in the removal of the electrofuge and refer to such processes as $S_E1(N)$ reactions.

3. *Effect of Solvent*.[47] In addition to the solvent effects on certain S_E1 reactions, mentioned earlier (p. 758), solvents can influence the mechanism that is preferred. As with nucleophilic substitution (p. 501), an increase in solvent polarity increases the possibility of an ionizing mechanism, in this case S_E1, in comparison with the second-order mechanisms, which do not involve ions. As previously mentioned (p. 758), the solvent can also exert an influence between the S_E2 (front or back) and S_Ei mechanisms in that the rates of S_E2 mechanisms should be increased by an increase in solvent polarity, while S_Ei mechanisms are much less affected.

REACTIONS

The reactions in this chapter are arranged in order of leaving group: hydrogen, metals, halogen, and carbon. Electrophilic substitutions at a nitrogen atom are treated last.

Hydrogen as Leaving Group

A. Hydrogen as the Electrophile

[45]For discussions, see Reutov, O.A. *Bull. Acad. Sci. USSR Div. Chem. Sci*. ***1980***, *29*, 1461; Beletskaya, I.P.; Butin, K.P.; Reutov, O.A. *Organomet. Chem. Rev. Sect. A* ***1971***, *7*, 51. See also, Deacon, G.B.; Smith, R.N.M. *J. Org. Chem. USSR* ***1982***, *18*, 1584; Dembech, P.; Eaborn, C.; Seconi, G. *J. Chem. Soc. Chem. Commun*. ***1985***, 1289.

[46]For a discussion, see Kitching, W. *Rev. Pure Appl. Chem*. ***1969***, *19*, 1.

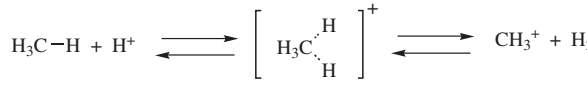
[47]For a discussion of solvent effects on organotin alkyl exchange reactions, see Petrosyan, V.S. *J. Organomet. Chem*. ***1983***, *250*, 157.

12-1 Hydrogen Exchange

Deuterio-de-hydrogenation or Deuteriation

$$R{-}H + D^+ \rightleftharpoons R{-}D + H^+$$

Hydrogen exchange can be accomplished by treatment with acids or bases. As with **11-1**, the exchange reaction is mostly used to study mechanistic questions, such as relative acidities, but it can be used synthetically to prepare deuterated or tritiated molecules. When ordinary strong acids, such as H_2SO_4 are used, only fairly acidic protons *n* carbon exchange, for example, acetylenic and allylic. However, primary, secondary, and tertiary hydrogens of alkanes can be exchanged by treatment with superacids (p. 236).[48] The order of hydrogen reactivity is tertiary > secondary > primary. Where C–C bonds are present, they may be cleaved also (**12-47**). The mechanism of the exchange (illustrated for methane) has been formulated as involving attack of H^+ on the C–H bond to give the pentavalent methanonium ion that loses H_2 to give a tervalent



Methanonium ion

carbocation.[49] The methanonium ion CH_5^+ has a three-center, two-electron bond.[50] It is not known whether the methanonium ion is a transition state or a true intermediate, but an ion CH_5^+ has been detected in the mass spectrum.[51] The IR spectrum of the ethanonium ion $C_2H_7^+$ has been measured in the gas phase.[52] Note that the two electrons in the three-center, two-electron bond can move in three directions, in accord with the threefold symmetry of such a structure. The electrons can move to unite the two hydrogens, leaving the CH_3^+ free (the forward reaction), or they can unite the CH_3 with either of the two hydrogens, leaving the other hydrogen as a free H^+ ion (the reverse reaction). Actually, the methyl cation is not stable under these conditions. It can go back to CH_4 by the route shown (leading to H^+ exchange) or it can react with additional CH_4 molecules (**12-20**) to eventually yield the *tert*-butyl cation, which is stable in these superacid solutions. Hydride ion can also be removed from alkanes (producing tervalent carbocations) by treatment with pure SbF_5 in the absence of any source of H^+.[53] Complete or almost complete perdeuteriation of cyclic alkenes has been achieved by treatment with dilute DCl/D_2O in sealed Pyrex tubes at 165–280°C.[54]

[48]For reviews, see Olah, G.A.; Prakash, G.K.S.; Sommer, J. *Superacids*, Wiley, NY, ***1985***, pp. 244–249; Olah, G.A. *Angew. Chem. Int. Ed.* ***1973***, *12*, 173; Brouwer, D.M.; Hogeveen, H. *Prog. Phys. Org. Chem.* ***1972***, *9*, 179, 180–203.

[49]The mechanism may not be this simple in all cases. For discussions, see McMurry, J.E.; Lectka, T. *J. Am. Chem. Soc.* ***1990***, *112*, 869; Culmann, J.; Sommer, J. *J. Am. Chem. Soc.* ***1990***, *112*, 4057.

[50]For a monograph on this type of species, see Olah, G.A.; Prakash, G.K.S.; Williams, R.E.; Field, L.D.; Wade, K. *Hypercarbon Chemistry*; Wiley, NY, ***1987***.

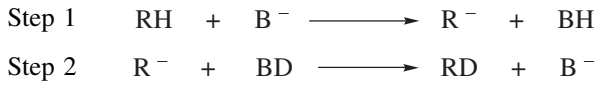
[51]See, for example, Sefcik, M.D.; Henis, J.M.S.; Gaspar, P.P. *J. Chem. Phys.* ***1974***, *61*, 4321.

[52]Yeh, L.I.; Pric, J.M.; Lee, Y.T. *J. Am. Chem. Soc.* ***1989***, *111*, 5597.

[53]Lukas, J.; Kramer, P.A.; Kouwenhoven, A.P. *Recl. Trav. Chim. Pays-Bas* ***1973***, *92*, 44.

[54]Werstiuk, N.H.; Timmins, G. *Can. J. Chem.* ***1985***, *63*, 530; ***1986***, *64*, 1564.

Exchange with bases involves an S_E1 mechanism.



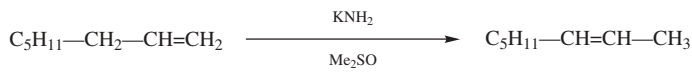
Of course, such exchange is most successful for relatively acidic protons, such as those a to a carbonyl group, but even weakly acidic protons can exchange with bases if the bases are strong enough (see p. 251).

Alkanes and cycloalkanes, of both low and high molecular weight, can be fully perdeuterated treatment with D_2 gas and a catalyst, such as Rh, Pt, or Pd.[55]

OS **VI**, 432.

12-2 Migration of Double Bonds

3/Hydro-de-hydrogenation



The double bonds of many unsaturated compounds are shifted[56] on treatment with strong bases.[57] In many cases, equilibrium mixtures are obtained and the thermodynamically most stable isomer predominates.[58] Thus, if the new double bond can be in conjugation with one already present or with an aromatic ring, the migration favors the conjugated compound.[59] If the choice is between an exocyclic and an endocyclic double bond (particularly with six-membered rings), it generally chooses the latter. In the absence of considerations like these, Zaitsev's rule (p. 1497) applies and the double bond goes to the carbon with the fewest hydrogens. All these considerations lead us to predict that terminal alkenes can be isomerized to internal ones, nonconjugated alkenes to conjugated, exo six-membered-ring alkenes to endo, and so on, and not the other way around. This is indeed usually the case.

[55]See, for example, Atkinson, J.G.; Luke, M.O.; Stuart, R.S. *Can. J. Chem.* ***1967***, *45*, 1511.

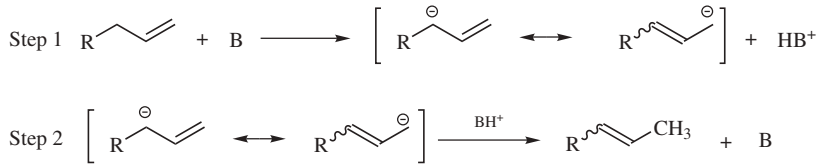
[56]For a list of methods used to shift double and triple bonds, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 220–226, 567–568.

[57]For reviews of double-bond migrations, see Pines, H.; Stalick, W.M. *Base-Catalyzed Reactions of Hydrocarbons and Related Compounds*, Academic Press, NY, ***1977***, pp. 25–123; DeWolfe, R.H., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9, Elsevier, NY, ***1973***, pp. 437–449; Yanovskaya, L.A.; Shakhidayatov, Kh. *Russ. Chem. Rev.* ***1970***, *39*, 859; Hubert, A.J.; Reimlinger, H. *Synthesis* ***1969***, 97; ***1970***, 405; Mackenzie, K., in *The Chemistry of Alkenes*, Vol. 1, Patai, S. pp. 416–436, vol. 2, Zabicky, J. pp. 132–148; Wiley, NY, 1964, ***1970***; Broaddus, C.D. *Acc. Chem. Res.* ***1968***, *1*, 231; Cram, D.J. *Fundamentals of Carbanion Chemistry*, Academic Press, NY, ***1965***, pp. 175–210.

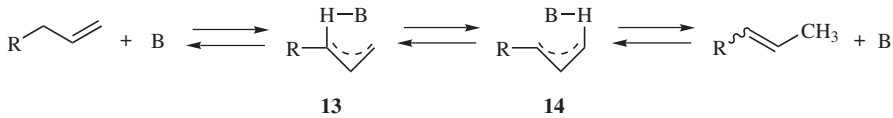
[58]For lists of which double bonds are more stable in conversions of $XCH_2CH{=}CHY$ to $XCH{=}CHCH_2Y$, see Hine, J.; Skoglund, M.J. *J. Org. Chem.* ***1982***, *47*, 4766. See also, Hine, J.; Linden, S. *J. Org. Chem.* ***1983***, *48*, 584.

[59]For a review of conversions of β,γ enones to α,β enones, see Pollack, R.M.; Bounds, P.L.; Bevins, C.L., in Patai, S.; Rappoport, Z. *The Chemistry of Enones*, pt. 1, Wiley, NY, ***1989***, pp. 559–597.

This reaction, for which the term *prototropic rearrangement* is sometimes used, is an example of electrophilic substitution with accompanying allylic rearrangement. The mechanism involves abstraction by a base to give a resonance-stabilized carbanion, which then combines with a proton at the position that will give the more stable alkene:[60]

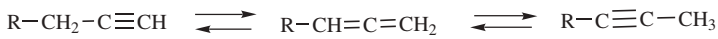


This mechanism is exactly analogous to the allylic-rearrangement mechanism for nucleophilic substitution (p. 468). UV spectra of allylbenzene and 1-propenylbenzene in solutions containing NH_2^- are identical, which shows that the same carbanion is present in both cases, as required by this mechanism.[61] The acid BH^+ protonates the position that will give the more stable product, although the ratio of the two possible products can vary with the identity of BH^+.[62] It has been shown that base-catalyzed double-bond shifts are partially intramolecular, at least in some cases.[63] The intramolecular nature has been ascribed to a *conducted tour mechanism* (p. 761) in which the base leads the proton from one carbanionic site to the other (**13** → **14**).[64]



13 **14**

Triple bonds can also migrate in the presence of bases,[65] but through the allene intermediate:[66]



[60]See, for example, Hassan, M.; Nour, A.R.O.A.; Satti, A.M.; Kirollos, K.S. *Int. J. Chem. Kinet*. ***1982***, *14*, 351; Pollack, R.M.; Mack, J.P.G.; Eldin, S. *J. Am. Chem. Soc*. ***1987***, *109*, 5048.

[61]Rabinovich, E.A.; Astaf'ev, I.V.; Shatenshtein, A.I. *J. Gen. Chem. USSR* ***1962***, *32*, 746.

[62]Hünig, S.; Klaunzer, N.; Schlund, R. *Angew. Chem. Int. Ed*. ***1987***, *26*, 1281.

[63]See, for example, Cram, D.J.; Uyeda, R.T. *J. Am. Chem. Soc*. ***1964***, *86*, 5466; Bank, S.; Rowe, Jr., C.A.; Schriesheim, A. *J. Am. Chem. Soc*. ***1963***, *85*, 2115; Doering, W. von E.; Gaspar, P.P. *J. Am. Chem. Soc*. ***1963***, *85*, 3043; Ohlsson, L.; Wold, S.; Bergson, G. *Ark. Kemi*., ***1968***, *29*, 351.

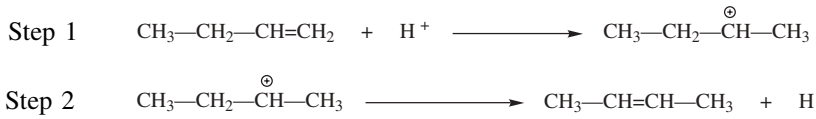
[64]Almy, J.; Cram, D.J. *J. Am. Chem. Soc*. ***1969***, *91*, 4459; Hussénius, A.; Matsson, O.; Bergson, G. *J. Chem. Soc. Perkin Trans. 2* ***1989***, 851.

[65]For reviews, see Pines, H.; Stalick, W.M. *Base-Catalyzed Reactions of Hydrocarbons and Related Compounds*, Academic Press, NY, ***1977***, pp. 124–204; Théron F.; Verny, M.; Vessière, R. in Patai, S. *The Chemistry of Carbon–Carbon Triple Bond*, pt. 1, Wiley, NY, ***1978***, pp. 381–445; Bushby, R.J. *Q. Rev. Chem. Soc*. ***1970***, *24*, 585; Iwai, I. *Mech. Mol. Migr*. ***1969***, *2*, 73; Wotiz, J.H., in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 365–424; Vartanyan, S.A.; Babanyan, Sh.O. *Russ. Chem. Rev*. ***1967***, *36*, 670.

[66]For a review of rearrangements involving allenes, see Huntsman, W.D., in Patai, S. *The Chemistry of Ketenes, Allenes, and Related Compounds*, pt. 2; Wiley, NY, ***1980***, pp. 521–667.

In general, strong bases, for example, $NaNH_2$, convert internal alkynes to terminal alkynes (a particularly good base for this purpose is potassium 3-aminopropylamide $NH_2CH_2CH_2CH_2NHK$[67]), because the equilibrium is shifted by formation of the acetylid ion. With weaker bases such as NaOH (which are not strong enough to remove the acetylenic proton), the internal alkynes are favored because of their greater thermodynamic stability. In some cases the reaction can be stopped at the allene stage.[68] The reaction then becomes a method for the preparation of allenes.[69] The reaction of propargylic alcohols with tosylhydrazine, PPh_3, and DEAD also generates allenes.[70]

Double-bond rearrangements can also take place on treatment with acids. Both proton and Lewis[71] acids can be used. The mechanism in the case of proton acids is the reverse of the previous one; first a proton is gained, giving a carbocation, and then another is lost:



As in the case of the base-catalyzed reaction, the thermodynamically most stable alkene is the one predominantly formed. However, the acid-catalyzed reaction is much less synthetically useful because carbocations give rise to many side products. If the substrate has several possible locations for a double bond, mixtures of all possible isomers are usually obtained. Isomerization of 1-decene, for example, gives a mixture that contains not only 1-decene and *cis*- and *trans*-2-decene, but also the cis and trans isomers of 3-, 4-, and 5-decene as well as branched alkenes resulting from rearrangement of carbocations. It is true that the most stable alkenes predominate, but many of them have stabilities that are close together. Acid-catalyzed migration of triple bonds (with allene intermediates) can be accomplished if very strong acids (e.g., HF–PF_5) are used.[72] If the mechanism is the same as that for double bonds, vinyl cations are intermediates.

Double-bond isomerization can also take place in other ways. Nucleophilic allylic rearrangements were discussed in Chapter 10 (p. 468). Electrocyclic and sigmatropic rearrangements are treated at **18-27**–**18-35**. Double-bond migrations have also been accomplished photochemically,[73] and by means of metallic ion (most

[67]Brown, C.A.; Yamashita, A. *J. Am. Chem. Soc*. ***1975***, *97*, 891; Macaulay, S.R. *J. Org. Chem*. ***1980***, *45*, 734; Abrams, S.R. *Can. J. Chem*. ***1984***, *62*, 1333.

[68]For an example, see Oku, M.; Arai, S.; Katayama, K.; Shioiri, T. *Synlett* ***2000***, 493.

[69]See Enomoto, M.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett*. ***1986***, *27*, 4599; Cunico, R.F.; Zaporowski, L.F.; Rogers, M. *J. Org. Chem*. ***1999***, *64*, 9307.

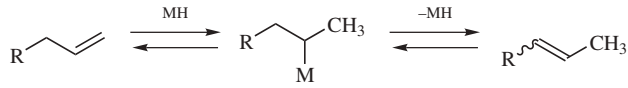
[70]Myers, A.G.; Zheng, B. *J. Am. Chem. Soc*. ***1996***, *118*, 4492. See Moghaddam, F.M.; Emami, R. *Synth. Commun*. ***1997***, *27*, 4073 for the formation of alkoxy allenes from propargyl ethers.

[71]For an example of a Lewis acid catalyzed rearrangement, see Cameron G.S.; Stimson, V.R. *Aust. J. Chem*. ***1977***, *30*, 923.

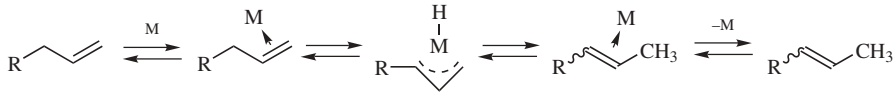
[72]Barry, B.J.; Beale, W.J.; Carr, M.D.; Hei, S.; Reid, I. *J. Chem. Soc. Chem. Commun*. ***1973***, 177.

[73]Schönberg, A. *Preparative Organic Photochemistry*, Springer, NY, ***1968***, pp. 22–24.

often complex ions containing Pt, Rh, or Ru) or metal carbonyl catalysts.[74] In the latter case, there are at least two possible mechanisms. One of these, which requires external hydrogen, is called the *metal hydride addition–elimination mechanism*:



The other mechanism, called the π-*allyl complex mechanism*, does not require external hydrogen and proceeds by hydrogen abstraction to form the η^3-π-allyl complex **15** (see p. 117 and **10-60**).



15

Another difference between the two mechanisms is that the former involves 1,2- and the latter 1,3-shifts. The isomerization of 1-butene by rhodium(I) is an example of a reaction that takes place by the metal hydride mechanism,[75] while an example of the π-allyl complex mechanism is found in the $Fe_3(CO)_{12}$-catalyzed isomerization of 3-ethyl-1-pentene.[76] A palladium catalyst was used to convert alkynones $RCOC{\equiv}CCH_2CH_2R'$ to 2,4-alkadien-1-ones, $RCOCH{=}CHCH{=}CHCHR'$.[77] The reaction of an en-yne with $HSiCl_3$ and a palladium catalyst generated an allene with moderate enantioselectivity (see p 148 for chiral allenes).[78]

The metal catalysis method has been used for the preparation of simple enols, by isomerization of allylic alcohols, for example,[79] these enols are stable enough for isolation (see p. 231), but slowly tautomerize to the aldehyde or ketone, with half-lives ranging from 40 to 50 min to several days.[79]

[74]For reviews, see Rodriguez, J.; Brun, P.; Waegell, B. *Bull. Soc. Chim. Fr.* ***1989***, 799–823; Jardine, F.R., in Hartley, F.R.; Patai, S. *The Chemistry of the Metal-Carbon Bond*, Vol. 4, Wiley, NY, pp. 733–818, 736–740; Otsuka, S.; Tani, K., in Morrison, J.D. *Asymmetric Synthesis*, Vol. 5, Academic Press, NY, ***1985***, pp. 171–191 (enantioselective); Colquhoun, H.M.; Holton, J.; Thompson, D.J.; Twigg, M.V. *New Pathways for Organic Synthesis*, Plenum, NY, ***1984***, pp. 173–193; Khan, M.M.T.; Martell, A.E. *Homogeneous Catalysis by Metal Complexes*, Academic Press, NY, ***1974***, pp. 9–37; Heck, R.F. *Organotransition Metal Chemistry*, Academic Press, NY, ***1974***, pp. 76–82; Jira, R.; Freiesleben, W. *Organomet. React.* ***1972***, *3*, 1, 133–149; Biellmann, J.F.; Hemmer, H.; Levisalles, J., in Hartley, F.R.; Patai, S. *The Chemistry of the Metal-Carbon Bond*, Vol. 2, Wiley, NY, pp. 224–230; Bird, C.W. *Transition Metal Intermediates in Organic Synthesis*, Academic Press, NY, ***1967***, pp. 69–87; Davies, N.R. *Rev. Pure Appl. Chem.* ***1967***, *17*, 83; Orchin, M. *Adv. Catal.* ***1966***, *16*, 1.

[75]Cramer, R. *J. Am. Chem. Soc.* ***1966***, *88*, 2272.

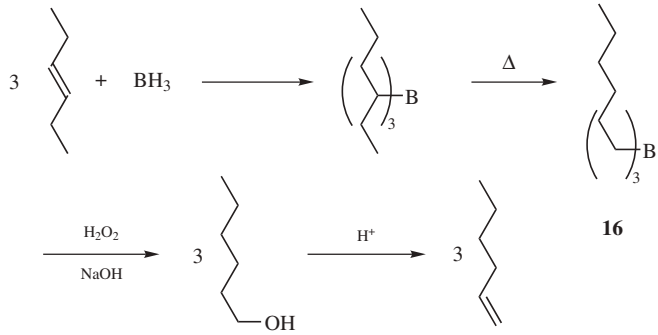
[76]Casey, C.P.; Cyr, C.R. *J. Am. Chem. Soc.* ***1973***, *95*, 2248.

[77]Trost, B.M.; Schmidt, T. *J. Am. Chem. Soc.* ***1988***, *110*, 2301.

[78]Han, J.W.; Tokunaga, N.; Hayashi, T. *J. Am. Chem. Soc.* ***2001***, *123*, 12915.

[79]Bergens, S.H.; Bosnich, B. *J. Am. Chem. Soc.* ***1991***, *113*, 958.

No matter which of the electrophilic methods of double-bond shifting is employed, the thermodynamically most stable alkene is usually formed in the largest amount in most cases, although a few anomalies are known. However, an indirect method of double-bond isomerization us known, leading to migration in the other direction. This involves conversion of the alkene to a borane (**15-16**), rearrangement of the borane (**18-11**), oxidation and hydrolysis of the newly formed borane to the alcohol **17** (see **12-31**), and dehydration of the alcohol (**17-1**) to the alkene. The reaction is driven by the fact that with heating the addition of borane is reversible, and the equilibrium favors formation of the less sterically hindered borane, which is **16** in this case.



Since the migration reaction is always toward the end of a chain, terminal alkenes can be produced from internal ones, so the migration is often opposite to that with the other methods. Alternatively, the rearranged borane can be converted directly to the alkene by heating with an alkene of molecular weight higher than that of the product (**17-15**). Photochemical isomerization can also lead to the thermodynamically less stable isomer.[80]

If a hydroxy group is present in the chain, *it* may lose a proton, so that a ketone is the product, for example,[81]

$$R_2C{=}CHCH_2CH_2CHOHCH_3 \xrightarrow[\text{acid}]{\text{polyphosphoric}} R_2CHCH_2CH_2CH_2COCH_3$$

Similarly, α-hydroxy triple-bond compounds have given α,β-unsaturated ketones.[82]

[80]For example, see Kropp, P.J.; Krauss, H.J. *J. Am. Chem. Soc*. ***1967***, *89*, 5199; Reardon, Jr., E.J.; Krauss, H. *J. Am. Chem. Soc*. ***1971***, *93*, 5593; Duhaime, R.M.; Lombardo, D.A.; Skinner, I.A.; Weedon, A.C. *J. Org. Chem*. ***1985***, *50*, 873.

[81]Colonge, J.; Brunie, J. *Bull. Soc. Chim. Fr.* ***1963***, 1799. For an example with basic catalysis, see Hoffmann, H.M.R.; Köver, A.; Pauluth, D. *J. Chem. Soc. Chem. Commun*. ***1985***, 812. For an example with a ruthenium complex catalyst, see Trost, B.M.; Kulawiec, R.J. *Tetrahedron Lett*. ***1991***, *32*, 3039.

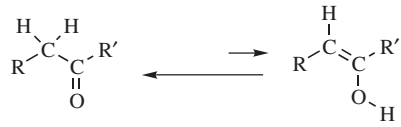
[82]For example, see Chabardes, P. *Tetrahedron Lett*. ***1988***, *29*, 6253.

See **15-1** for related reactions in which double bonds migrate or isomerize.

OS **II**, 140; **III**, 207; **IV**, 189, 192, 195, 234, 398, 683; **VI**, 68, 87, 815, 925; **VII**, 249; **VIII**, 146, 196, 251, 396, 553; **X**, 156, 165; **81**, 147

12-3 Keto–Enol Tautomerization

3/*O*-Hydro-de-hydrogenation



The tautomeric equilibrium between enols and ketones or aldehydes (keto–enol tautomerism) is a form of prototropy,[83] but is not normally a preparative reaction. For some ketones, however, both forms can be prepared (see p. 101 for a discussion of this and other aspects of tautomerism). Keto–enol tautomerism occurs in systems containing one or more carbonyl groups linked to sp^3 carbons bearing one or more hydrogen atoms. The keto tautomer is generally more stable than the enol tautomer for neutral systems, and for most ketones and aldehydes only the keto form is detectable under ordinary conditions. The availability of additional intramolecular stabilization through hydrogen bonding or complete electron delocalization (as in phenol), may cause the enol tautomer to be favored.

Keto–enol tautomerism cannot take place without at least a trace of acid or base,[84] since the acidic or basic center or both in the tautomeric substance is too weak.[85] In this equilibrium, the heteroatom is the basic site the proton is the acidic site. For tautomerism in general (see p 98),[86] the presence of an acid or a base is not necessary to initiate the isomerization since each tautomeric substance possesses amphiprotic properties.[85] Keto-enol tautomerism is therefore the exception.

[83]Patai, S. *The Chemistry of the Carbonyl Group*, Wiley, London, ***1966***; Rappoport, Z. *The Chemistry of Enols*, Wiley, NY, ***1990***; Kresge, A.J. *Chem. Soc. Rev.* ***1996***, *25*, 275; Karelson, M.; Maran, U.; Katritzky, A.R. *Tetrahedron* ***1996***, *52*, 11325; Rappoport, Z.; Frey, J.; Sigalov, M.; Rochlin, E. *Pure Appl. Chem.* ***1997***, *69*, 1933; Fontana, A.; De Maria, P.; Siani, G.; Pierini, M.; Cerritelli, S.; Ballini, R. *Eur. J. Org. Chem.* ***2000***, 1641; Iglesias, E. *Curr. Org. Chem.* ***2004***, *8*, 1.

[84]Bell, R.P. *Acid–Base Catalysis*, Oxford University Press, Oxford, ***1941***; Jones, J.R. *The Ionisation of Carbon Acids*, Academic Press, London, ***1973***; Pederson, K.J. *J. Phys. Chem.* ***1934***, *38*, 581; Lienhard, G.E.; Wang, T. C. *J. Am. Chem. Soc.* ***1969***, *91*, 1146; Toullec, J. *Adv. Phys. Org. Chem.* ***1982***, *18*, 1. See also, Chiang, Y.; Kresge, A.J.; Santaballa, J.A.; Wirz, J. *J. Am. Chem. Soc.* ***1988***, *110*, 5506.

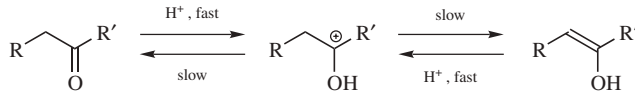
[85]Raczynska, E. D.; Kosinska, W.; Osmialowski, B.; Gawinecki, R. *Chem. Rev.* ***2005***, *105*, 3561.

[86]See Patai, S. *The Chemistry of the Carbonyl Group*, Wiley, London, ***1966***; Rappoport, Z. *The Chemistry of Enols*, Wiley, NY, ***1990***; Patai, S. *The Chemistry of the Thiol Group*, Wiley, London, ***1974***; Zabicky, J. *The Chemistry of Amides*, Wiley, London, ***1970***; Boyer, J. H. *The Chemistry of the Nitro and Nitroso Groups*, Interscience Publishers, NY, ***1969***; Patai, S. *The Chemistry of Amino, Nitroso, Nitro Compounds and their Derivatives*, Wiley, NY, ***1982***; Patai, S. *The Chemistry of Amino, Nitroso, Nitro and Related Groups, Supplement F2*,Wiley, Chichester, ***1996***; Cook, A. G. *Enamines*, 2nd ed., Marcel Dekker, NY, ***1998***.

Polar protic solvents, such as water or alcohol, may participate in the proton transfer by forming a cyclic or a linear complex with the tautomers.[87] Whether the complex formed is cyclic or linear depends on the conformation and configuration of the tautomers. In a strongly polar aprotic solvent and in the presence of an acid or a base, the tautomeric molecule may lose or gain a proton and form the corresponding mesomeric anion or cation, which, in turn, may gain or lose a proton, respectively, and yield a new tautomeric form.[88] The structural features of the carbonyl compound influences the equilibrium.[89] There is a rate acceleration when $LiN(SiMe_3)_2$–NEt_3 is used.[90] It has been shown that ring strain plays no significant role on the rate of base-catalyzed enolization.[91] Differing conjugative stabilization by CH-π orbital overlap does not directly influence stereoselectivity, and steric effects are generally not large enough to cause the several kcal/mol energy difference seen between transition structures unless there is exceptional crowding.[92] It is noted that sterically stabilized enols are known,[93] including arylacetaldehydes.[94] Torsional strain involving vicinal bonds does contribute significantly to stereoselectivity in enolate formation.[92]

The acid and base catalyzed mechanisms are identical to those in **12-2**.[95]

Acid-catalyzed



[87]Lledós, A.; Bertran, J. *Tetrahedron Lett*. ***1981***, *22*, 775; Zielinski, T.J.; Poirier, R.A.; Peterson, M.R.; Csizmadia, I.G. *J. Comput. Chem*. ***1983***, *4*, 419; Yamabe, T.; Yamashita, K.; Kaminoyama, M.; Koizumi, M.; Tachibana, A.; Fukui, K. *J. Phys. Chem*. ***1984***, *88*, 1459; Chen, Y.; Gai, F.; Petrich, J.W. *J. Am. Chem. Soc*. ***1993***, *115*, 10158; Herbich, J.; Dobkowski, J.; Thummel, R.P.; Hegde, V.; Waluk, J. *J. Phys. Chem. A* ***1997***, *101*, 5839; Gorb, L.; Leszczynski, J. *J. Am. Chem. Soc*. ***1998***, *120*, 5024; Guo, J. X.; Ho, J. J. *J. Phys. Chem. A* ***1999***, *103*, 6433.

[88]Watson, H.B. *Trans. Faraday Soc*. ***1941***, *37*, 713; Kabachnik, M.I. *Dokl. Akad. Nauk SSSR* ***1952***, *83*, 407; Perez Ossorio, R.; Hughes, E.D. *J. Chem. Soc*. ***1952***, 426; Briegleb, G.; Strohmeier, W. *Angew. Chem*. ***1952***, *64*, 409; Baddar, F.G.; Iskander, Z. *J. Chem. Soc*. ***1954***, 203.

[89]Hegarty, A.F.; Dowling, J.P.; Eustace, S.J.; McGarraghy, M. *J. Am. Chem. Soc*. ***1998***, *120*, 2290.

[90]Zhao, P.; Collum, D.B. *J. Am. Chem. Soc*. ***2003***, *125*, 4008.

[91]Cantlin, R.J.; Drake, J.; Nagorski, R.W. *Org. Lett*. ***2002***, *4*, 2433.

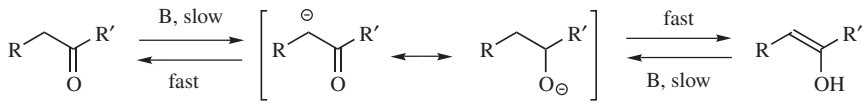
[92]Behnam, S.M.; Behnam, S.E.; Ando, K.; Green, N.S.; Houk, K.N. *J. Org. Chem*. ***2000***, *65*, 8970.

[93]Miller, A.R. *J. Org. Chem*., ***1976***, *41*, 3599.

[94]Fuson, R.C.; Southwick, P.L.; Rowland, Jr., S.P. *J. Am. Chem. Soc*. ***1944***, *66*, 1109; Fuson, R.C.; Tan, T.-L. *J. Am. Chem. Soc*. ***1948***, *70*, 602.

[95]For reviews of the mechanism, see Keeffe, J.R.; Kresge, A.J., in Rappoport, Z. *The Chemistry of Enols*, Wiley, NY, ***1990***, pp. 399–480; Toullec, J. *Adv. Phys. Org. Chem*. ***1982***, *18*, 1; Lamaty, G. *Isot. Org. Chem*. ***1976***, *2*, 33. For discussions, see Ingold, C.K. *Structure and Mechanism in Organic Chemistry*, 2nd ed., Cornell University Press, Ithaca, NY, ***1969***, pp. 794–837; Bell, R.P. *The Proton in Chemistry*, 2nd ed., Cornell University Press, Ithaca, NY, ***1973***, pp. 171–181; Bruice, P.Y.; Bruice, T.C. *J. Am. Chem. Soc*. ***1976***, *98*, 844; Shelly, K.P.; Venimadhavan, S.; Nagarajan, K.; Stewart, R. *Can. J. Chem*. ***1989***, *67*, 1274. For a review of stereoelectronic control in this mechanism, see Pollack, R.M. *Tetrahedron* ***1989***, *45*, 4913.

Base-catalyzed[96]



18

For each catalyst, the mechanism for one direction is the exact reverse of the other, by the principle of microscopic reversibility.[97] As expected from mechanisms in which the C–H bond is broken in the rate-determining step, substrates of the type RCD_2COR show deuterium isotope effects (of ~5) in both the basic-[98] and the acid[99]-catalyzed processes. The keto–enol/enolate anion equilibrium has been studied in terms of the influence of β-oxygen[100] or β-nitrogen[101] substituents.

Although the conversion of an aldehyde or a ketone to its enol tautomer is not generally a preparative procedure, the reactions do have their preparative aspects. If a full equivalent of base per equivalent of ketone is used, the enolate ion (**18**) is formed and can be isolated[102] (see, e.g., the alkylation reaction in **10-68**).[103] When enol ethers or esters are hydrolyzed, the enols initially formed immediately tautomerize to the aldehydes or ketones. In addition, the overall processes (forward plus reverse reactions) are often used for equilibration purposes. When an optically active compound in which the chirality is due to an stereogenic carbon α to a carbonyl group (as in **19**) is treated with acid or base, racemization results.[104]

[96]Another mechanism for base-catalyzed enolization has been reported when the base is a tertiary amine: See Bruice, P.Y. *J. Am. Chem. Soc.* ***1983***, *105*, 4982; ***1989***, *111*, 962; ***1990***, *112*, 7361.

[97]It has been proposed that the acid-catalyzed ketonization of simple enols is concerted; that is, both of the processes shown in the equation take place simultaneously. This would mean that in these cases the forward reaction is also concerted. For evidence in favor of this proposal, see Capon, B.; Siddhanta, A.K.; Zucco, C. *J. Org. Chem.* ***1985***, *50*, 3580. For evidence against it, see Chiang, Y.; Hojatti, M.; Keeffe, J.R.; Kresge, A.J.; Schepp, N.P.; Wirz, J. ***1987***, *109*, 4000 and references cited therein.

[98]Riley, T.; Long, F.A. *J. Am. Chem. Soc.* ***1962***, *84*, 522; Xie, L.; Saunders, Jr., W.H. *J. Am. Chem. Soc.* ***1991***, *113*, 3123.

[99]Swain, C.G.; Stivers, E.C.; Reuwer Jr., J.F.; Schaad, L.J. *J. Am. Chem. Soc.* ***1958***, *80*, 5885; Lienhard, G.E.; Wang, T. *J. Am. Chem. Soc.* ***1969***, *91*, 1146. See also Toullec, J.; Dubois, J.E. *J. Am. Chem. Soc.* ***1974***, *96*, 3524.

[100]Chiang, Y.; Kresge, A.J.; Meng, Q.; More, O'Farrall, R.A.; Zhu, Y. *J. Am. Chem. Soc.* ***2001***, *123*, 11562.

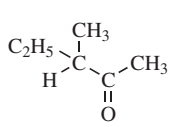
[101]Chiang, Y.; Griesbeck, A. G.; Heckroth, H.; Hellrung, B.; Kresge, A. J.; Meng, Q.; O'Donoghue, A. C.; Richard, J. P.; Wirz, J. *J. Am. Chem. Soc.* ***2001***, *123*, 8979.

[102]For nmr studies of the Li enolate of acetaldehyde in solution, see Wen, J.Q.; Grutzner, J.B. *J. Org. Chem.* ***1986***, *51*, 4220.

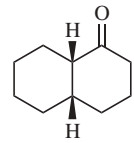
[103]For a review of the preparation and uses of enolates, see d'Angelo, J. *Tetrahedron* ***1976***, *32*, 2979. For a discussion of solid state enolate chemistry, see Fruchart, J.-S.; Lippens, G.; Kuhn, C.; Gran-Masse, H.; Melnyk, O. *J. Org. Chem.* ***2002***, *67*, 526.

[104]For an exception, see Guthrie, R.D.; Nicolas, E.C. *J. Am. Chem. Soc.* ***1981***, *103*, 4637.

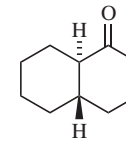
If there is another



19

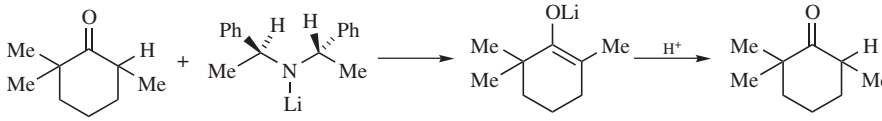


cis-Decalone



trans-Decalone

stereogenic center in the molecule, the less stable epimer can be converted to the more stable one in this manner, and this is often done. For example, *cis*-decalone can be equilibrated to the trans isomer. Isotopic exchange can also be accomplished at the a position of an aldehyde or ketone in a similar manner. The role of additives, such as $ZnCl_2$ on the stereogenic enolization reactions using chiral cases has been discussed.[105] Enantioselective enolate anion protonation reactions have been studied.[106] For the acid-catalyzed process, exchange or equilibration is accomplished only if the carbonyl compound is completely converted to the enol and then back, but in the base-catalyzed process exchange or equilibration can take place if only the first step (conversion to the enolate ion) takes place. The difference is usually academic. In cyclic compounds, cis- to trans-isomerization can occur via the enol.[107]



20 **21** **22** **20**

Racemic Optically active

In the case of the ketone **20**, a racemic mixture was converted to an optically active mixture (optical yield 46%) by treatment with the chiral base **21**.[108] This happened because **21** reacted with one enantiomer of **20** faster than with the other (an example of kinetic resolution). The enolate **22** must remain coordinated with the chiral amine, and it is the amine that reprotonate **22**, not an added proton donor.

Enolizable hydrogens can be replaced by deuterium (and ^{16}O by ^{18}O) by passage of a sample through a deuterated (or ^{18}O-containing) gas-chromatography column.[109]

[105]Coggins, P.; Gaur, S.; Simpkins, N.S. *Tetrahedron Lett*. ***1995***, *36*, 1545.
[106]Vedejs, E.; Kruger, A.W.; Suna, E. *J. Org. Chem*. ***1999***, *64*, 7863.
[107]Dechoux, L.; Doris, E. *Tetrahedron Lett*. ***1994***, *35*, 2017.
[108]Eleveld, M.B.; Hogeveen, H. *Tetrahedron Lett*. ***1986***, *27*, 631. See also, Shirai, R.; Tanaka, M.; Koga, K. *J. Am. Chem. Soc*. ***1986***, *108*, 543; Cain, C.M.; Cousins, R.P.C.; Coumbarides, G.; Simpkins, N.S. *Tetrahedron* ***1990***, *46*, 523.
[109]Senn, M.; Richter, W.J.; Burlingame, A.L. *J. Am. Chem. Soc*. ***1965***, *87*, 680; Richter, W.J.; Senn, M.; Burlingame, A.L. *Tetrahedron Lett*. ***1965***, 1235.

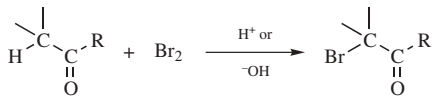
There are many enol-keto interconversions and acidification reactions of enolate ions to the keto forms listed in *Organic Syntheses*. No attempt is made to list them here.

B. Halogen Electrophiles

Halogenation of unactivated hydrocarbons is discussed in **14-1**.

12-4 Halogenation of Aldehydes and Ketones

Halogenation or **Halo-de-hydrogenation**



Aldehydes and ketones can be halogenated in the a position with bromine, chlorine, or iodine.[110] The reaction is not successful with fluorine.[111] Sulfuryl chloride,[112] $NaClO_2/Mn(acac)_3$,[113] $Me_3SiCl–Me_2SO$,[114] $Me_3SiCl–MnO_2$,[115] and cupric chloride[116] have been used as reagents for chlorination, and *N*-bromosuccinimide (see **14-3**),[117] *t*-BuBr–DMSO,[118] Me_3SiBr–DMSO,[119] tetrabutylammonium tribromide,[120] and bromine • dioxane on silica with microwave irradiation[121] for bromination. Bromination of methyl ketones was done using PhI(OH)OTs with microwave irradiation, followed by treatment with $MgBr_2$ and microwave irradiation.[122] α-Chloro aldehydes are formed with Cl_2 and a catalytic amount of tetraethylammonium chloride.[123] Chlorination of aldehydes with good enantioselectivity was

[110]For a review, see House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 459–478. For lists of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp.709–719. For a monograph, see De Kimpe, N.; Verhé, R. *The Chemistry of a Haloketones, α-Haloaldehydes, and α-Haloimines,* Wiley, NY, 1988.

[111]For a review of the preparation of α-fluoro carbonyl compounds, see Rozen, S.; Filler, R. *Tetrahedron* ***1985***, *41*, 1111. For a monograph, see German, L.; Zemskov, S. *New Fluorinating Agents in Organic Chemistry*, Springer, NY, ***1989***.

[112]For a review of sulfuryl chloride, see Tabushi, I.; Kitaguchi, H. in Pizey, J.S. *Synthetic Reagents*, Vol. 4; Wiley, NY, ***1981***, pp. 336–396.

[113]Yakabe, S.; Hirano, M.; Morimoto, T. *Synth. Commun*. ***1998***, *28*, 131.

[114]Bellesia, F.; Ghelfi, F.; Grandi, R.; Pagnoni, U.M. *J. Chem. Res. (S)* ***1986***, 426; Fraser, R.R.; Kong, F. *Synth. Commun*. ***1988***, *18*, 1071.

[115]Bellesia, F.; Ghelfi, F.; Pagnoni, U.M.; Pinetti, A. *J. Chem. Res. (S)* ***1990***, 188.

[116]For a review, see Nigh, W.G., in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. B, Academic Press, NY, ***1973***, pp. 67–81. Cupric chloride has been used to chlorinate α,β-unsaturated aldehydes and ketones in the γ position: Dietl, H.K.; Normark, J.R.; Payne, D.A.; Thweatt, J.G.; Young, D.A. *Tetrahedron Lett*. ***1973***, 1719.

[117]For an example, see Tanemura, K.; Suzuki, T.; Nishida, Y.; Satsumabayashi, K.; Horaguchi, T. *Chem. Commun*. ***2004***, 470.

[118]Armani, E.; Dossena, A.; Marchelli, R.; Casnati, G. *Tetrahedron* ***1984***, *40*, 2035.

[119]Bellesia, F.; Ghelfi, F.; Grandi, R.; Pagnoni, U.M. *J. Chem. Res. (S)* ***1986***, 428.

[120]Kajigaeshi, S.; Kakinami, T.; Okamoto, T.; Fujisaki, S. *Bull. Chem. Soc. Jpn*. ***1987***, *60*, 1159.

[121]Paul, S.; Gupta, V.; Gupta, R.; Loupy, A. *Tetrahedron Lett*. ***2003***, *44*, 439.

[122]Lee, J.C.; Park, J.Y.; Yoon, S.Y.; Bae, Y.H.; Lee, S.J. *Tetrahedron Lett*. ***2004***, *45*, 191.

[123]Bellesia, F.; DeBuyck, L.; Ghelfi, F.; Pagnoni, U.M.; Parson, A.F.; Pinetti, A. *Synthesis* ***2003***, 2173.

reported using a chlorinated quinone and L-proline, with the reaction proceeding via the chiral enamine.[124] Iodination has been accomplished with I_2–$HgCl_2$,[125] with I_2-cerium(IV) ammonium nitrate,[126] and with iodine using 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate), known as Selectfluor F–TEDA–BF_4, in methanol.[127] Treatment of a ketone with (hydroxy-*p*-nitrobenzenesulfonyloxy)benzene followed by SmI_2 give the α-iodo ketone.[128] Methyl ketones react with *N*-iodosuccinimide (NIS) and tosic acid with microwave irradiation without solvent to give the α-iodo ketone.[129] Several methods have been reported for the preparation of α-fluoro aldehydes and ketones.[130] Another Selectfluor, 1-Fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) has been used for the monofluorination of ketones,[131] as has a mixture of KI–KIO_3–H_2SO_4.[132] Active compounds, such as β-keto esters and β-diketones, have been fluorinated with an *N*-fluoro-*N*-alkylsulfonamide[133] (this can result in enantioselective fluorination, if an optically active *N*-fluorosulfonamide is used[134]), with F_2/N_2–HCOOH,[135] with NF_3O/Bu_4NOH,[136] and with acetyl hypofluorite.[137] The last reagent also fluorinates simple ketones in the form of their lithium enolates.[138]

For unsymmetrical ketones, the preferred position of halogenation is usually the more substituted: a CH group, then a CH_2 group, and then CH_3;[139] however, mixtures are frequent. With aldehydes the aldehydic hydrogen is sometimes replaced (see **14-4**). It is also possible to prepare di- and polyhalides. When basic catalysts are used, one a position of a ketone is completely halogenated before the other is

[124]Brochu, M.P.; Brown, S.P.; MacMillan, D.W.C. *J. Am. Chem. Soc*. ***2004***, *126*, 4108. For this chlorination using a chiral pyrrolidine derivative with NCS, see Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jorgensen, K.A. *J. Am. Chem. Soc*. ***2004***, *126*, 4790. See Wack, H.; Taggi, A.E.; Hafez, A.M.; Drury III, W. J.; Lectka, T. *J. Am. Chem. Soc*. ***2001***, *123*, 1531; Hafez, A.M.; Taggi, A.E.; Wack, H.; Esterbrook III, J.; Lectka, T. *Org. Lett*. ***2001***, *3*, 2049.

[125]Barluenga, J.; Martinez-Gallo, J.M.; Najera, C.; Yus, M. *Synthesis* ***1986***, 678.

[126]Horiuchi, C.A.; Kiji, S. *Bull. Chem. Soc. Jpn*. ***1997***, *70*, 421. For another reagent, see Sket, B.; Zupet, P.; Zupan, M.; Dolenc, D. *Bull. Chem. Soc. Jpn*. ***1989***, *62*, 3406.

[127]Jereb, M.; Stavber, S.; Zupan, M. *Tetrahedron* ***2003***, *59*, 5935.

[128]Lee, J.C.; Jin, Y.S. *Synth. Commun*. ***1999***, *29*, 2769.

[129]Lee, J.C.; Bae, Y.H. *Synlett* ***2003***, 507.

[130]Davis, F.A.; Kasu, P.V.N. *Org. Prep. Proceed. Int*. ***1999***, *31*, 125.

[131]Stavber, S.; Zupan, M. *Tetrahedron Lett*. ***1996***, *37*, 3591.

[132]Okamoto, T.; Kakinami, T.; Nishimura, T.; Hermawan, I.; Kajigaeshi, S. *Bull. Chem. Soc. Jpn*. ***1992***, *65*, 1731.

[133]Barnette, W.E. *J. Am. Chem. Soc*. ***1984***, *106*, 452; Ma, J.-A. For an example using a chiral copper catalyst for asymmetric induction, see Cahard, D. *Tetrahedron Asymm* ***2004***, *15*, 1007.

[134]Differding, E.; Lang, R.W. *Tetrahedron* ***1988***, *29*, 6087.

[135]Chambers, R.D.; Greenhall, M.P.; Hutchinson, J. *J. Chem. Soc. Chem. Commun*. ***1995***, 21.

[136]Gupta, O.D.; Shreeve, J.M. *Tetrahedron Lett*. ***2003***, *44*, 2799.

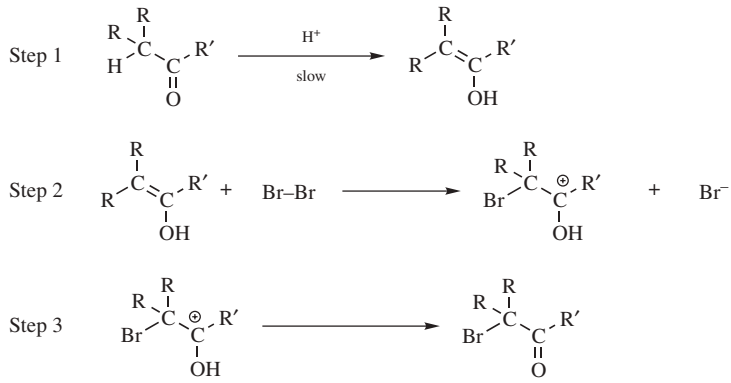
[137]Lerman, O.; Rozen, S. *J. Org. Chem*. ***1983***, *48*, 724. See also Purrington, S.T.; Jones, W.A. *J. Org. Chem*. ***1983***, *48*, 761.

[138]Rozen, S.; Brand, M. *Synthesis* ***1985***, 665. For another reagent, see Davis, F.A.; Han, W. *Tetrahedron Lett*. ***1991***, *32*, 1631.

[139]For chlorination this is reversed if the solvent is methanol: Gallucci, R.R.; Going, R. *J. Org. Chem*. ***1981***, *46*, 2532.

attacked, and the reaction cannot be stopped until all the hydrogens of the first carbon have been replaced (see below). If one of the groups is methyl, the haloform reaction (**12-44**) takes place. With acid catalysts, it is easy to stop the reaction after only one halogen has entered, although a second halogen can be introduced by the use of excess reagent. In chlorination the second halogen generally appears on the same side as the first,[140] while in bromination the α,α'-dibromo product is found.[141] Actually, with both halogens it is the α,α-dihalo ketone that is formed first, but in the case of bromination this compound isomerizes under the reaction conditions to the α,α' isomer.[140] α,α'-Dichloro ketones are formed by reaction of a methyl ketone with an excess of $CuCl_2$ and LiCl in DMF[142] or with HCl and H_2O_2 in methanol.[143] Aryl methyl ketones can be dibrominated ($ArCOCH_3 \rightarrow ArCOCHBr_2$) in high yields with benzyltrimethylammonium tribromide.[144] Active methylene compounds are chlorinated with NCS and $Mg(ClO_4)_2$.[145] Similar chlorination in the presence of a chiral copper catalyst led to α-chlorination with modest enantioselectivity.[146]

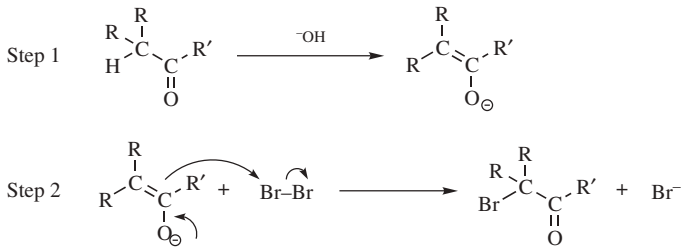
It is not the aldehyde or ketone itself that is halogenated, but the corresponding enol or enolate ion. The purpose of the catalyst is to provide a small amount of enol or enolate. The reaction is often done without addition of acid or base, but traces of acid or base are always present, and these are enough to catalyze formation of the enol or enolate. With acid catalysis the mechanism is



[140]Rappe, C. *Ark. Kemi* ***1965***, *24*, 321. But see also Teo, K.E.; Warnhoff, E.W. *J. Am. Chem. Soc*. ***1973***, *95*, 2728.
[141]Rappe, C.; Schotte, L. *Acta Chem. Scand.* ***1962***, *16*, 2060; Rappe, C. *Ark. Kemi* ***1964***, *21*, 503; Garbisch, Jr., E.W. *J. Org. Chem.* ***1965***, *30*, 2109.
[142]Nobrega, J.A.; Gonalves, S.M.C.; Reppe, C. *Synth. Commun*. ***2002***, *32*, 3711.
[143]Terent'ev, A.O.; Khodykin, S.V.; Troitskii, N.A.; Ogibin, Y.N.; Nikishin, G.I. *Synthesis* ***2004***, 2845.
[144]Kajigaeshi, S.; Kakinami, T.; Tokiyama, H.; Hirakawa, T.; Okamoto, T. *Bull. Chem. Soc. Jpn*. ***1987***, *60*, 2667.
[145]Yang, D.; Yan, Y.-L.; Lui, B. *J. Org. Chem*. ***2002***, *67*, 7429.
[146]Marigo, M.; Kumaragurubaran, N.; Jørgensen, K.A. *Chem. Eur. J*. ***2004***, *10*, 2133.

The first step, as we have already seen (**12-3**), actually consists of two steps. The second step is very similar to the first step in electrophilic addition to double bonds (p. 999). There is a great deal of evidence for this mechanism: (*1*) the rate is first order in substrate; (*2*) bromine does not appear in the rate expression at all,[147] a fact consistent with a rate-determining first step;[148] (*3*) the reaction rate is the same for bromination, chlorination, and iodination under the same conditions;[149] (*4*) the reaction shows an isotope effect; and (*5*) the rate of the step 2–step 3 sequence has been independently measured (by starting with the enol) and found to be very fast.[150]

With basic catalysts the mechanism may be the same as that given above (since bases also catalyze formation of the enol), or the reaction may go directly through the enolate ion without formation of the enol:



It is difficult to distinguish the two possibilities. It was mentioned above that in the base-catalyzed reaction, if the substrate has two or three a halogens on the same side of the C=O group, it is not possible to stop the reaction after just one halogen atom has entered. The reason is that the electron-withdrawing field effect of the first halogen increases the acidity of the remaining hydrogens, that is, a CHX group is more acidic than a CH_2 group, so that initially formed halo ketone is converted to enolate ion (and hence halogenated) more rapidly than the original substrate. Other halogenating agents can be used in this reaction. Reaction of a lithium enolate anion with tosyl chloride gave the corresponding α-chloro ketone.[151] When an aldehyde was treated with a catalytic amount of 2,5-lutidine to generate the enolate anion, reaction with 35% HCl in dichloromethane gave the α,α-dichloroaldehyde.[152]

[147]When the halogenating species is at low concentration or has a low reactivity, it can appear in the rate expression. The reaction becomes first order in the halogenating species. See, for example, Tapuhi, E.; Jencks, W.P. *J. Am. Chem. Soc.* ***1982***, *104*, 5758. For a case in which the reaction is first order in bromine, even at relatively high Br_2 contentration, see Pinkus, A.G.; Gopalan, R. *J. Am. Chem. Soc.* ***1984***, *106*, 2630. For a study of the kinetics of iodination, see Pinkus, A.G.; Gopalan, R. *Tetrahedron* ***1986***, *42*, 3411.

[148]Under some conditions it is possible for step 2 to be rate-determining: Deno, N.C.; Fishbein, R. *J. Am. Chem. Soc.* ***1973***, *95*, 7445.

[149]Bell, R.P.; Yates, K. *J. Chem. Soc.* ***1962***, 1927.

[150]Hochstrasser, R.; Kresge, A.J.; Schepp, N.P.; Wirz, J. *J. Am. Chem. Soc.* ***1988***, *110*, 7875.

[151]Brummond, K.M.; Gesenberg, K.D. *Tetrahedron Lett.* ***1999***, *40*, 2231.

[152]Bellesia, F.; DeBuyck, L.; Ghelfi, F.; Libertini, E.; Pagnoni, U.M.; Roncaglia, F. *Tetrahedron* ***2000***, *56*, 7507.

Regioselectivity in the halogenation of unsymmetrical ketones can be attained by treatment of the appropriate enol borinate of the ketone with *N*-bromo- or *N*-chlorosuccinimide.[153] The desired halo

ketone is formed in high yield. Another method for achieving the same result involves bromination of the appropriate lithium enolate at a low temperature[154] (see p. 630 for the regioselective formation of enolate ions). In a similar process, α-halo aldehydes have been prepared in good yield by treatment of silyl enol ethers $R_2C{=}CHOSiMe_3$ with Br_2 or Cl_2,[155] with sulfuryl chloride SO_2Cl_2;[156] or with I_2 and silver acetate.[157] Other chlorinating agents can be used with a variety of silyl enol ethers to generate α-chloroketones with good enantioselectivity, including $ZrCl_4$ in conjunction with an α,α-dichloromalonate ester.[158] Silyl enol ethers can also be fluorinated, with XeF_2[159] or with 5% F_2 in N_2 at –78°C in $FCCl_3$.[160] Enol acetates have been regioselectively iodinated with I_2 and either thallium(I) acetate[161] or copper(II) acetate.[162]

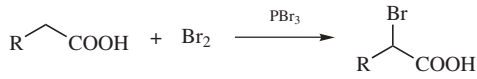
α,β-Unsaturated ketones can be converted to α-halo-α,β-unsaturated ketones by treatment with phenylselenium bromide or chloride,[163] and to α-halo-β,γ-unsaturated ketones by two-phase treatment with HOCl.[164] Conjugated ketones were converted to the α-bromo conjugated ketone (a vinyl bromide) using the Dess–Martin periodinane (see p. 1723) and tetraethylammonium bromide.[165]

OS **I**, 127; **II**, 87, 88, 244, 480; **III**, 188, 343, 538; **IV**, 110, 162, 590; **V**, 514; **VI**, 175, 193, 368, 401, 512, 520, 711, 991; **VII**, 271; **VIII**, 286. See also, OS **VI**, 1033; **VIII**, 192.

[153]Hooz, J.; Bridson, J.N. *Can. J. Chem.* ***1972***, *50*, 2387.
[154]Stotter, P.L.; Hill, K.A. *J. Org. Chem.* ***1973***, *38*, 2576.
[155]Reuss, R.H.; Hassner, A. *J. Org. Chem.* ***1974***, *39*, 1785; Blanco, L.; Amice, P.; Conia, J.M. *Synthesis* ***1976***, 194.
[156]Olah, G.A.; Ohannesian, L.; Arvanaghi, M.; Prakash, G.K.S. *J. Org. Chem.* ***1984***, *49*, 2032.
[157]Rubottom, G.M.; Mott, R.C. *J. Org. Chem.* ***1979***, *44*, 1731.
[158]Zhang, Y.; Shibatomi, K.; Yamamoto, H. *J. Am. Chem. Soc.* ***2004***, *126*, 15038.
[159]Tsushima, T.; Kawada, K.; Tsuji, T. *Tetrahedron Lett.* ***1982***, *23*, 1165.
[160]Purrington, S.T.; Bumgardner, C.L.; Lazaridis, N.V.; Singh, P. *J. Org. Chem.* ***1987***, *52*, 4307.
[161]Cambie, R.C.; Hayward, R.C.; Jurlina, J.L.; Rutledge, P.S.; Woodgate, P.D. *J. Chem. Soc. Perkin Trans. 1* ***1978***, 126.
[162]Horiuchi, C.A.; Satoh, J.Y. *Synthesis* ***1981***, 312.
[163]Ley, S.V.; Whittle, A.J. *Tetrahedron Lett.* ***1981***, *22*, 3301.
[164]Hegde, S.G.; Wolinsky, J. *Tetrahedron Lett.* ***1981***, *22*, 5019.
[165]Fache, F.; Piva, O. *Synlett* ***2002***, 2035.

12-5 Halogenation of Carboxylic Acids and Acyl Halides

Halogenation or Halo-de-hydrogenation



Using a phosphorus halide as catalyst, the α hydrogens of carboxylic acids can be replaced by bromine or chlorine.[166] The reaction, known as the *Hell–Volhard–Zelinskii reaction*, is not applicable to iodine or fluorine. When there are two α hydrogens, one or both may be replaced, although it is often hard to stop with just one. The reaction actually takes place on the acyl halide formed from the carboxylic acid and the catalyst. The acids alone are inactive, except for those with relatively high enol content, such as malonic acid. Less than one full mole of catalyst (per mole of substrate) is required, because of the exchange reaction between carboxylic acids and acyl halides (see **16-79**). Each molecule of acid is α halogenated while it is in the acyl halide stage. The halogen from the catalyst does not enter the α position. For example, the use of Cl_2 and PBr_3 results in α chlorination, not bromination. As expected from the foregoing, acyl halides undergo a halogenation without a catalyst. An enantioselective α-halogenation was reported yielding via an alkaloid catalyzed reaction of acyl halides with perhaloquinone-derived reagents to give to chiral α-haloesters.[167] So do anhydrides and many compounds that enolize easily (e.g., malonic ester and aliphatic nitro compounds). The mechanism is usually regarded as proceeding through the enol as in **12-4**.[168] If chlorosulfuric acid $ClSO_2OH$ is used as a catalyst, carboxylic acids can be α-iodinated,[169] as well as chlorinated or brominated.[170] *N*-Bromosuccinimide in a mixture of sulfuric acid–trifluoroacetic acid can mono-brominate simple carboxylic acids.[171]

A number of other methods exist for the a halogenation of carboxylic acids or their derivatives.[172] Under electrolytic conditions with NaCl, malonates are converted to 2-chloro malonates.[173] Acyl halides can be a brominated or chlorinated by use of *N*-bromo- or *N*-chlorosuccinimide and HBr or HCl.[174] The latter is an ionic, not a free-radical halogenation (see **14-3**). Direct iodination of carboxylic acids has been achieved with I_2–Cu(II) acetate in HOAc.[175] Acyl chlorides can

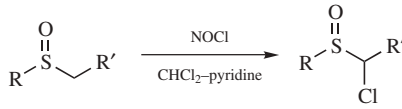
[166]For a review, see Harwood, H.J. *Chem. Rev.* ***1962***, *62*, 99, pp. 102-103.
[167]Wack, H.; Taggi, A.E.; Hafez, A.M.; Drury III, W.J.; Lectka, T. *J. Am. Chem. Soc.* ***2001***, *123*, 1531. See also, France, S.; Wack, H.; Taggi, A.E.; Hafez, A.M.; Wagerle, Ty.R.; Shah, M.H.; Dusich, C.L.; Lectka, T. *J. Am. Chem. Soc.* ***2004***, *126*, 4245.
[168]See, however, Kwart, H.; Scalzi, F.V. *J. Am. Chem. Soc.* ***1964***, *86*, 5496.
[169]Ogata, Y.; Watanabe, S. *J. Org. Chem.* ***1979***, *44*, 2768; ***1980***, *45*, 2831.
[170]Ogata, Y.; Adachi, K. *J. Org. Chem.* ***1982***, *47*, 1182.
[171]Zhang, L.H.; Duan, J.; Xu, Y.; Dolbier, Jr., W.R. *Tetrahedron Lett.* ***1998***, *39*, 9621.
[172]For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 730–738.
[173]Okimoto, M.; Takahashi, Y. *Synthesis* ***2002***, 2215.
[174]Harpp, D.N.; Bao, L.Q.; Black, C.J.; Gleason, J.G.; Smith, R.A. *J. Org. Chem.* ***1975***, *40*, 3420.
[175]Horiuchi, C.A.; Satoh, J.Y. *Chem. Lett.* ***1984***, 1509.

be a iodinated with I_2 and a trace of HI.[176] Carboxylic esters can be a halogenated by conversion to their enolate ions with lithium *N*-isopropylcyclohexylamide in THF and treatment of this solution at -78° with I_2[176] or with a carbon tetrahalide.[177] Carboxylic acids, esters, and amides have been α-fluorinated at $-78°C$ with F_2 diluted in N_2.[178] Amides have been α-iodinated using iodine and s-collidine.[179]

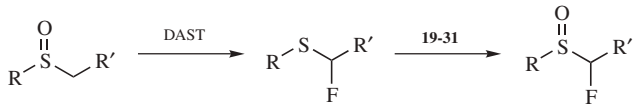
OS **I**, 115, 245; **II**, 74, 93; **III**, 347, 381, 495, 523, 623, 705, 848; **IV**, 254, 348, 398, 608, 616; **V**, 255; **VI**, 90, 190, 403; **IX**, 526. Also see, OS **IV**, 877; **VI**, 427.

12-6 Halogenation of Sulfoxides and Sulfones

Halogenation or **Halo-de-hydrogenation**



Sulfoxides can be chlorinated in the α position[180] by treatment with Cl_2[181] or *N*-chlorosuccinimide,[182] in the presence of pyridine. These methods involve basic conditions. The reaction can also be accomplished in the absence of base with SO_2Cl_2 in CH_2Cl_2,[183] or with $TsNCl_2$.[184] The bromination of sulfoxides with bromine[185] and with NBS-bromine[186] have also been reported. Sulfones have been chlorinated by treatment of their conjugate bases $RSO_2C^{\ominus}HR'$ with various reagents, among them SO_2Cl_2, CCl_4,[187] *N*-chlorosuccinimide,[188] and hexachloroethane.[189] The α fluorination of sulfoxides has been accomplished in a two-step procedure. Treatment with diethylaminosulfur trifluoride Et_2NSF_3 (DAST) produces an



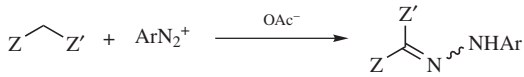
[176]Rathke, M.W.; Lindert, A. *Tetrahedron Lett*. ***1971***, 3995.
[177]Arnold, R.T.; Kulenovic, S.T. *J. Org. Chem*. ***1978***, *43*, 3687.
[178]Purrington, S.T.; Woodard, D.L. *J. Org. Chem*. ***1990***, *55*, 3423.
[179]Kitagawa, O.; Hanano, T.; Hirata, T.; Inoue, T.; Taguchi, T. *Tetrahedron Lett*. ***1992***, *33*, 1299.
[180]For a review, see Venier, C.G.; Barager III, H.J. *Org. Prep. Proced. Int*. ***1974***, *6*, 77, pp. 81–84.
[181]Tsuchihashi, G.; Iriuchijima, S. *Bull. Chem. Soc. Jpn*. ***1970***, *43*, 2271.
[182]Ogura, K.; Imaizumi, J.; Iida, H.; Tsuchihashi, G. *Chem. Lett*. ***1980***, 1587.
[183]Tin, K.; Durst, T. *Tetrahedron Lett*. ***1970***, 4643.
[184]Kim, Y.H.; Lim, S.C.; Kim, H.R.; Yoon, D.C. *Chem. Lett*. ***1990***, 79.
[185]Cinquini, M.; Colonna, S. *J. Chem. Soc. Perkin Trans. 1* 1972, 1883. See also, Cinquini, M.; Colonna, S. *Synthesis* **1972**, 259.
[186]Iriuchijima, S.; Tsuchihashi, G. *Synthesis* ***1970***, 588.
[187]Regis, R.R.; Doweyko, A.M. *Tetrahedron Lett*. ***1982***, *23*, 2539.
[188]Paquette, L.A.; Houser, R.W. *J. Org. Chem*. ***1971***, *36*, 1015.
[189]Kattenberg, J.; de Waard, E.R.; Huisman, H.O. *Tetrahedron* ***1973***, *29*, 4149; ***1974***, *30*, 463.

α-fluoro thioether, usually in high yield. Oxidation of this compound with *m*-chloroperoxybenzoic acid gives the sulfoxide.[190]

C. Nitrogen Electrophiles

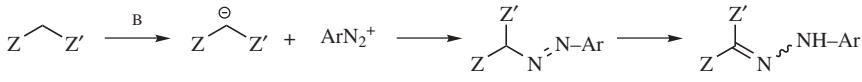
12-7 Aliphatic Diazonium Coupling

Arylhydrazono-de-dihydro-bisubstitution



If a C–H bond is acidic enough, it couples with diazonium salts in the presence of a base, most often aqueous sodium acetate.[191] The reaction is commonly carried out on compounds of the form Z–CH_2–Z′, where Z and Z′ are as defined on p. 1358, for example, β-keto esters, β-keto amides, malonic ester.

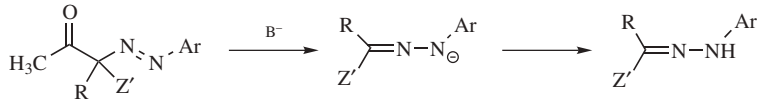
The mechanism is probably of the simple S_E1 type:



23

Aliphatic azo compounds in which the carbon containing the azo group is attached to a hydrogen are unstable and tautomerize to the isomeric hydrazones (**23**), which are therefore the products of the reaction.

When the reaction is carried out on a compound of the form Z–CHR–Z′, so that the azo compound does not have a hydrogen that can undergo tautomerism, if at least one Z is acyl or carboxyl, this group usually cleaves:

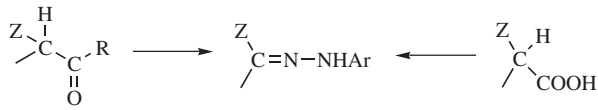


24

so the product in this case is also the hydrazone, and not the azo compound. In fact, compounds of the type **24** are seldom isolable from the reaction, although this has been accomplished.[192] The cleavage step shown is an example of **12-43** and, when a carboxyl group cleaves, of **12-40**. The overall process in this case is called the *Japp–Klingemann reaction*[193] and involves conversion of a ketone (**25**) or a

[190]McCarthy, J.R.; Pee, N.P.; LeTourneau, M.E.; Inbasekaran, M. *J. Am. Chem. Soc.* ***1985***, *107*, 735. See also, Umemoto, T.; Tomizawa, G. *Bull. Chem. Soc. Jpn.* ***1986***, *59*, 3625.
[191]For a review, see Parmerter, S.M. *Org. React.* ***1959***, *10*, 1.
[192]See, for example, Yao, H.C.; Resnick, P. *J. Am. Chem. Soc.* ***1962***, *84*, 3514.
[193]For a review, see Phillips, R.R. *Org. React.* ***1959***, *10*, 143.

carboxylic acid (**26**)



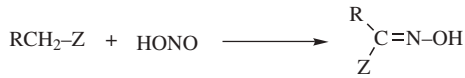
25 **26** **27**

to a hydrazone (**27**). When an acyl and a carboxyl group are both present, the leaving group order has been reported to be MeCO > COOH > PhCO.[194] When there is no acyl or carboxyl group present, the aliphatic azo compound is stable.

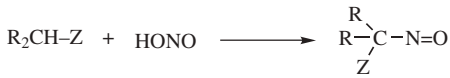
OS **III**, 660; **IV**, 633.

12-8 Nitrosation at a Carbon Bearing an Active Hydrogen

Hydroxyimino-de-dihydro-bisubstitution



Nitrosation or Nitroso-de-hydrogenation



Carbons adjacent to a Z group (as defined on p. 622) can be nitrosated with nitrous acid or alkyl nitrites.[195] The initial product is the *C*-nitroso compound, but these are stable only when there is no hydrogen that can undergo tautomerism. When there is, the product is the more stable oxime. The situation is analogous to that with azo compounds and hydrazones (**12-7**). The mechanism is similar to that in **12-7**:[196] R–H → R^- + $^+$N=O → R–N=O. The attacking species is either NO^+ or a carrier of it. When the substrate is a simple ketone, the mechanism goes through the enol (as in halogenation **12-4**):

Evidence is that the reaction, in the presence of X^- (Br^-, Cl^-, or SCN^-), was first order in ketone and in H^+, but zero order in HNO_2 and X^-.[197] Furthermore, the rate of the nitrosation was about the same as that for enolization of the same ketones. The species NOX is formed by $HONO + X^- + H^+ \rightarrow HOX + H_2O$. In

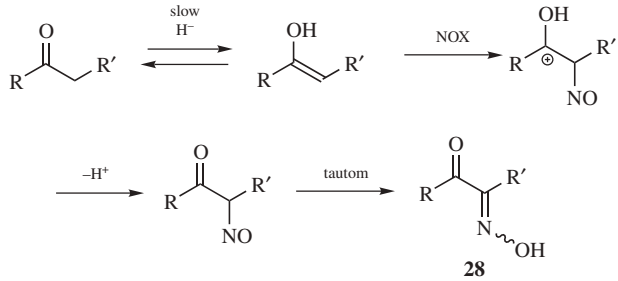
[194]Neplyuev, V.M.; Bazarova, I.M.; Lozinskii, M.O. *J. Org. Chem. USSR* ***1989***, *25*, 2011. This paper also includes a sequence of leaving group ability for other Z groups.

[195]For a review, see Williams, D.L.H. *Nitrosation*, Cambridge University Press, Cambridge, ***1988***, pp. 1–45.

[196]For a review, see Williams, D.L.H. *Adv. Phys. Org. Chem*. ***1983***, *19*, 381. See also Williams, D.L.H. *Nitrosation*, Cambridge Univ. Press, Cambridge, ***1988***.

[197]Leis, J.R.; Peña, M.E.; Williams, D.L.H.; Mawson, S.D. *J. Chem. Soc. Perkin Trans. 2* ***1988***, 157.

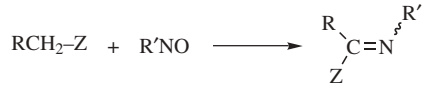
the cases of $F_3CCOCH_2COCF_3$ and malononitrile the nitrosation went entirely through the enolate ion rather than the enol.[198]



28

As in the Japp–Klingemann reaction, when Z is an acyl or carboxyl group (in the case of R_2CH–Z), it can be cleaved. Since oximes and nitroso compounds can be reduced to primary amines, this reaction often provides a route to amino acids. As in the case of **12-4**, the silyl enol ether of a ketone can be used instead of the ketone itself.[199] Good yields of α-oximinoketones (**28**) can be obtained by treating ketones with *tert*-butyl thionitrate.[200]

Imines can be prepared in a similar manner by treatment of an active hydrogen compound with a nitroso compound:

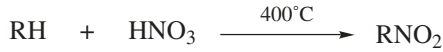


Alkanes can be nitrosated photochemically, by treatment with NOCl and UV light.[201] For nitration at an activated carbon, see **12-9**. Trialkyltin enol ethers ($C{=}C{-}O{-}SnR_3$) react with PhNO to give α-(*N*-hydroxylamino)ketones.[202]

OS **II**, 202, 204, 223, 363; **III**, 191, 513; **V**, 32, 373; **VI**, 199, 840. Also see, OS **V**, 650.

12-9 Nitration of Alkanes

Nitration or **Nitro-de-hydrogenation**



[198]Iglesias, E.; Williams, D.L.H. *J. Chem. Soc. Perkin Trans. 2* ***1989***, 343; Crookes, M.J.; Roy, P.; Williams, D.L.H. *J. Chem. Soc. Perkin Trans. 2* ***1989***, 1015. See also Graham, A.; Williams, D.L.H. *J. Chem. Soc. Chem. Commun*. ***1991***, 407.
[199]Rasmussen, J.K.; Hassner, A. *J. Org. Chem*. ***1974***, *39*, 2558.
[200]Kim, Y.H.; Park, Y.J.; Kim, K. *Tetrahedron Lett*. ***1989***, *30*, 2833.
[201]For a review, see Pape, M. *Fortschr. Chem. Forsch*. ***1967***, *7*, 559.
[202]Momiyama, N.; Yamamoto, H. *Org. Lett*. ***2002***, *4*, 3579.

Nitration of alkanes[203] can be carried out in the gas phase at ~400°C or in the liquid phase. The reaction is not practical for the production of pure products for any alkane except methane. For other alkanes, not only does the reaction produce mixtures of the mono-, di-, and polynitrated alkanes at every combination of positions, but extensive chain cleavage occurs.[204] A free-radical mechanism is involved.[205]

Activated positions (e.g., ZCH_2Z' compounds) can be nitrated by fuming nitric acid in acetic acid, by acetyl nitrate and an acid catalyst,[206] or by alkyl nitrates under alkaline conditions.[207] In the latter case, it is the carbanionic form of the substrate that is actually nitrated. What is isolated under these alkaline conditions is the conjugate base of the nitro compound. Yields are not high. Of course, the mechanism in this case is not of the free-radical type, but is electrophilic substitution with respect to the carbon (similar to the mechanisms of **12-7** and **12-8**). Positions activated by only one electron-withdrawing group, for example, a positions of simple ketones, nitriles, sulfones, or *N*,*N*-dialkyl amides, can be nitrated with alkyl nitrates if a very strong base, for example, *t*-BuOK or $NaNH_2$, is present to convert the substrate to the carbanionic form.[208]

Electrophilic nitration of alkanes has been performed with nitronium salts, for example, $NO_2^+ PF_6^-$ and with HNO_3–H_2SO_4 mixtures, but mixtures of nitration and cleavage products are obtained and yields are generally low.[209] The reaction of alkanes with nitric acid and *N*-hydroxysuccinimide (NHS), however, gave moderate-to-good yields of the corresponding nitroalkane.[210] Similar nitration was accomplished with NO_2, NHS and air.[211]

Aliphatic nitro compounds can be a nitrated [$R_2C^{\ominus}NO_2 \rightarrow R_2C(NO_2)_2$] by treatment of their conjugate bases $RCNO_2$ with $NO_2^-$and $K_3Fe(CN)_6$.[212]

[203]For reviews, see Olah, G.A.; Malhotra, R.; Narang, S.C. *Nitration*, VCH, NY, ***1989***, pp. 219–295; Ogata, Y. in Trahanovsky, W.S. *Oxidation in Organic Chemisry*, part C, Academic Press, NY, ***1978***, pp. 295–342; Ballod, A.P.; Shtern, V.Ya. *Russ. Chem. Rev.* ***1976***, *45*, 721.

[204]For a discussion of the mechanism of this cleavage, see Matasa, C.; Hass, H.B. *Can. J. Chem.* ***1971***, *49*, 1284.

[205]Titov, A.I. *Tetrahedron* ***1963***, *19*, 557.

[206]Sifniades, S. *J. Org. Chem.* ***1975***, *40*, 3562.

[207]For a review, see Larson, H.O., in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, Vol. 1, Wiley, NY, ***1969***, pp. 310–316.

[208]For examples, see Truce, W.E.; Christensen, L.W. *Tetrahedron* ***1969***, *25*, 181; Pfeffer, P.E.; Silbert, L.S. *Tetrahedron Lett*. ***1970***, 699; Feuer, H.; Spinicelli, L.F. *J. Org. Chem*. ***1976***, *41*, 2981; Feuer, H.; Van Buren II, W.D.; Grutzner, J.B. *J. Org. Chem*. ***1978***, *43*, 4676.

[209]Olah, G.A.; Lin, H.C. *J. Am. Chem. Soc*. ***1973***, *93*, 1259. See also, Bach, R.D.; Holubka, J.W.; Badger, R.C.; Rajan, S. *J. Am. Chem. Soc*. ***1979***, *101*, 4416.

[210]Isozaki, S.; Nishiwaki, Y.; Sakaguchi, S.; Ishii, Y. *Chem. Commun*. ***2001***, 1352.

[211]Sakaguchi, S.; Nishiwaki, Y.; Kitamura, T.; Ishii, Y. *Angew. Chem. Int. Ed*. ***2001***, *40*, 222; Nishiwaki, Y.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem*. ***2002***, *67*, 5663.

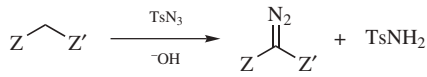
[212]Matacz, Z.; Piotrowska, H.; Urbanski, T. *Pol. J. Chem*. ***1979***, *53*, 187; Kornblum, N.; Singh, H.K.; Kelly, W.J. *J. Org. Chem*. ***1983***, *48*, 332; Garver, L.C.; Grakauskas, V.; Baum, K. *J. Org. Chem*. ***1985***, *50*, 1699.

A novel reaction converted a vinyl methyl moiety to a vinyl nitro. The reaction of MeCH=C(Ph)CN with NO_x and iodine gave $O_2NCH=C(Ph)CN$.[213]

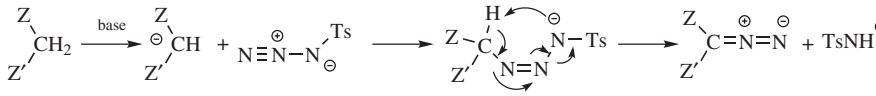
OS **I**, 390; **II**, 440, 512.

12-10 Direct Formation of Diazo Compounds

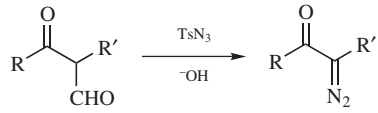
Diazo-de-dihydro-bisubstitution



Compounds containing a CH_2 bonded to two Z groups (active methylene compounds, with Z as defined on p. 622) can be converted to diazo compounds on treatment with tosyl azide in the presence of a base.[214] The use of phase-transfer catalysis increases the convenience of the method.[215] *p*-Dodecylbenzenesulfonyl azide,[216] methanesulfonyl azide,[217] and *p*-acetamidobenzenesulfonyl azide[218] also give the reaction. The reaction, which is called the *diazo-transfer reaction*, can also be applied to other reactive positions (e.g., the 5 position of cyclopentadiene).[219] The mechanism is probably as follows:



A diazo group can be introduced adjacent to a single carbonyl group indirectly by first converting the ketone to an α-formyl ketone (**16-85**) and then treating it with tosyl azide. As in the similar cases of



12-7 and **12-8**, the formyl group is cleaved during the reaction.[220]

OS **V**, 179; **VI**, 389, 414.

[213]Navarro-Ocaña, A.; Barzana, E.; López-González, D.; Jiménez-Estrada, M. *Org. Prep. Proceed. Int.* ***1999***, *31*, 117.

[214]For reviews, see Regitz, M.; Maas, G. *Diazo Compounds*, Academic Press, NY, ***1986***, pp. 326–435; Regitz, M. *Synthesis* ***1972***, 351; *Angew. Chem. Int. Ed.* ***1967***, *6*, 733; *Newer Methods Prep. Org. Chem.* ***1971***, *6*, 81. See also, Hünig, S. *Angew. Chem. Int. Ed.* ***1968***, *7*, 335; Koskinen, A.M.P.; Muñoz, L. *J. Chem. Soc. Chem. Commun.* ***1990***, 652.

[215]Ledon, H. *Synthesis* ***1974***, 347, *Org. Synth.* ***VI***, 414. For another convenient method, see Ghosh, S.; Datta, I. *Synth. Commun.* ***1991***, *21*, 191.

[216]Hazen, G.G.; Weinstock, L.M.; Connell, R.; Bollinger, F.W. *Synth. Commun.* ***1981***, *11*, 947.

[217]Taber, D.F.; Ruckle Jr., R.E.; Hennessy, M.J. *J. Org. Chem.* ***1986***, *51*, 4077.

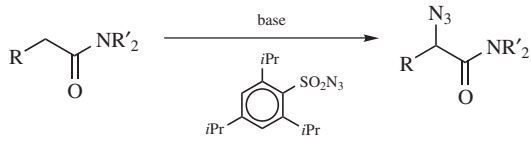
[218]Baum, J.S.; Shook, D.A.; Davies, H.M.L.; Smith, H.D. *Synth. Commun.* ***1987***, *17*, 1709.

[219]Doering, W. von E.; DePuy, C.H. *J. Am. Chem. Soc.* ***1953***, *75*, 5955.

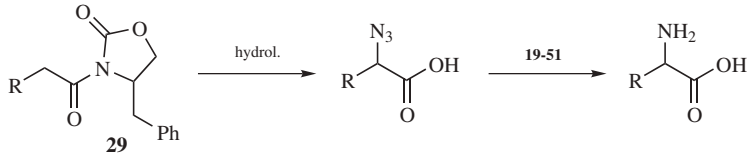
[220]For a similar approach, see Danheiser, R.L.; Miller, R.F.; Brisbois, R.G.; Park, S.Z. *J. Org. Chem.* ***1990***, *55*, 1959.

12-11 Conversion of Amides to α-Azido Amides

Azidation or **Azido-de-hydrogenation**

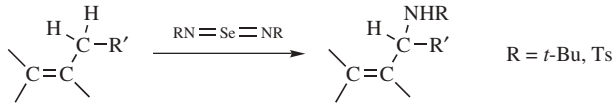


In reaction **12-10**, treatment of Z–CH_2–Z′ with tosyl azide gave the α-diazo compound via diazo transfer. When this reaction is performed on a compound with a single Z group such as an amide, formation of the azide becomes a competing process via the enolate anion.[221] Factors favoring azide formation rather than diazo transfer include K^+ as the enolate counterion rather than Na^+ or Li^+ and the use of 2,4,6-triisopropylbenzenesulfonyl azide rather than TsN_3. When the reaction was applied to amides with a chiral R', such as the oxazolidinone derivative **29**, it was highly stereoselective, and the product could be converted to an optically active amino acid.[221]



12-12 Direct Amination at an Activated Position

Alkyamino-de-hydrogenation, and so on



Alkenes can be aminated[222] in the allylic position by treatment with solutions of imido selenium compounds R–N=Se=N–R.[223] The reaction, which is similar to the allylic oxidation of alkenes with SeO_2 (see **19-14**), has been performed with R = *t*-Bu and R = Ts. The imido sulfur compound TsN=S=NTs has also been used,[224] as well

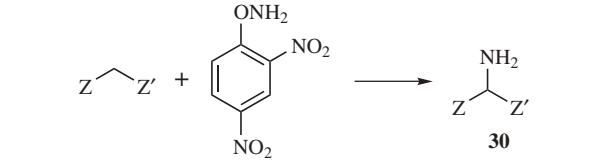
[221]Evans, D.A.; Britton, T.C. *J. Am. Chem. Soc.* ***1987***, *109*, 6881, and references cited therein.

[222]For a review of direct aminations, see Sheradsky, T., in Patai, S. *The Chemistry of Functional Groups, Supplement F*, pt. 1, Wiley, NY, ***1982***, pp. 395–416.

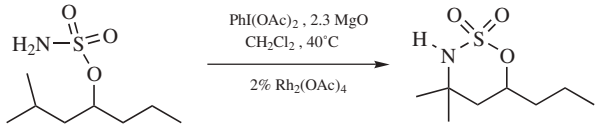
[223]Sharpless, K.B.; Hori, T.; Truesdale, L.K.; Dietrich, C.O. *J. Am. Chem. Soc.* ***1976***, *98*, 269. For another method, see Kresze, G.; Münsterer, H. *J. Org. Chem.* ***1983***, *48*, 3561. For a review, see Cheikh, R.B.; Chaabouni, R.; Laurent, A.; Mison, P.; Nafti, A. *Synthesis* ***1983***, 685, pp. 691–696.

[224]Sharpless, K.B.; Hori, T. *J. Org. Chem.* ***1979***, *41*, 176; Singer, S.P.; Sharpless, K.B. *J. Org. Chem.* ***1978***, *43*, 1448. For other reagents, see Mahy, J.P.; Bedi, G.; Battioni, P.; Mansuy, D. *Tetrahedron Lett.* ***1988***, *29*, 1927; Tsushima, S.; Yamada, Y.; Onami, T.; Oshima, K.; Chaney, M.O.; Jones, N.D.; Swartzendruber, J.K. *Bull. Chem. Soc. Jpn.* ***1989***, *62*, 1167.

as PhNHOH–$FeCl_2$/$FeCl_3$.[225] Benzylic positions can be aminated with *t*-BuOO-CONHTs in the presence of a catalytic amount of $Cu(OTf)_2$.[226] In another reaction, compounds containing an active hydrogen can be converted to primary amines (**30**) in moderate yields by treatment with *O*-(2,4-dinitrophenyl)hydroxylamine.[227]



30



31 **32**

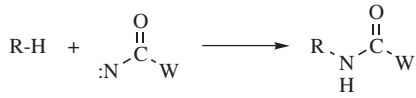
Tertiary alkyl hydrogen can be replaced in some cases via C–H nitrogen insertion. The reaction of sulfamate ester **31** with $PhI(OAc)_2$, MgO and a dinuclear Rh carboxylate catalyst, for example, generated oxathiazinane **32**.[228] This transformation is a formal oxidation, and primary carbamates have been similarly converted to oxazolidin-2-ones.[229]

In an indirect amination process, acyl halides are converted to amino acids.[230] Reaction of the acyl halide with a chiral oxazolidinone leads to a chiral amide, which reacts with the N=N unit of a dialkyl azodicarboxylate[R^2O_2C–N=N–CO_2R']. Hydrolysis and catalytic hydrogenation leads to an amino acid with good enantioselectivity.[226]

See also, **10-39**.

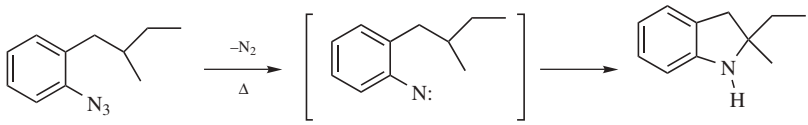
12-13 Insertion by Nitrenes

***CH*-[Acylimino]-insertion**, and so on



[225]Srivastava, R.S.; Nicholas, K.M. *Tetrahedron Lett*. ***1994***, *35*, 8739.
[226]Kohmura, Y.; Kawasaki, K.; Katsuki, T. *Synlett*, ***1997***, 1456.
[227]Sheradsky, T.; Salemnick, G.; Nir, Z. *Tetrahedron* ***1972***, *28*, 3833; Radhakrishna, A.; Loudon, G.M.; Miller, M.J. *J. Org. Chem*. ***1979***, *44*, 4836.
[228]Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc*. ***2001***, *123*, 6935.
[229]Espino, C.G.; Du Bois, J. *Angew. Chem. Int. Ed*. ***2001***, *40*, 598.
[230]Trimble, L.A.; Vederas, J.C. *J. Am. Chem. Soc*. ***1986***, *108*, 6397; Evans, D.A.; Britton, T.C.; Dorow, R.L.; Dellaria, J.F. *Tetrahedron* ***1988***, *44*, 5525; Gennari, C.; Colombo, L.; Bertolini, G. *J. Am. Chem. Soc*. ***1986***, *108*, 6394; Oppolzer, W.; Moretti, R. *Helv. Chim. Acta* ***1986***, *69*, 1923; *Tetrahedron* ***1988***, *44*, 5541; Guanti, G.; Banfi, L.; Narisano, E. *Tetrahedron* ***1988***, *44*, 5523.

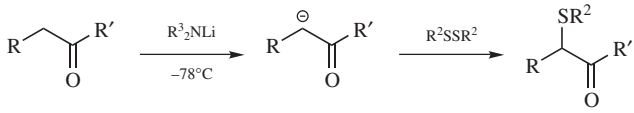
Carbonylnitrenes: NCOW (W = R′, Ar, or OR′) are very reactive species (p. 293) and insert into the C–H bonds of alkanes to give amides (W = R′ or Ar) or carbamates (W = OR′).[231] The nitrenes are generated as discussed on p. 293. The order of reactivity among alkane C–H bonds is tertiary > secondary > primary.[232] Indications are that in general it is only singlet and not triplet nitrenes that insert.[233] Retention of configuration is found at a chiral carbon.[234] The mechanism is presumably similar to the simple one-step mechanism for insertion of carbenes (**12-21**). Other nitrenes [e.g., cyanonitrene (NCN)[235] and arylnitrenes (NAr)[236]] can also insert into C–H bonds, but alkylnitrenes usually undergo rearrangement before they can react with the alkane. *N*-Carbamoyl nitrenes undergo insertion reactions that often lead to mixtures of products, but exceptions are known,[237] chiefly in cyclizations.[238] For example, heating of 2-(2-methylbutyl)phenyl azide gave ~60% 2-ethyl-2-methylindoline.[234] Enantioselective nitrene insertion reactions are known.[239]



D. Sulfur Electrophiles

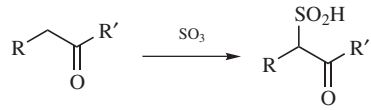
12-14 Sulfenylation, Sulfonation, and Selenylation of Ketones and Carboxylic Esters

Alkylthio-de-hydrogenation, and so on



[231]For a review, see Lwowski, W., in Lwowski, W. *Nitrenes*, Wiley, NY, ***1970***, pp. 199–207.
[232]For example, see Maslak, P. *J. Am. Chem. Soc*. ***1989***, *111*, 8201. Nitrenes are much more selective (and less reactive) in this reaction than carbenes (**12-17**). For a discussion, see Alewood, P.F.; Kazmaier, P.M.; Rauk, A. *J. Am. Chem. Soc*. ***1973***, *95*, 5466.
[233]For example, see Simson, J.M.; Lwowski, W. *J. Am. Chem. Soc*. ***1969***, *91*, 5107; Inagaki, M.; Shingaki, T.; Nagai, T. *Chem. Lett*. ***1981***, 1419.
[234]Smolinsky, G.; Feuer, B.I. *J. Am. Chem. Soc*. ***1964***, *86*, 3085.
[235]For a review of cyanonitrenes, see Anastassiou, A.G.; Shepelavy, J.N.; Simmons, H.E.; Marsh, F.D., in Lwowski, W. *Nitrenes*, Wiley, NY, ***1970***, pp. 305–344.
[236]For a review of arylnitrenes, see Scriven, E.F.V. *Azides and Nitrenes*, Academic Press, NY, ***1984***, pp. 95–204.
[237]For a synthetically useful noncyclization example, see Meinwald, J.; Aue, D.H. *Tetrahedron Lett*. ***1967***, 2317.
[238]For a list of examples, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1148–1149.
[239]For a review, see Müller, P.; Fruit, C. *Chem. Rev*. ***2003***, *103*, 2905.

Sulfonation or **Sulfo-de-hydrogenation**



Ketones, carboxylic esters (including lactones),[240] and amides (including lactams)[241] can be sulfenylated[242] in the α position by conversion to the enolate ion with a base, such as lithium *N*-isopropylcyclohexylamide and subsequent treatment with a disulfide.[243] The reaction, shown above for ketones, involves nucleophilic substitution at sulfur. Analogously, α-phenylseleno ketones RCH(SePh)COR′ and α-phenylseleno esters RCH(SePh)COOR′ can be prepared[244] by treatment of the corresponding enolate anions with PhSeBr,[245] PhSeSePh,[246] or benzeneseleninic anhydride PhSe(O)OSe(O)Ph.[247] Another method for the introduction of a phenylseleno group into the α position of a ketone involves simple treatment of an ethyl acetate solution of the ketone with PhSeCl (but not PhSeBr) at room temperature.[248] This procedure is also successful for aldehydes, but not for carboxylic esters. *N*-Phenylselenophthalimide has been used to convert ketones[249] and aldehydes[250] to the α- PhSe derivative. In another method that avoids the use of PhSeX reagents, a ketone enolate is treated with selenium to give an R′COCHRSe– ion, which is treated with MeI, producing the α-methylseleno ketone R′COCHRSeMe.[251] This method has also been applied to carboxylic esters.

[240]Trost, B.M.; Salzmann, T.N. *J. Am. Chem. Soc*. ***1973***, *95*, 6840; Seebach, D.; Teschner, M. *Tetrahedron Lett*. ***1973***, 5113. For discussions, see Trost, B.M. *Pure Appl. Chem*. ***1975***, *43*, 563, pp. 572–578; Caine, D., in Augustine, R.L. *Carbon–Carbon Bond Formation*, Vol. 1, Marcel Dekker, NY, ***1979***, pp. 278–282.

[241]Zoretic, P.A.; Soja, P. *J. Org. Chem*. ***1976***, *41*, 3587; Gassman, P.G.; Balchunis, R.J. *J. Org. Chem*. ***1977***, *42*, 3236.

[242]For a discussion of the synthesis of sulfenates, see Sandrinelli, F.; Fontaine, G.; Perrio, S.; Beslin, P. *J. Org. Chem*. ***2004***, *69*, 6916.

[243]For another reagent, see Scholz, D. *Synthesis* ***1983***, 944.

[244]For reviews of selenylations, see Back, T.G., in Liotta, D.C. *Organoselenium Chemistry*, Wiley, NY, ***1987***, pp. 1–125; Paulmier, C. *Selenium Reagents and Intermediates in Organic Synthesis*, Pergamon, Elmsford, NY, ***1986***, pp. 95–98.

[245]Reich, H.J.; Reich, I.J.; Renga, J.M. *J. Am. Chem. Soc*. ***1973***, *95*, 5813; Clive, D.L.J. *J. Chem. Soc. Chem. Commun*. ***1973***, 695; Brocksom, T.J.; Petragnani, N.; Rodrigues, R. *J. Org. Chem*. ***1974***, *39*, 2114; Schwartz, J.; Hayasi, Y. *Tetrahedron Lett*. ***1980***, *21*, 1497. See also Liotta, D. *Acc. Chem. Res*. ***1984***, *17*, 28.

[246]Grieco, P.A.; Miyashita, M. *J. Org. Chem*. ***1974***, *39*, 120. α-Phenylselenation can also be accomplished with PhSeSePh, SeO_2, and an acid catalyst: Miyoshi, N.; Yamamoto, T.; Kambe, N.; Murai, S.; Sonoda, N. *Tetrahedron Lett*. ***1982***, *23*, 4813.

[247]Barton, D.H.R.; Morzycki, J.W.; Motherwell, W.B.; Ley, S.V. *J. Chem. Soc. Chem. Commun*. ***1981***, 1044.

[248]Sharpless, K.B.; Lauer, R.F.; Teranishi, A.Y. *J. Am. Chem. Soc*. ***1973***, *95*, 6137.

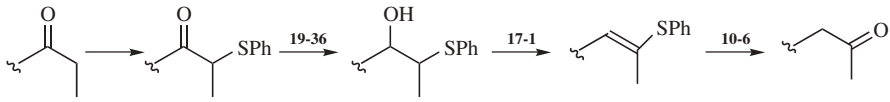
[249]Cossy, J.; Furet, N. *Tetrahedron Lett*. ***1993***, *34*, 7755.

[250]Wang, W.; Wang, K.; Li, H. *Org. Lett*. ***2004***, *6*, 2817.

[251]Saindane, M.; Barnum, C.; Ensley, H.; Balakrishnan, P. *Tetrahedron Lett*. ***1981***, *22*, 3043; Liotta, D. *Acc. Chem. Res*. ***1984***, *17*, 28.

Silyl enol ethers are converted to α-thioalkyl and α-thioaryl ketones via a sulfenylation method, driven by aromatization of an added quinone mono-*O*,*S*-acetal in the presence of Me_3SiOTf.[252]

The α-seleno and α-sulfenyl carbonyl compounds prepared by this reaction can be converted to α,β-unsaturated carbonyl compounds (**17-12**). The sulfenylation reaction has also been used[253] as a key step in a sequence for moving the position of a carbonyl group to an adjacent carbon.[254]



OS VI, 23, 109; 68, 8.

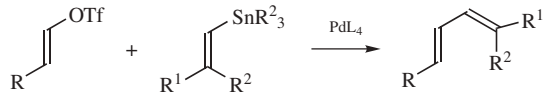
Aldehydes, ketones, and carboxylic acids containing α hydrogens can be sulfonated with sulfur trioxide.[255] The mechanism is presumably similar to that of **12-4**. Sulfonation has also been accomplished at vinylic hydrogen.

OS **VI**, 23, 109; **VIII**, 550. OS **IV**, 846, 862.

E. Carbon Reagents

12-15 Arylation and Alkylation of Alkenes

Alkylation or **Alkyl-de-oxysulfonation (de-halogenation)**, **Arylation** or **Aryl-de-oxysulfonation (de-halogenation)**, and so on



Vinyl triflates ($C{=}C\text{-}OSO_2CF_3$) react with vinyl tin derivatives in the presence of palladium catalysts to form dienes, in what is known as the *Stille coupling*.[256] Vinyl triflates can be prepared from the enolate by reaction with *N*-phenyl trifilimide.[257] Vinyltin compounds are generally prepared by the reaction of an alkyne with an trialkyltin halide (see **15-17** and **15-21**).[258] Still cross-coupling reactions are quite important.[259] Stille reactions are compatible with many functional groups,

[252]Matsugi, M.; Murata, K.; Gotanda, K.; Nambu, H.; Anilkumar, G.; Matsumoto, K.; Kita, Y. *J. Org. Chem*., ***2001***, *66*, 2434.

[253]Trost, B.M.; Hiroi, K.; Kurozumi, S. *J. Am. Chem. Soc*. ***1975***, *97*, 438.

[254]There are numerous other ways of achieving this conversion. For reviews, see Morris, D.G. *Chem. Soc. Rev*. ***1982***, *11*, 397; Kane, V.V.; Singh, V.; Martin, A.; Doyle, D.L. *Tetrahedron* ***1983***, *39*, 345.

[255]For a review, see Gilbert, E.E. *Sulfonation and Related Reactions*, Wiley, NY, ***1965***, pp. 33–61.

[256]Scott, W.J.; Crisp, G.T.; Stille, J.K. *J. Am. Chem. Soc*. ***1984***, *106*, 4630. See Roth, G.P.; Farina, V.; Liebeskind, L.S.; Peña-Cabrera, E. *Tetrahedron Lett*. ***1995***, *36*, 2191 for an optimized version of this reaction.

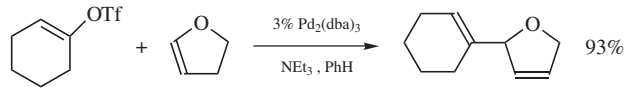
[257]McMurry, J.E.; Scott, W.J. *Tetrahedron Lett*. ***1983***, *24*, 979.

[258]For an example, see Maleczka Jr., R.E.; Lavis, J.M.; Clark, D.H.; Gallagher, W.P. *Org. Lett*. ***2000***, *2*, 3655.

[259]Stille, J.K. *Angew. Chem. Int. Ed*. ***1986***, *25*, 508; Stille, J.K.; Groh, B.L. *J. Am. Chem. Soc*. ***1987***, *109*, 813; Farina, V.; Krishnamurthy, V.; Scott, W.J. *Org. React*. ***1997***, *50*, 1.

proceed with a retention of geometry of the C=C units, and are usually regiospecific with respect to the newly formed C–C σ-bond. Vinyl halides can be used,[260] and allenic tin compounds have been used.[261] Intamolecualr reactions are possible.[262] Stille coupling has been done using microwave irradiation,[263] in fluorous solvents,[264] and in supercritical carbon dioxide (see p. 415).[265] One-pot hydrostannylation/Stille coupling has been reported using catalytic amounts of tin with alkyne substrates reacting with vinyl halides.[266]

This reaction is highly stereoselective. Cine substitution is known with this reaction, and its mechanism has been studied.[267] Using $ArSnCl_3$ derivatives, Stille coupling can be done in aq. KOH.[268] A related reaction couples reagents with C=C–I^+Ph reagents, in the presence of a palladium catalyst.[269] Aryl halides[270] and heteroaryl halides[271] can be coupled to vinyltin reagents[272] using a palladium catalyst. Vinylation of heteroaryl triflates[273] also possible. Vinyl halides can be coupled to alkenes to form dienes.[274] The reaction of dihydrofurans with vinyl triflates and a palladium catalyst leads to a nonconjugated diene, **33**.[275] This example illustrates that the product is formed by an elimination step, as with the Heck reaction (**13-10**), and double bond migration can occur resulting in allylic rearrangement.



33

[260]Johnson, C.R.; Adams, J.P.; Braun, M.P.; Senanayake, C.B.W. *Tetrahedron Lett.* ***1992***, *33*, 919.
[261]Badone, D.; Cardamone, R.; Guzzi, U. *Tetrahedron Lett.* ***1994***, *35*, 5477.
[262]Segorbe, M.M.; Adrio, J.; Carretero, J.C. *Tetrahedron Lett.* ***2000***, *41*, 1983.
[263]Larhed, M.; Hoshino, M.; Hadida, S.; Curran, D.P.; Hallberg, A. *J. Org. Chem.* ***1997***, *62*, 5583; Olofsson, K.; Kim, S.-Y.; Larhed, M.; Curran, D.P.; Hallberg, A. *J. Org. Chem.* ***1999***, *64*, 4539.
[264]Olofsson, K.; Kim, S.-Y.; Larhed, M.; Curran, D.P.; Hallberg, A. *J. Org. Chem.* ***1999***, *64*, 4539; Hoshino, M.; Degenkolb, P.; Curran, D.P. *J. Org. Chem.* ***1997***, *62*, 8341; Curran, D.P.; Hadida, S. *J. Am. Chem. Soc.* ***1996***, *118*, 2531.
[265]Jessop, P. G.; Ikariya, T.; Noyori, R. *Chem. Rev.* ***1999***, *99*, 475.
[266]Maleczka Jr., R.E.; Gallagher, W.P.; Terstiege, I. *J. Am. Chem. Soc.* ***2000***, *122*, 384; Gallagher, W.P.; Terstiege, I.; Maleczka Jr., R.E. *J. Am. Chem. Soc.* ***2001***, *123*, 3194.
[267]Farina, V.; Hossain, M.A. *Tetrahedron Lett.* ***1996***, *37*, 6997.
[268]Rai, R.; Aubrecht, K.B.; Collum, D.B. *Tetrahedron Lett.* ***1995***, *36*, 3111.
[269]Moriarty, R.M.; Epa, W.R. *Tetrahedron Lett.* ***1992***, *33*, 4095.
[270]Corriu, R.J.P.; Geng, B.; Moreau, J.J.E. *J. Org. Chem.* ***1993***, *58*, 1443; Levin, J.I. *Tetrahedron Lett.* ***1993***, *34*, 6211; Littke, A.F.; Fu, G.C. *Angew. Chem. Int. Ed.* ***1999***, *38*, 2411.
[271]Barchín, B.M.; Valenciano, J.; Cuadro, A.M.; Builla-Alvarez, J.; Vaquero, J.J. *Org. Lett.* ***1999***, *1*, 545; Clapham, B.; Sutherland, A.J. *J. Org. Chem.* ***2001***, *66*, 9033.
[272]For a coupling reaction using a butenolide-vinyltin reagent, see Rousset, S.; Abarbri, M.; Thibonnet, J.; Duchêne, A.; Parrain, J.-L. *Org. Lett.* ***1999***, *1*, 701. For a vinyltin reagent with a nitrogen substituent (a tinylated enamide), see Minière, S.; Cintrat, J.-C. *J. Org. Chem.* ***2001***, *66*, 7385.
[273]Bernabé, P.; Rutjes, P.J.T.; Hiemstra, H.; Speckamp, W.N. *Tetrahedron Lett.* ***1996***, *37*, 3561; Schaus, J.V.; Panek, J.S. *Org. Lett.* ***2000***, *2*, 469.
[274]Voigt, K.; Schick, U.; Meyer, F.E.; de Meijere, A. *Synlett* ***1994***, 189.
[275]Gilbertson, S.R.; Fu, Z.; Xie, D. *Tetrahedron Lett.* ***2001***, *42*, 365.

The accepted mechanism for the Stille reaction involves a catalytic cycle[276] in which an oxidative addition[277] and a reductive elimination step[278] are fast, relative to Sn/Pd transmetallation (the rate-determining step).[279] It appears that the more coordinatively unsaturated species, probably with a coordinated solvent molecule, is involved in the electrophilic substitution at tin. Another mechanism has been proposed, in which oxidative addition of the vinyl triflate to the ligated palladium gives a *cis*-palladium complex that isomerizes rapidly to *trans*-palladium complex, which then reacts with the organotin compound following a S_E2 (cyclic) mechanism, with release of a ligand.[280] This pathway gives a bridged intermediate, and subsequent elimination of $XSnBu_3$ yields a three-coordinate species cis-palladium complex, which readily gives the coupling product.[280]

Cyclopropylboronic acids (**12-28**) couple with vinylic halides[281] or vinyl triflates[282] to give vinylcyclopropanes, using a palladium catalyst. Vinyl borates (**12-28**) were coupled to vinyl triflates using a palladium catalyst.[283] In a variation, phenylboronic acid reacted with a symmetrical internal alkyne and a nickel catalyst to give a conjugated diene bearing a phenyl group.[284] Stille coupling to enols has been reported.[285] A variation of this latter reaction coupled vinyl triflates to vinyl ethers, without a palladium catalyst, but using microwave irradiation.[286] The

[276]Stanforth, S.P. *Tetrahedron* ***1998***, *54*, 263; Farina, V.; Roth, G.P. *Adv. Metalorg. Chem.* ***1996***, *5*, 1; Curran, D.P.; Hoshino, M. *J. Org. Chem.* ***1996***, *61*, 6480; Mateo, C.; Cárdenas, D.J.; Fernández-Rivas, C.; Echavarren, A.M. *Chem. Eur. J.* ***1996***, *2*, 1596; Roth, G.P.; Farina, V.; Liebeskind, L.S.; Peña-Cabrera, E. *Tetrahedron Lett.* ***1995***, *36*, 2191; Mitchell, T.N. *Synthesis* ***1992***, 803; Scott, W.J.; Stille, J.K. *J. Am. Chem. Soc.* ***1986***, *108*, 3033; Stille, J.K. *Angew. Chem., Int. Ed.* ***1986***, *25*, 508; Beletskaya, I.P. *J. Organomet. Chem.* ***1983***, *250*, 551; Farina, V., in, Abel, E. W., Stone, F. G. A., Wilkinson, G. *Comprehensive Organometallic Chemistry II*, Vol. 12, Pergamon, Oxford, U.K., ***1995***, Chapter 3.4.; Brown, J.M.; Cooley, N.A. *Chem. Rev.* ***1988***, *88*, 1031.

[277]Amatore, C.; Jutand, A.; Suarez, A. *J. Am. Chem. Soc.* ***1993***, *115*, 9531; Amatore, C.; Pflüger, F. *Organometallics* ***1990***, *9*, 2276, and references cited therein.

[278]Ozawa, F.; Fujimori, M.; Yamamoto, T.; Yamamoto, A. *Organometallics* ***1986***, *5*, 2144; Tatsumi, K.; Hoffmann, R.; Yamamoto, A.; Stille, J.K. *Bull. Chem. Soc. Jpn.* ***1981***, *54*, 1857; Ozawa, F.; Ito, T.; Nakamura, Y.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* ***1981***, *54*, 1868; Moravsikiy, A.; Stille, J.K. *J. Am. Chem. Soc.* ***1981***, *103*, 4182; Loar, M.K.; Stille, J.K. *J. Am. Chem. Soc.* ***1981***, *103*, 4174; Ozawa, F.; Ito, T.; Yamamoto, A. *J. Am. Chem. Soc.* ***1980***, *102*, 6457; Gillie, A.; Stille, J.K. *J. Am. Chem. Soc.* ***1980***, *102*, 4933; Komiya, S.; Albright, T.A.; Hoffmann, R.; Kochi, J.K. *J. Am. Chem. Soc.* ***1976***, *98*, 7255.

[279]Labadie, J.W.; Stille, J.K. *J. Am. Chem. Soc.* ***1983***, *105*, 6129; Eaborn, C.; Odell, K.J.; Pidcock, A. *J. Chem. Soc., Dalton Trans.* ***1978***, 357; Eaborn, C.; Odell, K.J.; Pidcock, A. *J. Chem. Soc., Dalton Trans.* ***1979***, 758; Deacon, G.B.; Gatehouse, B.M.; Nelson-Reed, K.T. *J. Organomet. Chem.* ***1989***, *359*, 267.

[280]Casado, A.L.; Espinet, P.; Gallego, A.M. *J. Am. Chem. Soc.* ***2000***, *122*, 11771; Casado, A.L.; Espinet, P. *J. Am. Chem. Soc.* ***1998***, *120*, 8978.

[281]Zhou, S.-m.; Deng, M.-z. *Tetrahedron Lett.* ***2000***, *41*, 3951.

[282]Yao, M.-L.; Deng, M.-Z. *J. Org. Chem.* ***2000***, *65*, 5034; Yao, M.-L.; Deng, M.-Z. *Tetrahedron Lett.* ***2000***, *41*, 9083.

[283]Occhiato, E.G.; Trabocchi, A.; Guarna, A. *J. Org. Chem.* ***2001***, *66*, 2459.

[284]Shirakawa, E.; Takahashi, G.; Tsuchimoto, T.; Kawakami, Y. *Chem. Commun.* ***2001***, 2688.

[285]See Fu, X.; Zhang, S.; Yin, J.; McAllister, T.L.; Jiang, S.A.; Tann, C.-H.; Thiruvengadam, T.K.; Zhang, F. *Tetrahedron Lett.* ***2002***, *43*, 573.

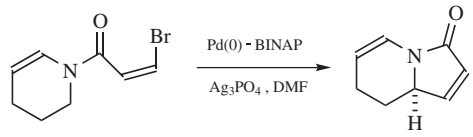
[286]Vallin, K.S.A.; Larhed, M.; Johansson, K.; Hallberg, A. *J. Org. Chem.* ***2000***, *65*, 4537.

coupling of vinyl silanes to give the symmetrically conjugated diene using CuCl and air was reported.[287] Vinyl zinc halides were coupled to 1-halo enol ether to give a conjugated diene bearing a vinyl ether unit, using a palladium catalyst.[288] Tertiary propargyl alcohols (R-C=C-CMe_2OH) are coupled to conjugated alkenes in a Heck-like process using a palladium catalyst and oxygen to give the conjugated ene-yne.[289]

Coupling is not restricted to two vinyl units or an aryl with a vinyl. 1-Lithioalkynes were coupled to vinyl tellurium compounds (C=C–TeBu) using a nickel catalyst[290] or a palladium catalyst[291] to give a conjugated en-yne. 2-Alkynes (R-C=C-Me) react with $HgCl_2$, *n*-butyllithium, and $ZnBr_2$, sequentially, and then with vinyl iodides and a palladium catalyst to give the nonconjugated en-yne.[292] Alkynyl groups can be coupled to vinyl groups to give ene-ynes, via reaction of silver alkynes (Ag-C=C-R) with vinyl triflates and a palladium catalyst.[293] In the presence of CuI and a palladium catalyst, vinyl triflates[294] or vinyl halides[295] couple to terminal alkynes. Alkynyl zinc reagents (R-C=C-ZnBr) can be coupled to vinyl halides with a palladium catalyst to give the conjugate ene-yne.[296]

Alkyl groups can be coupled to a vinyl unit to give substituted alkenes. The reaction of vinyl iodides and EtZnBr, with a palladium catalyst, gave the ethylated alkene (C=C–Et).[297] A similar coupling reaction was observed with RZnI reagents and vinyl nitro compounds (C=C–NO_2), which gave the alkyne (C=C–R) with microwave irradiation.[298] Aliphatic alkyl bromides reacted with vinyltin compounds to give the alkylated alkene using a palladium catalyst.[299] Allylic tosylates were coupled to conjugated alkenes to give a non-conjugated diene using a palladium catalyst.[300] An internal coupling reaction was reported in which an alkenyl enamide (**34**) reacted with Ag_3PO_4 and a chiral palladium catalyst to give **35** enantioselectively.[301]

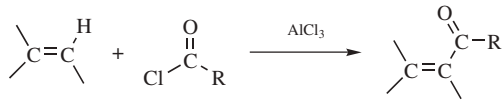
[287]Nishihara, Y.; Ikegashira, K.; Toriyama, F.; Mori, A.; Hiyama, T. *Bull. Chem. Soc. Jpn*. ***2000***, *73*, 985.
[288]Su, M.; Kang, Y.; Yu, W.; Hua, Z.; Jin, Z. *Org. Lett*. ***2002***, *4*, 691.
[289]Nishimura, T.; Araki, H.; Maeda, Y.; Uemura, S. *Org. Lett*. ***2003***, *5*, 2997.
[290]Raminelli, C.; Gargalak, Jr., J.; Silveira, C.C.; Comasseto, J.V. *Tetrahedron Lett*. ***2004***, *45*, 4927; Silveira, C.C.; Braga, A.L.; Vieira, A.S.; Zeni, G. *J. Org. Chem*. ***2003***, *68*, 662.
[291]Zeni, G.; Comasseto, J.V. *Tetrahedron Lett*. ***1999***, *40*, 4619.
[292]Ma, S.; Zhang, A.; Yu, Y.; Xia, W. *J. Org. Chem*. ***2000***, *65*, 2287.
[293]Dillinger, S.; Bertus, P.; Pale, P. *Org. Lett*. ***2001***, *3*, 1661. See Halbes, U.; Bertus, P.; Pale, P. *Tetrahedron Lett*. ***2001***, *42*, 8641; Bertus, P.; Halbes, U.; Pale, P. *Eur. J. Org. Chem*. ***2001***, 4391.
[294]Braga, A.L.; Emmerich, D.J.; Silveira, C.C.; Martins, T.L.C.; Rodrigues, O.E.D. *Synlett* ***2001***, 369.
[295]Lee, J.-H.; Park, J.-S.; Cho, C.-G. *Org. Lett*. ***2002***, *4*, 1171. For an example using another copper catalyst, see Bates, C.G.; Saejueng, P.; Venkataraman, D. *Org. Lett*. ***2004***, *6*, 1441.
[296]Negishi, E.; Qian, M.; Zeng, F.; Anastasia, L.; Babinski, D. *Org. Lett*. ***2003***, *5*, 1597.
[297]Abarbri, M.; Parrain, J.-L.; Kitamura, M.; Noyori, R.; Duchêne, A. *J. Org. Chem*. ***2000***, *65*,7475.
[298]Hu, Y.; Yu, J.; Yang, S.; Wang, J.-X.; Yin, Y. *Synth. Commun*. ***1999***, *29*, 1157.
[299]Menzel, K.; Fu, G.C. *J. Am. Chem. Soc*. ***2003***, *125*, 3718.
[300]Tsukada, N.; Sato, T.; Inoue, Y. *Chem. Commun*. ***2003***, 2404.
[301]Kiewel, K.; Tallant, M.; Sulikowski, G.A. *Tetrahedron Lett.* ***2001***, *42*, 6621.



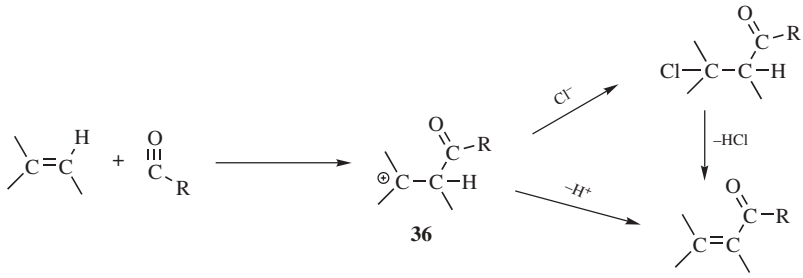
34 **35**

12-16 Acylation at an Aliphatic Carbon

Acylation or **Acyl-de-hydrogenation**



Alkenes can be acylated with an acyl halide and a Lewis acid catalyst in what is essentially a Friedel–Crafts reaction at an aliphatic carbon.[302] The product can arise by two paths. The initial attack is by the π-bond of the alkene unit on the acyl cation (RCO^+; or on the acyl halide free or complexed; see **11-17**) to give a carbocation, **36**.

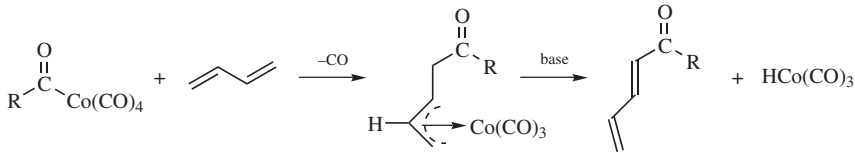


Ion **36** can either lose a proton or combine with chloride ion. If it loses a proton, the product is an unsaturated ketone; the mechanism is similar to the tetrahedral mechanism of Chapter 10, but with the charges reversed. If it combines with chloride, the product is a β-halo ketone, which can be isolated, so that the result is addition to the double bond (see **15-47**). On the other hand, the β-halo ketone may, under the conditions of the reaction, lose HCl to give the unsaturated ketone, this time by an addition–elimination mechanism. In the case of unsymmetrical alkenes, the more stable alkene is formed (the more highly substituted and/or conjugated alkene, following Markovnikov's rule, see p. 1019). Anhydrides and carboxylic acids (the latter with a proton acid such as anhydrous HF, H_2SO_4, or polyphosphoric acid as a catalyst) are sometimes used instead of acyl halides. With some sub-

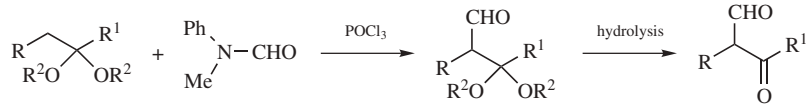
[302]For reviews, see Groves, E.E. *Chem. Soc. Rev.* ***1972***, *1*, 73; Satchell, D.P.N.; Satchell, R.S., in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***, pp. 259–266, 270–273; Nenitzescu, C.D.; Balaban, A.T., in Olah A, G.A. *Friedel-Crafts and Related Reactions*, Vol. 3, Wiley, NY, ***1964***, pp. 1033–1152.

strates and catalysts double-bond migrations are occasionally encountered so that, for example, when 1-methylcyclohexene was acylated with acetic anhydride and zinc chloride, the major product was 6-acetyl-1-methylcyclohexene.[303]

Conjugated dienes can be acylated by treatment with acyl- or alkylcobalt tetracarbonyls, followed by base-catalyzed cleavage of the resulting π-allyl carbonyl derivatives[304] (π-allyl metal complexes were discussed on p. 117. The reaction is very general. With unsymmetrical dienes, the acyl group generally substitutes most readily at a cis double bond, next at a terminal alkenyl group, and least readily at a trans double bond. The most useful bases are strongly basic, hindered amines, such as dicyclohexylethylamine. The use of an alkylcobalt tetracarbonyl $RCo(CO)_4$ gives the same product as that shown above. Acylation of vinylic ethers has been accomplished with aromatic acyl chlorides, a base, and a palladium catalyst: $ROCH{=}CH_2 \rightarrow ROCH{=}CHCOAr$.[305]



Formylation of alkenes can be accomplished with *N*-disubstituted formamides and $POCl_3$.[306] This is an aliphatic Vilsmeier reaction (see **11-18**). Vilsmeier formylation can also be performed on the α position of acetals and ketals, so that hydrolysis of the products gives keto aldehydes or dialdehydes:[307] A variation of this reaction heated a 1,1-dibromoalkene with a secondary amine in aq. DMF to give the corresponding amide.[308]



Acetylation of acetals or ketals can be accomplished with acetic anhydride and BF_3-etherate.[309] The mechanism with acetals or ketals also involves attack at an

[303]Deno, N.C.; Chafetz, H. *J. Am. Chem. Soc*. ***1952***, *74*, 3940. For other examples, see Beak, P.; Berger, K.R. *J. Am. Chem. Soc*. ***1980***, *102*, 3848; Dubois, J.E.; Saumtally, I.; Lion, C. *Bull. Soc. Chim. Fr.* ***1984***, II-133; Grignon-Dubois, M.; Cazaux, M. *Bull. Soc. Chim. Fr.* ***1986***, 332.

[304]For a review, see Heck, R.F., in Wender, I.; Pino, P. *Organic Syntheses via Metal Carbonyls*, Vol. 1, Wiley, NY, ***1968***, pp. 388–397.

[305]Andersson, C.; Hallberg, A. *J. Org. Chem*. ***1988***, *53*, 4257.

[306]For reviews, see Burn, D. *Chem. Ind. (London)* ***1973***, 870; Satchell, D.P.N.; Satchell, R.S., in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***, pp. 281–282.

[307]Youssefyeh, R.D. *Tetrahedron Lett*. ***1964***, 2161.

[308]Shen, W.; Kunzer, A. *Org. Lett*. ***2002***, *4*, 1315.

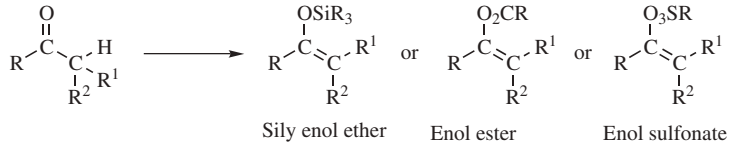
[309]Youssefyeh, R.D. *J. Am. Chem. Soc*. ***1963***, *85*, 3901.

alkenyl carbon, since enol ethers are intermediates.[309] Ketones can be formylated in the α position by treatment with CO and a strong base.[310]

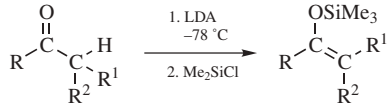
OS **IV**, 555, 560; **VI**, 744. Also see OS **VI**, 28.

12-17 Conversion Of Enolates to Silyl Enol Ethers, Silyl Enol Esters, and Silyl Enol Sulfonate Esters

3/*O*-Trimethylsilyl-de-hydrogenation



Silyl enol ethers,[311] important reagents with a number of synthetic uses (see, e.g., **10-68**, **12-4**, **15-24**, **15-64**, **16-36**), can be prepared by base treatment of a ketone (converting it to its enolate anion) followed by addition of a trialkylchlorosilane. Other silylating agents have also been used.[312] Both strong bases, e.g., lithium diisopropylamide (LDA), and weaker bases (e.g. Et_3N) have been used for this purpose.



In some cases, the base and the silylating agent can be present at the same time.[313] Enolates prepared in other ways (e.g., as shown on p. 603) also give the reaction.[314] The reaction can be applied to aldehydes by the use of the base KH in 1,2-dimethoxyethane.[315] A particularly mild method for conversion of ketones

[310]See, for example, van der Zeeuw, A.J.; Gersmann, H.R. *Recl. Trav. Chim. Pays-Bas* ***1965***, *84*, 1535.

[311]For reviews of these compounds, see Poirier, J. *Org. Prep. Proced. Int*. ***1988***, *20*, 319; Brownbridge, P. *Synthesis* ***1983***, 1, 85; Rasmussen, J.K. *Synthesis* ***1977***, 91. For monographs on silicon reagents in organic synthesis, see Colvin, E.W. *Silicon Reagents in Organic Synthesis*, Academic Press, NY, ***1988***. For reviews, see Colvin, E.W., in Hartley, C.R.; Patai, S. *The Chemistry of the Metal-Carbon Bond*, Vol. 4, Wiley, NY, pp. 539–621; Ager, D.J. *Chem. Soc. Rev*. ***1982***, *11*, 493; Colvin, E.W. *Chem. Soc. Rev*. ***1978***, *7*, 15, pp. 43–50.

[312]For a review of silylating agents, see Mizhiritskii, M.D.; Yuzhelevskii, Yu.A. *Russ. Chem. Rev*. ***1987***, *56*, 355. For a list, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1488–1491.

[313]Corey, E.J.; Gross, A.W. *Tetrahedron Lett*. ***1984***, *25*, 495. See Lipshutz, B.H.; Wood, M.R.; Lindsley, C.W. *Tetrahedron Lett*. ***1995***, *36*, 4385 for a discussion of the role of Me_3SiCl in deprotonations with $LiNR_2$.

[314]See Cahiez, G.; Figadère, B.; Cléry, P. *Tetrahedron Lett*. ***1994***, *35*, 6295.

[315]Ladjama, D.; Riehl, J.J. *Synthesis* ***1979***, 504. This base has also been used for ketones: See Orban, J.; Turner, J.V.; Twitchin, B. *Tetrahedron Lett*. ***1984***, *25*, 5099.

or aldehydes to silyl enol ethers uses Me_3SiI and the base hexamethyldisilazane, $(Me_3Si)_2NH$.[316] Cyclic ketones can be converted to silyl enol ethers in the presence of acyclic ketones, by treatment with Me_3SiBr, tetraphenylstibonium bromide, Ph_4SbBr, and an aziridine.[317] bis(Trimethylsilyl)acetamide is an effective reagent for the conversion of ketones to the silyl enol ether, typically giving the thermodynamic product (see below).[318] Silyl enol ethers have also been prepared by the direct reaction of a ketone and a silane (R_3SiH) with a platinum complex catalyst.[319]

Unsymmetrical ketones can give the more substituted (thermodynamic) silyl enol ether or the less substituted (kinetic) product, depending on the use of thermodynamic conditions (protic solvents, e.g., ethanol, water, or ammonia; a base generating a conjugate acid stronger than the starting ketone; more ionic counterions, e.g., K or Na; higher temperatures and longer reaction times) or kinetic conditions (aprotic solvents, such as ether or THF; a base generating a conjugate acid weaker than the starting ketone; more covalent counterions, e.g., Li; lower temperatures and relatively short reaction times). Other reaction conditions have been developed to control or influence the relative amounts of kinetic or thermodynamic silyl enol ether. Magnesium diisopropyl amide has been used to prepare kinetic silyl enol ethers in virtual quantitative yield.[320] Reaction with Me_3SiCl/KI in DMF gives primarily the thermodynamic silyl enol ether.[321] The reaction of an unsymmetrical ketone with Mg and TMSCl in DMF gives a roughly 2:1 mixture of thermodynamic: kinetic silyl enol ether.[322]

An interesting synthesis of silyl enol ethers involves chain extension of an aldehyde. Aldehydes are converted to the silyl enol ether of a ketone upon reaction with lithium (trimethylsilyl)diazomethane and then a dirhodium catalyst.[323] Initial reaction of lithium(trimethylsilyl)diazomethane [LTMSD, prepared *in situ* by reaction of butyllithium with (trimethylsilyl)diazomethane] to the aldehyde (e.g., **37**) gave the alkoxide addition product. Protonation, and then capture by a transition-metal catalyst, and a 1,2-hydride migration gave the silyl enol ether, **38**.

[316]Miller, R.D.; McKean, D.R. *Synthesis* ***1979***, 730; *Synth. Commun*. ***1982***, *12*, 319. See also, Cazeau, P.; Duboudin, F.; Moulines, F.; Babot, O.; Dunogues, J. *Tetrahedron* ***1987***, *43*, 2075, 2089; Ahmad, S.; Khan, M.A.; Iqbal, J. *Synth. Commun*. ***1988***, *18*, 1679.

[317]Fujiwara, M.; Baba, A.; Matsuda, H. *Chem. Lett*. ***1989***, 1247.

[318]Smietana, M.; Mioskowski, C. *Org. Lett*. ***2001***, *3*, 1037. See also, Tanabe, Y.; Misaki, T.; Kurihara, M.; Iida, A.; Nishii, Y. *Chem. Commun*. ***2002***, 1628.

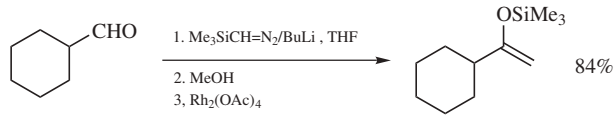
[319]Ozawa, F.; Yamamoto, S.; Kayagishi, S.; Hiraoka, M.; Ideda, S.;Minami, T.; Ito, S.; Yoshifuji, M. *Chem. Lett*. ***2001***, 972. For the conversion of a conjugated ketone to a silyl enol ether with R_3SiH and a triarylborane catalyst, see Blackwell, J.M.; Morrison, D.J.; Piers, W.E. *Tetahedron* ***2002***, *58*, 8247. For the conversion of a conjugated ketone to a silyl enol ether with R_3SiH and a rhodium catalyst, see Mori, A.; Kato, T. *Synlett* ***2002***, 1167.

[320]Lessène, G.; Tripoli, R.; Cazeau, P.; Biran, C.; Bordeau, M. *Tetrahedron Lett*. ***1999***, *40*, 4037.

[321]Lin, J.-M.; Liu, B.-S. *Synth. Commun*. ***1997***, *27*, 739.

[322]Patonay, T.; Hajdu, C.; Jekö, J.; Lévai, A.; Micskei, K.; Zucchi, C. *Tetrahedron Lett*. ***1999***, *40*, 1373.

[323]Aggarwal, V. K.; Sheldon, C. G.; Macdonald, G. J.; Martin, W. P. *J. Am. Chem. Soc*. ***2002***, *124*, 10300.



37 **38**

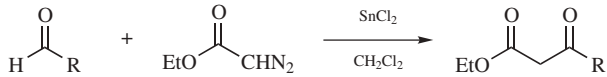
Enol acetates are generally prepared by the reaction of an enolate anion with a suitable acylating reagent.[324] Enolate anions react with acyl halides and with anhydrides to give the acylated product. Both *C*-acylation and *O*-acylation are possible, but in general *O*-acylation predominates.[325] Note that the extent of *O*- versus *C*-acylation is very dependent on the local environment and electronic effects within the enolate anion.[326] Silyl sulfonate esters can be prepared by similar methods, using sulfonic acid anhydrides rather than carboxylic anhydrides. A polymer-supported triflating agent was used to prepare silyl enol triflate from ketones, in the presence of diisopropylethylamine.[327]

When a silyl enol ether is the trimethylsilyl derivative (Me_3Si–O-C=C), treatment with methyllithium will regenerate the lithium enolate anion and the volatile trimethylsilane (Me_3SiH).[328] The enolate anion can be used in the usual reactions. In a similar reaction, a trimethylsilyl enol ether was treated with Cp_2Zr (from Cp_2ZrCl_2/2 BuLi/THF/–78°C), and subsequent quenching with D_2O led to incorporation of deuterium at the vinyl carbon (C=C–D).[329]

OS **VI**, 327, 445; **VII**, 282, 312, 424, 512; **VIII**, 1, 286, 460; **IX**, 573. See also OS **VII**, 66, 266. For the conversion of ketones to vinylic triflates,[330] see OS **VIII**, 97, 126.

12-18 Conversion of Aldehydes to β-Keto Esters or Ketones

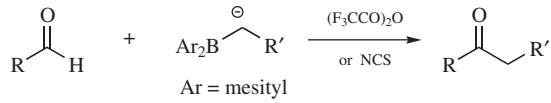
Alkoxycarbonylalkylation or **Alkoxycarbonylalkyl-de-hydrogenation**



β-Keto esters have been prepared in moderate to high yields by treatment of aldehydes with diethyl diazoacetate in the presence of a catalytic amount of a Lewis acid, such as $SnCl_2$, BF_3, or $GeCl_2$.[331] The reaction was successful for both aliphatic and aromatic aldehydes, but the former react more rapidly than the latter, and the

[324]For the synthesis of enol acetates, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, 1484–1485.
[325]See Krapcho, A.P.; Diamanti, J.; Cayen, C.; Bingham, R. *Org. Synth. Coll. Vol. V* ***1973***, 198.
[326]For example, see Honda, T.; Namiki, H.; Kudoh, M.; Watanabe, N.; Nagase, H.; Mizutani, H. *Tetrahedron Lett*. ***2000***, *41*, 5927.
[327]Wentworth, A.D.; Wentworth, Jr., P.; Mansoor, U.F.; Janda, K.D. *Org. Lett*. ***2000***, *2*, 477.
[328]House, H.O.; Czuba, L.J.; Gall, M.; Olmstead, H.D. *J. Org. Chem.* ***1969***, *34*, 2324.
[329]Ganchegui, B.; Bertus, P.; Szymoniak, J. *Synlett* ***2001***, 123.
[330]Comins, D.L.; Dehghani, A. *Tetrahedron Lett*. ***1992***, *33*, 6299.
[331]Holmquist, C.R.; Roskamp, E.J. *J. Org. Chem*. ***1989***, *54*, 3258.

difference is great enough to allow selective reactivity. In a similar process, aldehydes react with certain carbanions stabilized by boron, in the presence of $(F_3CCO)_2O$ or NCS, to give ketones.[332]

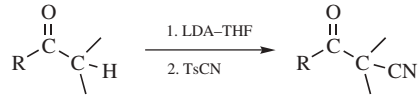


Ketones can be prepared from aryl aldehydes (ArCHO) by treatment with a rhodium complex $(Ph_3P)_2Rh(CO)Ar'$, whereby the Ar group is transferred to the aldehyde, producing the ketone, Ar–CO–Ar′.[333] In a rhodium catalyzed reaction, aryl aldehydes (ArCHO) react with Me_3SnAr' to give the diaryl ketone Ar–CO–Ar′.[334]

12-19 Cyanation or Cyano-de-hydrogenation

There are several reactions in which a C–H unit is replaced by C–CN. In virtually all cases, the hydrogen being replaced is on a carbon α to a heteroatom or functional group. There are several examples.

Introduction of a cyano group α to the carbonyl group of a ketone can be accomplished by prior formation of the enolate anion with LDA in THF and addition of this solution to *p*-TsCN at −78°C.[335] The products are formed in moderate to high yields but the reaction is not applicable to methyl ketones. Treatment of $TMSCH_2N(Me)C{=}Nt\text{-}Bu$ with *sec*-butyllithium and $R_2C{=}O$, followed by iodomethane and NaOMe leads to the nitrile, $R_2CH–CN$.[336]



Cyanation has been shown to occur α to a nitrogen, specifically in *N,N*-dimethylaniline derivatives. Treatment with a catalytic amount of $RuCl_3$ in the presence of oxygen and NaCN leads to the corresponding cyanomethylamine.[337]

[332]Pelter, A.; Smith, K.; Elgendy, S.; Rowlands, M. *Tetrahedron Lett*. ***1989***, *30*, 5643.
[333]Krug, C.; Hartwig, J. F *J. Am. Chem. Soc*. ***2002***, *124*, 1674.
[334]Pucheault, M.; Darses, S.; Genet, J.-P. *J. Am. Chem. Soc*. ***2004***, *126*, 15356.
[335]Kahne, D.; Collum, D.B. *Tetrahedron Lett*. ***1981***, *22*, 5011.
[336]Santiago, B.; Meyers, A.I. *Tetrahedron Lett*. ***1993***, *34*, 5839.
[337]Murahashi, S.-I.; Komiya, N.; Terai, H.; Nakae, T. *J. Am. Chem. Soc*. ***2003***, *125*, 15312; North, M. *Angew. Chem. Int. Ed*. ***2004***, *43*, 4126.

In a different kind of reaction, nitro compounds are α-cyanated by treatment with ^{-}CN and $K_3Fe(CN)_6$.[338] The mechanism probably involves ion radicals. In still another reaction, secondary amines are converted to α-cyanoamines by treatment with phenylseleninic anhydride and NaCN or Me_3SiCN.[339] The compound Me_3SiCN has also been used in a reaction that cyanates benzylic positions.[340]

12-20 Alkylation of Alkanes

Alkylation or **Alkyl-de-hydrogenation**

$$RH + R'^{+} \longrightarrow R{-}R' + H^{+}$$

Alkanes can be alkylated by treatment with solutions of stable carbocations[341] (p. 235), but the availability of such carbocations is limited and mixtures are usually obtained. In a typical experiment, the treatment of propane with isopropyl fluoroantimonate (Me_2C^{+} SbF_6–) gave 26% 2,3-dimethylbutane, 28% 2-methylpentane, 14% 3-methylpentane, and 32% *n*-hexane, as well as some butanes, pentanes (formed by **12-47**), and higher alkanes. Mixtures arise in part because intermolecular hydrogen exchange ($RH + R'^{+}$ $R^{+} + R'H$) is much faster than alkylation, so that alkylation products are also derived from the new alkanes and carbocations formed in the exchange reaction. Furthermore, the carbocations present are subject to rearrangement (Chapter 18), giving rise to new carbocations. Products result from all the hydrocarbons and carbocations present in the system. As expected from their relative stabilities, secondary alkyl cations alkylate alkanes more readily than tertiary alkyl cations (the *tert*-butyl cation does not alkylate methane or ethane). Stable primary alkyl cations are not available, but alkylation has been achieved with complexes formed between CH_3F or C_2H_5F and SbF_5.[342] The mechanism of alkylation can be formulated (similar to that shown in hydrogen exchange with superacids, **12-1**) as

$$R{-}H + R'^{+} \longrightarrow \left[\begin{array}{c} H \\ R \\ R' \end{array}\right]^{+} \xrightarrow{-H^{+}} R{-}R'$$

[338]Matacz, Z.; Piotrowska, H.; Urbanski, T. *Pol. J. Chem.* ***1979***, *53*, 187; Kornblum, N.; Singh, N.K.; Kelly, W.J. *J. Org. Chem.* ***1983***, *48*, 332.

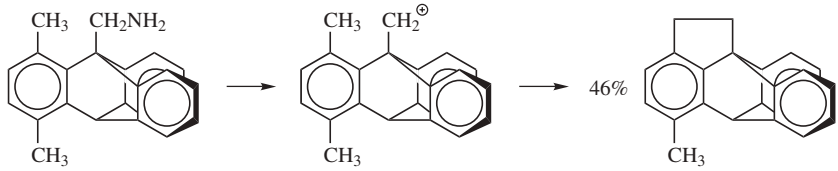
[339]Barton, D.H.R.; Billion, A.; Boivin, J. *Tetrahedron Lett.* ***1985***, *26*, 1229.

[340]Lemaire, M.; Doussot, J.; Guy, A. *Chem. Lett.* ***1988***, 1581. See also, Hayashi, Y.; Mukaiyama, T. *Chem. Lett.* ***1987***, 1811.

[341]Olah, G.A.; Mo, Y.K.; Olah, J.A. *J. Am. Chem. Soc.* ***1973***, *95*, 4939. For reviews, see Olah, G.A.; Farooq, O.; Prakash, G.K.S., in Hill, C.L. *Activation and Functionalization of Alkanes*, Wiley, NY, ***1989***, pp. 27–78; Ref. 48. For a review of the thermodynamic behavior of alkanes in superacid media, see Fabre, P.; Devynck, J.; Trémillon, B. *Chem. Rev.* ***1982***, *82*, 591. See also, Olah, G.A.; Prakash, G.K.S.; Williams, R.E.; Field, L.D.; Wade, K. *Hypercarbon Chemistry*, Wiley, NY, ***1987***.

[342]Olah, G.A.; DeMember, J.R.; Shen, J. *J. Am. Chem. Soc.* ***1973***, *95*, 4952. See also, Sommer, J.; Muller, M.; Laali, K. *Nouv. J. Chem.* ***1982***, *6*, 3.

It is by means of successive reactions of this sort that simple alkanes like methane and ethane give *tert*-butyl cations in superacid solutions (p. 236).[343]



39 **40**

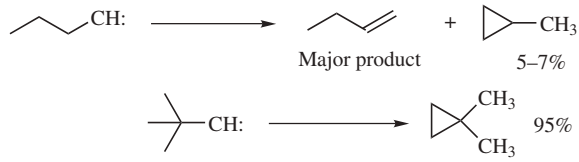
Intramolecular insertion has been reported. The positively charged carbon of the carbocation **40**, generated from the diazonium salt of the triptycene compound **39**, reacted with the CH_3 group in close proximity with it.[344]

12-21 Insertion by Carbenes

CH-Methylene-insertion

$$RH + :CH_2 \longrightarrow RCH_3$$

The highly reactive species methylene ($:CH_2$) inserts into C–H bonds,[345] both aliphatic and aromatic,[346] although with aromatic compounds subsequent ring expansion is also possible (see **15-64**). This is effectively a homologation reaction.[347] The methylene insertion reaction has limited utility because of its nonselectivity (see p. 284). The insertion reaction of carbenes has been used for synthetic purposes.[348] The carbenes can be generated in any of the ways mentioned in Chapter 5 (p. 287). Alkylcarbenes usually rearrange rather than give



[343]For example, see Hogeveen, H.; Roobeek, C.F. *Recl. Trav. Chim. Pays-Bas* ***1972***, *91*, 137.
[344]Yamamoto, G.; Ō ki, M. *Chem. Lett*. ***1987***, 1163.
[345]First reported by Meerwein, H.; Rathjen, H.; Werner, H. *Berchtt*. ***1942***, *75*, 1610. For reviews, see Bethell, D., in McManus, S.P. *Organic Reactive Intermediates*, Academic Press, NY, ***1973***, pp. 92–101; Kirmse, W. *Carbene Chemistry*, 2nd ed., Academic Press, NY, ***1971***, pp. 209–266.
[346]Terao, T.; Shida, S. *Bull. Chem. Soc. Jpn*. ***1964***, *37*, 687. See also, Moss, R.A.; Fedé, J.-M.; Yan, S. *J. Am. Chem. Soc*. ***2000***, *122*, 9878.
[347]For a discussion of organozinc carbenoid homologation reactions, see Marek, I. *Tetrahedron* ***2002***, *58*, 9463.
[348]For some examples of intramolecular carbene insertions used synthetically, see Gilbert, J.C.; Giamalva, D.H.; Weerasooriya, U. *J. Org. Chem*. ***1983***, *48*, 5251; Taber, D.F.; Ruckle, Jr., R.E. *J. Am. Chem. Soc*. ***1986***, *108*, 7686; Paquette, L.A.; Kobayashi, T.; Gallucci, J.C. *J. Am. Chem. Soc*. ***1988***, *110*, 1305; Adams, J.; Poupart, M.; Grenier, L.; Schaller, C.; Ouimet, N.; Frenette, R. *Tetrahedron Lett*. ***1989***, *30*, 1749; Doyle, M.P.; Bagheri, V.; Pearson, M.M.; Edwards, J.D. *Tetrahedron Lett*. ***1989***, *30*, 7001.

insertion (p. 291), but, when this is impossible, *intramolecular* insertion[349] is found rather than intermolecular.[350] Methylene ($:CH_2$) generated by photolysis of diazomethane (CH_2N_2) in the liquid phase is indiscriminate (totally nonselective) in its reactivity (p. 288). Methylene ($:CH_2$) generated in other ways and monoalkyl and dialkyl carbenes are less reactive and insert in the order tertiary > secondary > primary.[351] Carbene insertion with certain allylic systems can proceed with rearrangement of the double bond.[352] Carbenes have been generated in the presence of ultrasound.[353] Halocarbenes ($:CCl_2$, $:CBr_2$, etc.) insert much less readily, although a number of instances have been reported.[354] Insertion into the O–H bond of alcohols, to produce ethers, has been reported using a diazocarbonyl compound and an $In(OTf)_3$ catalyst.[355]

For the similar insertion reaction of nitrenes, see **12-13**.

The metal carbene insertion reaction, in contrast to the methylene insertion reaction, can be highly selective,[356] is very useful in synthesis,[357] and there are numerous examples, usually requiring a catalyst.[358] The catalyst typically convert a diazoalkane or diazocarbonyl compound to the metal carbene *in situ*, allowing the subsequent insertion reaction. Intermolecular reactions are known, including diazoalkane insertion reaction with a dirhodium catalyst.[359] When chiral ligands are present good enantioselectivity is observed in the insertion product.[360] Insertion at an allylic carbon of alkenes has been reported.[361] Insertion into a 2-pyrrolidinone derivative using $Me_3SiCH_2N_2$ followed by $AgCO_2Ph$ with ultrasound gave a

[349]Kirmse, W.; Doering, W. von E. *Tetrahedron* ***1960***, *11*, 266; Friedman, L.; Berger, J.G. *J. Am. Chem. Soc*. ***1961***, *83*, 492, 500. See Padwa, A.; Krumpe, K.E. *Tetrahedron* ***1992***, *48*, 5385.

[350]For a review of the intramolecular insertions of carbenes or carbenoids generated from diazocarbonyl compounds, see Burke, S.D.; Grieco, P.A. *Org. React*. ***1979***, *26*, 361.

[351]Doering, W. von E.; Knox, L.H. *J. Am. Chem. Soc*. ***1961***, *83*, 1989.

[352]Carter, D.S.; Van Vranken, D.L. *Org. Lett*. ***2000***, *2*, 1303; Kirmse, W.; Kapps, M. *Chem. Ber*. ***1968***, *101*, 994; Doyle, M.P.; Griffin, J.H.; Chinn, M.S.; van Leusen, D. *J. Org. Chem*. ***1984***, *49*, 1917; Doyle, M.P.; McKervey, M.A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*, Wiley,NY, ***1998***; Meyer, O.; Cagle, P.C.; Weickhardt, K.; Vichard, D.; Gladysz, J.A. *Pure Appl. Chem*. ***1996***, *68*, 79.

[353]Bertram, A.K.; Liu, M.T.H. *J. Chem. Soc. Chem. Commun*. ***1993***, 467.

[354]For example, see Parham, W.E.; Koncos, R. *J. Am. Chem. Soc*. ***1961***, *83*, 4034; Fields, E.K. *J. Am. Chem. Soc*. ***1962***, *82*, 1744; Anderson, J.C.; Lindsay, D.G.; Reese, C.B. *J. Chem. Soc*. ***1964***, 4874; Seyferth, D.; Cheng, Y.M. *J. Am. Chem. Soc*. ***1973***, *95*, 6763; *Synthesis* ***1974***, 114; Steinbeck, K. *Tetrahedron Lett*. ***1978***, 1103; Boev, V.I. *J. Org. Chem. USSR* ***1981***, *17*, 1190.

[355]Matusamy, S.; Arulananda, S.; Babu, A.; Gunanathan, C. *Tetrahedron Lett*. ***2002*** *43*, 3133.

[356]Particularly the C–H insertion reaction, see Sulikowski, G.A.; Cha, K.L.; Sulikowski, M.M. *Tetrahedron Asymmetry*, ***1998***, *9*, 3145; Taber, D.F.; Meagley, R.P. *Tetrahedron Lett*. ***1994***, *35*, 7909.

[357]Ye, T.; McKervey, M.A. *Chem. Rev*. ***1994***, *94*, 1091.

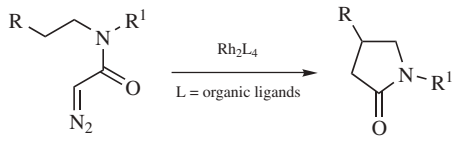
[358]Doyle, M.P. *Pure Appl. Chem*. ***1998***, *70*, 1123. See Taber, D.F.; Malcolm, S.C. *J. Org. Chem*. ***1998***, *63*, 3717 for a discussion of transition state geometry in rhodium mediated C—H insertion.

[359]Davies, H.M.; Hansen, T.; Churchill, M.R. *J. Am. Chem. Soc*. ***2000***, *122*, 3063; Davies, H.M.L.; Jin, Q.; Ren, P.; Kovalensky, A.Yu. *J. Org. Chem*. ***2002***, *67*, 4165; Davies, H.M.L.; Beckwith, R.E.J.; Antoulinakis, E.G.; Jin, Q. *J. Org. Chem*. ***2003***, *68*, 6126; Davies, H.M.L.; Jin, Q. *Org. Lett*. ***2004***, *6*, 1769. For a review, see Davies, H.M.L.; Loe, Ø. *Synthesis* ***2004***, 2595.

[360]For a review, see Davies, H.M.L.; Beckwith, R.E.J. *Chem. Rev*. ***2003***, *103*, 2861.

[361]Davies, H.M.L.; Ren, P.; Jin, Q. *Org. Lett*. ***2001***, *3*, 3587.

2-piperidone derivative.[362] The copper-catalyzed insertion of a diazo ester into an oxetane gives the ring-expanded tetrahydrofuran derivative.[363] Dirhodium catalyzed insertion into H–C^{sp2} bonds is also known,[364] and also H–C^{sp} bonds.[365] Insertion of diazoalkane and diazocarbonyl compounds can be catalyzed by copper compounds[366] and silver compounds[367] as well. Intramolecular insertion reactions are well known, and tolerate a variety of functional groups.[368] Intramolecular insertion at the α-carbon of a ketone by a diazoketone, using $TiCl_4$, gives a bicyclic 1,3-diketone.[369] A typical example is the insertion of the diazocarbonyl unit into the C–H bond to give the lactam.[370] Similar insertion at the α-carbon of an ether leads to cyclic ethers, with high enantioselectivity when a chiral ligand is used with a rhodium catalyst.[371] Similar insertion at the α-carbon of silyl ethers has been reported.[372] Aryl ketenes react with Me_3SiCHN_2 and then silica to give 2-indanone derivatives.[373]

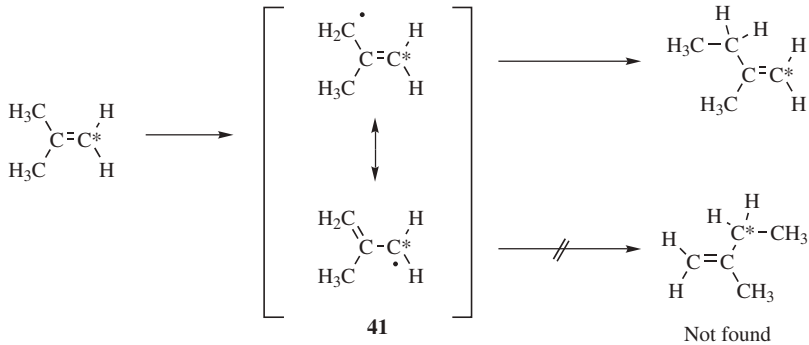


The mechanism[374] of the insertion reaction is not known with certainty, but there seem to be at least two possible pathways.

[362]Coutts, I.G.C.; Saint, R.E.; Saint, S.L.; Chambers-Asman, D.M. *Synthesis* ***2001***, 247.
[363]Lo, M.M.-C.; Fu, G.C. *Tetrahedron* ***2001***, *57*, 2621.
[364]Gibe, R.; Kerr, M.A. *J. Org. Chem.* ***2002***, *67*, 6247.
[365]Arduengo III, A.J.; Calabrese, J.C.; Davidson, F.; Dias, H.V.R.; Goerlich, J.R.; Krafczyk, R.; Marshall, W.J.; Tamm, M.; Schmutzler, R. *Helv. Chim. Acta.* ***1999***, *82*, 2348.
[366]See Caballero, A.; Díaz-Requejo, M.M.; Belderraín, T.R.; Nicasio, M.C.; Trofimenko, S.; Pérez, P. J. *J. Am. Chem. Soc*. ***2003***, *125*, 1446.
[367]Dias, H.V.R.; Browning, R.G.; Polach, S.A.; Diyabalanage, H.V.K.; Lovely, C.J. *J. Am. Chem. Soc*. ***2003***, *125*, 9270.
[368]For examples, see Marmsäter, F.P.; Murphy, G.K.; West, F.G. *J. Am. Chem. Soc*. ***2003***, *125*, 14724; Müller, P.; Polleux, P. *Helv. Chim. Acta* ***1994***, *77*, 645; Doyle, M.P.; Kalinin, A.V. *Synlett*, ***1995***, 1075; Watanabe, N.; Ohtake, Y.; Hashimoto, S.; Shiro, M.; Ikegami, S. *Tetrahedron Lett*. ***1995***, *36*, 1491; Maruoka, K.; Concepcion, A.B.; Yamamoto, H. *J. Org. Chem*. ***1994***, *59*, 4725; Spero, D.M.; Adams, J. *Tetrahedron Lett*. ***1992***, *33*, 1143.
[369]Muthusamy, S.; Babu, S.A.; Gunanathan, C. *Synth. Commun*. ***2001***, *31*, 1205.
[370]Doyle, M.P.; Protopopova, M.N.; Winchester, W.R.; Daniel, K.L. *Tetrahedron Lett*. ***1992***, *33*, 7819. See also, Wang, J.; Hou, Y.; Wu, P. *J. Chem. Soc., Perkin Trans. 1* ***1999***, 2277; Clark, J.S.; Hodgson, P.B.; Goldsmith, M.D.; Street, L.J. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 3312. For a related reaction, see Yang, H.; Jurkauskas, V.; Mackintosh, N.; Mogren, T.; Stephenson, C.R.J.; Foster, K.; Brown, W.; Roberts, E. *Can. J. Chem*. ***2000***, *78*, 800.
[371]Davies, H.M.L.; Grazini, M.V.A.; Aouad, E. *Org. Lett*. ***2001***, *3*, 1475.
[372]Yoon, C.H.; Zaworotko, M.J.; Moulton, B.; Jung, K.W. *Org. Lett*. ***2001***, *3*, 3539.
[373]Dalton, A.M.; Zhang, Y.; Davie, C.P.; Danheiser, R.L. *Org. Lett*. ***2002***, *4*, 2465.
[374]For a discussion, see Bethell, D. *Adv. Phys. Org. Chem*. ***1969***, *7*, 153, pp. 190–194.

1. A simple one-step process involving a three-center cyclic transition state:

The most convincing evidence for this mechanism is that in the reaction between isobutene-1-^{14}C and carbene the product 2-methyl-1-butene was labeled only in the 1 position.[375] This rules out a free radical or a carbocation or carbanion intermediate. If **41** (or a corresponding ion) were an intermediate, resonance would ensure that some carbene attacked at the 1 position:



Other evidence is that retention of configuration, which is predicted by this mechanism, has been found in a number of instances.[376] An ylid intermediate was trapped in the reaction of $:CH_2$ with allyl alcohol.[377]

2. A free-radical process in which the carbene directly abstracts a hydrogen from the substrate to generate a pair of free radicals:

$$RH + CH_2 \longrightarrow R\bullet + \bullet CH_3$$
$$R\bullet + \bullet CH_3 \longrightarrow RCH_3$$

One fact supporting this mechanism is that among the products obtained (beside butane and isobutane) on treatment of propane with CH_2 (generated by photolysis of diazomethane and ketene) were propene and ethane,[378] which could arise, respectively, by

$$2\,CH_3CH_2CH_2\bullet \longrightarrow CH_3CH{=}CH_2 + CH_3CH_2CH_3 \quad \text{(disproportionation)}$$

[375]Doering, W. von E.; Prinzbach, H. *Tetrahedron* ***1959***, *6*, 24.
[376]See, for example, Kirmse, W.; Buschhoff, M. *Chem. Ber.* ***1969***, *102*, 1098; Seyferth, D.; Cheng, Y.M. *J. Am. Chem. Soc*. ***1971***, *93*, 4072.
[377]Sobery, W.; DeLucca, J.P. *Tetrahedron Lett*. ***1995***, *36*, 3315.
[378]Frey, H.M. *Proc. Chem. Soc*. ***1959***, 318.

and

$$CH_3CH_2CH_3 + :CH_2 \longrightarrow CH_3CH_2CH_2\bullet + \bullet CH_3$$
$$2 \bullet CH_3 \longrightarrow CH_3CH_3$$

That this mechanism can take place under suitable conditions has been demonstrated by isotopic labeling[379] and by other means.[380] However, the formation of disproportionation and dimerization products does not always mean that the free-radical abstraction process takes place. In some cases, these products arise in a different manner.[381] We have seen that the product of the reaction between a carbene and a molecule may have excess energy (p. 288). Therefore it is possible for the substrate and the carbene to react by mechanism 1 (the direct-insertion process) and for the excess energy to cause the compound thus formed to cleave to free radicals. When this pathway is in operation, the free radicals are formed *after* the actual insertion reaction.

The mechanism of cyclopropylcarbene reactions has also been discussed.[382]

It has been suggested[383] that singlet carbenes insert by the one-step direct-insertion process and triplets (which, being free radicals, are more likely to abstract hydrogen) by the free-radical process. In support of this suggestion is that CIDNP signals[384] (p. 269) were observed in the ethylbenzene produced from toluene and triplet CH_2, but not from the same reaction with singlet CH_2.[385] Carbenoids (e.g., compounds of the form R_2CMCl, see **12-39**) can insert into a C–H bond by a different mechanism, similar to pathway 2, but involving abstraction of a hydride ion rather than a hydrogen atom.[386]

An interesting insertion reaction involves $EtZnCH_2I$ and β-keto carbonyl compounds. The reaction of this reagent with *N,N*-dibutyl-**3**-oxobutanamide, for example, gives the methylene insertion product *N,N*-dibutyl 4-oxopentanamide.[387]

The reaction in which aldehydes are converted to methyl ketones, $RCHO + CH_2N_2 \rightarrow RCOCH_3$, while apparently similar, does not involve a free carbene intermediate. It is considered in Chapter 18 (**18-9**).

OS **VII**, 200.

[379]Halberstadt, M.L.; McNesby, J.R. *J. Chem. Phys.* ***1966***, *45*, 1666; McNesby, J.R.; Kelly, R.V. *Int. J. Chem. Kinet.*, ***1971***, *3*, 293.
[380]Ring, D.F.; Rabinovitch, B.S. *J. Am. Chem. Soc.* ***1966***, *88*, 4285; *Can J. Chem.* ***1968***, *46*, 2435.
[381]Bell, J.A. *Prog. Phys. Org. Chem.* ***1964***, *2*, 1, pp. 30–43.
[382]Cummins, J.M.; Porter, T.A.; Jones Jr., M. *J. Am. Chem. Soc.* ***1998***, *120*, 6473.
[383]Richardson, D.B.; Simmons, M.C.; Dvoretzky, I. *J. Am. Chem. Soc.* ***1961***, *83*, 1934.
[384]For a review of the use of CIDNP to study carbene mechanisms, see Roth, H.D. *Acc. Chem. Res.* ***1977***, *10*, 85.
[385]Roth, H.D. *J. Am. Chem. Soc.* ***1972***, *94*, 1761. See also Closs, G.L.; Closs, L.E. *J. Am. Chem. Soc.* ***1969***, *91*, 4549; Bethell, D.; McDonald, K. *J. Chem. Soc. Perkin Trans. 2* ***1977***, 671.
[386]See Oku, A.; Yamaura, Y.; Harada, T. *J. Org. Chem.* ***1986***, *51*, 3730; Ritter, R.H.; Cohen, T. *J. Am. Chem. Soc.* ***1986***, *108*, 3718.
[387]Hilgenkamp, R.; Zercher, C.K. *Tetrahedron* ***2001***, *57*, 8793.

F. Metal Electrophiles

12-22 Metalation With Organometallic Compounds

Metalation or **Metalo-de-hydrogenation**

$$RH + R'M \longrightarrow RM + R'M$$

Many organic compounds can be metalated by treatment with an organometallic compound.[388] Since the reaction involves a proton transfer, the equilibrium lies on the side of the weaker acid.[389] For example, fluorene reacts with butyllithium to give butane and 9-fluoryllithium. Since aromatic hydrocarbons are usually stronger acids than aliphatic ones, R is most often aryl. The most common reagent is butyllithium.[390] Normally, only active aromatic rings react with butyllithium. Benzene itself reacts very slowly and in low yield, although benzene can be metalated by butyllithium either in the presence of *t*-BuOK[391] or by *n*-butyllithium that is coordinated with various diamines.[392] Metalation of aliphatic RH is most successful when the carbanions are stabilized by resonance (allylic, benzylic, propargylic,[393] etc.) or when the negative charge is at an *sp* carbon (at triple bonds). Very good reagents for allylic metalation are trimethylsilylmethyl potassium Me_3SiCH_2K[394] and a combination of an organolithium compound with a bulky alkoxide (LICKOR superbase).[395] The former is also useful for benzylic positions. A combination of BuLi, *t*-BuOK, and tetramethylethylenediamine has been used to convert ethylene to vinylpotassium.[396] In certain cases, *gem*-dialkali metal or 1,1,1-trialkali metal compounds can be prepared.[397] Examples are the conversion of phenylacetonitrile

[388]For reviews, see Wardell, J.L., in Zuckerman,J.J. *Inorganic Reactions and Methods*, Vol. 11, VCH, NY, ***1988***, pp. 44–107; Wardell, J.L., in Hartley, F.R.; Patai, S. *The Chemistry of the Metal-Carbon Bond*, Vol. 4, Wiley, NY, pp. 1–157, 27–71; Narasimhan, M.S.; Mali, R.S. *Synthesis* ***1983***, 957; Biellmann, J.F.; Ducep, J. *Org. React.* ***1982***, *27*, 1; Gschwend, H.W.; Rodriguez, H.R. *Org. React.* ***1979***, *26*, 1; Mallan, J.M.; Bebb, R.L. *Chem. Rev.* ***1969***, *69*, 693.

[389]See Saá, J.M.; Martorell, G.; Frontera, A. *J. Org. Chem.* ***1996***, *61*, 5194 for a discussion of the mechanism of lithiation of aromatic species.

[390]For a review, see Durst, T., in Buncel, E.; Durst, T. *Comprehensive Carbanion Chemistry*, Vol. 5, pt. B, Elsevier, NY, ***1984***, pp. 239–291, 265–279. For an article on the safe handling of RLi compounds, see Anderson, R. *Chem. Ind. (London)* ***1984***, 205.

[391]Schlosser, M. *J. Organomet. Chem.* ***1967***, *8*, 9. See also, Schlosser, M.; Katsoulos, G.; Takagishi, S. *Synlett*, ***1990***, 747.

[392]Eberhardt, G.G.; Butte, W.A. *J. Org. Chem.* ***1964***, *29*, 2928; Langer, Jr., A.W. *Trans. N.Y. Acad. Sci.* ***1965***, *27*, 741; Eastham, J.F.; Screttas, C.G. *J. Am. Chem. Soc.* ***1965***, *87*, 3276; Rausch, M.D.; Ciappenelli, D.J. *J. Organomet. Chem.* ***1967***, *10*, 127.

[393]For a review of directive effects in allylic and benzylic metallation, see Klein, J. *Tetrahedron* ***1983***, *39*, 2733. For a review of propargylic metallation, see Klein, J., in Patai, S. *The Chemistry of the Carbon-Carbon Triple Bond*, pt. 1, Wiley, NY, ***1978***, pp. 343–379.

[394]Hartmann, J.; Schlosser, M. *Helv. Chim. Acta* ***1976***, *59*, 453.

[395]Schlosser, M. *Pure Appl. Chem.* ***1988***, *60*, 1627. For sodium analogs, see Schlosser, M.; Hartmann, J.; Stähle, M.; Kramăr, J.; Walde, A.; Mordini, A. *Chimia*, ***1986***, *40*, 306.

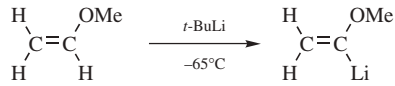
[396]Brandsma, L.; Verkruijsse, H.D.; Schade, C.; Schleyer, P.v.R. *J. Chem. Soc. Chem. Commun.* ***1986***, 260.

[397]For a review of di- and polylithium compounds, see Maercker, A.; Theis, M. *Top. Curr. Chem.* ***1987***, *138*, 1.

to 1,1-dilithiophenylacetonitrile ($PhCLi_2CN$)[398] and propyne to tetralithiopropyne ($Li_3CC{\equiv}CLi$)[399] in each case by treatment with excess butyllithium. The reaction can be used to determine relative acidities of very weak acids by allowing two R–H compounds to compete for the same R′M and to determine which proton in a molecule is the most acidic.[400]

In general, the reaction can be performed only with organometallics of active metals such as lithium, sodium, and potassium, but Grignard reagents abstract protons from a sufficiently acidic C–H bond, as in R–C≡C–H → R–C≡C–MgX. This is the best method for the preparation of alkynyl Grignard reagents.[401]

When a heteroatom, such as N, O, S,[402] or a halogen,[403] is present in a molecule containing an aromatic ring or a double bond, lithiation is usually quite regioselective.[404] The lithium usually bonds with the sp^2 carbon closest to the heteroatom, probably because the attacking species coordinates with the heteroatom.[405] Such reactions with compounds such as anisole are often called directed metalations.[406] In the case of aromatic rings this means attack at the ortho position,[407] but this is considered in **13-17**.



Ref. 408

[398]Kaiser, E.M.; Solter, L.E.; Schwartz, R.A.; Beard, R.D.; Hauser, C.R. *J. Am. Chem. Soc.* ***1971***, *93*, 4237. See also, Kowalski, C.J.; O'Dowd, M.L.; Burke, M.C.; Fields, K.W. *J. Am. Chem. Soc.* ***1980***, *102*, 5411.

[399]Priester, W.; West, R. *J. Am. Chem. Soc.* ***1976***, *98*, 8421, 8426, and references cited therein.

[400]For examples, see Broaddus, C.D.; Logan, T.J.; Flautt, T.J. *J. Org. Chem.* ***1963***, *28*, 1174; Finnegan, R.A.; McNees, R.S. *J. Org. Chem.* ***1964***, *29*, 3234; Shirley, D.A.; Hendrix, J.P. *J. Organomet. Chem.* ***1968***, *11*, 217.

[401]For a review of the synthetic applications of metallation by Grignard reagents at positions other than at triple bonds, see Blagoev, B.; Ivanov, D. *Synthesis* ***1970***, 615.

[402]For example, see Figuly, G.D.; Loop, C.K.; Martin, J.C. *J. Am. Chem. Soc.* ***1989***, *111*, 654; Block, E.; Eswarakrishnan, V.; Gernon, M.; Ofori-Okai, G.; Saha, C.; Tang, K.; Zubieta, J. *J. Am. Chem. Soc.* ***1989***, *111*, 658; Smith, K.; Lindsay, C.M.; Pritchard, G.J. *J. Am. Chem. Soc.* ***1989***, *111*, 665.

[403]Fluorine is an especially powerful ortho director in lithiation of aromatic systems: Gilday, J.P.; Negri, J.T.; Widdowson, D.A. *Tetrahedron* ***1989***, *45*, 4605.

[404]For a review of regioselective lithiation of heterocycles, see Katritzky, A.R.; Lam, J.N.; Sengupta, S. *Prog. Heterocycl. Chem.* ***1989***, *1*, 1.

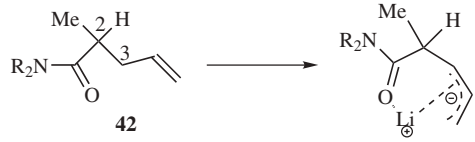
[405]For many examples with references, see Ref. 388; Beak, P.; Meyers, A.I. *Acc. Chem. Res.* ***1986***, *19*, 356; Beak, P.; Snieckus, V. *Acc. Chem. Res.* ***1982***, *15*, 306; Snieckus, V. *Bull. Soc. Chim. Fr.* ***1988***, 67; Narasimhan, N.S.; Mali, R.S. *Top. Curr. Chem.* ***1987***, *138*, 63; Reuman, M.; Meyers, A.I. *Tetrahedron* ***1985***, *41*, 837; and the papers in *Tetrahedron* ***1983***, *39*, 1955.

[406]Slocum, D.W.; Moon, R.; Thompson, J.; Coffey, D.S.; Li, J.D.; Slocum, M.G.; Siegel, A.; Gayton-Garcia, R. *Tetrahedron Lett.* ***1994***, *35*, 385; Slocum, D.W.; Coffey, D.S.; Siegel, A.; Grimes, P. *Tetrahedron Lett.* ***1994***, *35*, 389.

[407]For reviews of ortho metallation, see Snieckus, V. *Chem. Rev.* ***1990***, *90*, 879; *Pure Appl. Chem.* ***1990***, *62*, 2047. For a discussion of the mechanism, see Bauer, W.; Schleyer, P. v.R. *J. Am. Chem. Soc.* ***1989***, *111*, 7191.

[408]Baldwin, J.E.; Höfle, G.A.; Lever, Jr., O.W. *J. Am. Chem. Soc.* ***1974***, *96*, 7125.

In the case of γ,δ-unsaturated disubstituted amides (**42**),the lithium does not go to the closest position, but in this case too the regiochemistry is controlled



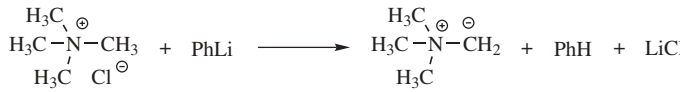
42

by coordination to the oxygen.[409]

The mechanism involves an attack by R′– (or a polar R′) on the *hydrogen*[410] (an acid–base reaction) Evidence is that resonance effects of substituents in R seem to make little difference. When R is aryl, OMe and CF_3 *both* direct ortho, while isopropyl directs meta and para (mostly meta).[411] These results are exactly what would be expected from pure field effects, with no contribution from resonance effects, which implies that attack occurs at the hydrogen and not at R. Other evidence for the involvement of H in the rate-determining step is that there are large isotope effects.[412] The nature of R′ also has an effect on the rate. In the reaction between triphenylmethane and R′Li, the rate decreased in the order R′ = allyl > Bu > Ph > vinyl > Me, although this order changed with changing concentration of R′Li, because of varying degrees of aggregation of the R′Li.

With respect to the reagent, this reaction is a special case of **12-24**.

A closely related reaction is formation of nitrogen ylids[414] from quaternary ammonium salts (see **17-8**):



Phosphonium salts undergo a similar reaction (see **16-44**).

OS **II**, 198; **III**, 413, 757; **IV**, 792; **V**, 751; **VI**, 436, 478, 737, 979; **VII**, 172, 334, 456, 524; **VIII**, 19, 391, 396, 606.

[409]Beak, P.; Hunter, J.E.; Jun, Y.M.; Wallin, A.P. *J. Am. Chem. Soc.* ***1987***, *109*, 5403. See also, Stork, G.; Polt, R.L.; Li, Y.; Houk, K.N. *J. Am. Chem. Soc.* ***1988***, *110*, 8360; Barluenga, J.; Foubelo, F.; Fañanas, F.J.; Yus, M. *J. Chem. Res. (S)* ***1989***, 200.

[410]Benkeser, R.A.; Trevillyan, E.A.; Hooz, J. *J. Am. Chem. Soc.* ***1962***, *84*, 4971.

[411]Bryce-Smith, D. *J. Chem. Soc.* ***1963***, 5983; Benkeser, R.A.; Hooz, J.; Liston, T.V.; Trevillyan, E.A. *J. Am. Chem. Soc.* ***1963***, *85*, 3984.

[412]Bryce-Smith, D.; Gold, V.; Satchell, D.P.N. *J. Chem. Soc.* ***1954***, 2743; Pocker, Y.; Exner, J.H. *J. Am. Chem. Soc.* ***1968***, *90*, 6764.

West, P.; Waack, R.; Purmort, J.I. *J. Am. Chem. Soc.* ***1970***, *92*, 840.

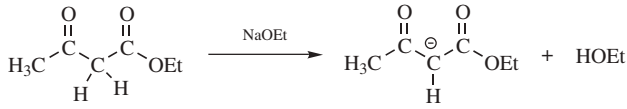
[414]Zugravescu, I.; Petrovanu, M. *Nitrogen-Ylid Chemistry*, McGraw-Hill, NY, ***1976***, pp 251–283; Kröhnke, F. *Berchtt* ***1935***, *68*, 1177; Wittig, G.; Wetterling, M. *Ann.* ***1947***, *557*, 193; Wittig, G.; Rieber, M. *Ann.* ***1949***, *562*, 177; Wittig, G.; Polster, R. *Ann.* ***1956***, *599*, 1.

12-23 Metalation With Metals and Strong Bases

Metalation or **Metalo-de-hydrogenation**

$$2\ RH + M \longrightarrow 2\ RM + H_2$$

Organic compounds can be metalated at suitably acidic positions by active metals and by strong bases.[415] The reaction has been used to study the acidities of very weak acids (see p. 250). The conversion of terminal alkynes to acetylid ions is one important application.[416] Synthetically, an important use of the method is to convert aldehydes and ketones,[417] carboxylic esters, and similar compounds to their enolate forms,[418] for example,



for use in nucleophilic substitutions (**10-67**, **10-68**, and **13-14**) and in additions to multiple bonds (**15-24** and **16-53**). It has been shown that lithiation with lithium amides can also be regioselective (see **12-22**).[419] Lithium enolates exist as aggregates in solution.[420] For very weak acids, the most common reagents for synthetic purposes are lithium amides, especially LDA, which has the structure $(i\text{Pr})_2\text{NLi}$.[421] The mechanism for this deprotonation reaction has been studied,[422] as has the rate of deprotonation.[423]

OS **I**, 70, 161, 490; **IV**, 473; **VI**, 468, 542, 611, 683, 709; **VII**, 229, 339. Conversions of ketones or esters to enolates are not listed.

[415]For a review, see Durst, T., in Buncel, E.; Durst, T. *Comprehensive Carbanion Chemistry*, Vol. 5, pt. B, Elsevier, NY, ***1984***, pp. 239–291. For reviews with respect to lithium, see Wardell, J.L. Ref. 388; Wakefield, B.J. *Organolithium Methods*, Academic Press, NY, ***1988***, pp. 32–44.

[416]For a review, see Ziegenbein, W., in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 170–185. For an improved method, see Fisch, A.; Coisne, J.M.; Figeys, H.P. *Synthesis* ***1982***, 211.

[417]Hegarty, A.F.; Dowling, J.P.; Eustace, S.J.; McGarraghy, M. *J. Am. Chem. Soc*. ***1998***, *120*, 2290.

[418]For a review, see Caine, D. in Augustine, R.L. *Carbon–Carbon Bond Formation*, Vol. 1, Marcel Dekker, NY,***1979***, pp. 95–145, 284–291.

[419]For example, see Comins, D.L.; Killpack, M.O. *J. Org. Chem*. ***1987***, *52*, 104. See Xie, L.; Isenberger, K.M.; Held, G.; Dahl, M. *J. Org. Chem*. ***1997***, *62*, 7516 for steric versus electronic effects in kinetic enolate formation.

[420]Abu-Hasanayn, F.; Stratakis, M.; Streitwieser, A. *J. Org. Chem*. ***1995***, *60*, 4688; Jackman, L.M.; Szeverenyi, N.M. *J. Am. Chem. Soc*. ***1977***, *99*, 4954; Jackman, L.M.; Lange, B.C. *J. Am. Chem. Soc*. ***1981***, *103*, 4494; House, H.O.; Gall, M.; Olmstead, H.D. *J. Org. Chem*. ***1971***, *36*, 2361; Zook, H.D.; Kelly, W.L.; Posey, I.Y. *J. Org. Chem*. ***1968***, *33*, 3477; Stork, G.; Hudrlik, P.F. *J. Am. Chem. Soc*. ***1968***, *90*, 4464.

[421]The alkali metal hydrides, LiH, NaH, and KH, when prepared in a special way, are very rapid metallation agents: Klusener, P.A.A.; Brandsma, L.; Verkruijsse, H.D.; Schleyer, P.v.R.; Friedl, T.; Pi, R. *Angew. Chem. Int. Ed*. ***1986***, *25*, 465.

[422]Romesberg, F.E.; Collum, D.B. *J. Am. Chem. Soc*. ***1995***, *117*, 2166; Sun, X.; Kenkre, S.L.; Remenar, J.F.; Gilchrist, J.H. *J. Am. Chem. Soc*. ***1997***, *119*, 4765.

[423]Majewski, M.; Nowak, P. *Tetrahedron Lett*. ***1998***, *39*, 1661.

METALS AS LEAVING GROUPS

A. Hydrogen as the Electrophile

12-24 Replacement of Metals by Hydrogen

Hydro-de-metallation or **Demetallation**

$$RM + HA \longrightarrow RH + MA$$

Organometallic compounds, including enolate anions, react with acids in reactions in which the metal is replaced by hydrogen.[424] The R group may be aryl (see **11-41**). The reaction is often used to introduce deuterium or tritium into susceptible positions. For Grignard reagents, water is usually a strong enough acid, but stronger acids are also used. An important method for the reduction of alkyl halides consists of the process RX → RMgX → RH.

Other organometallic compounds that are hydrolyzed by water are those of sodium, potassium, lithium, zinc, and so on, the ones high in the electromotive series. Enantioselective protonation of lithium enolates[425] and cyclopropyllithium compounds[426] have been reported. When the metal is less active, stronger acids are required. For example, R_2Zn compounds react explosively with water, R_2Cd slowly, and R_2Hg not at all, although the latter can be cleaved with concentrated HCl. However, this general statement has many exceptions, some hard to explain. For example, BR_3 compounds are completely inert to water, and GaR_3 at room temperature cleave just one R group, but AlR_3 react violently with water. However, BR_3 can be converted to RH with carboxylic acids.[427] For less active metals it is often possible to cleave just one R group from a multivalent metal. For example,

$$R_2Hg + HCl \longrightarrow RH + RHgCl$$

Organometallic compounds of less active metals and metalloids (e.g., silicon,[428] antimony, and bismuth, are quite inert to water. Organomercury compounds (RHgX or R_2Hg) can be reduced to RH by H_2, $NaBH_4$, or other reducing agents.[429] The reduction with $NaBH_4$ takes place by a free-radical mechanism.[430] Alkyl–Si

[424]For reviews, see Abraham, M.H.; Grellier, P.L., in Hartley, FR.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 2, Wiley, NY, pp. 25–149, 105–136; Abraham, M.H. *Comprehensive Chemical Kinetics*, Bamford, C.H.; Tipper, C.F.H., eds., Vol. 12, Elsevier, NY, ***1973***, pp. 107–134; Jensen, F.R.; Rickborn, B. *Electrophilic Substitution of Organomercurials*, McGaw-Hill, NY, ***1968***, pp. 45–74; Schlosser, M. *Angew. Chem. Int. Ed*. ***1964***, *3*, 287, 362; *Newer Methods Prep. Org. Chem*. ***1968***, *5*, 238.
[425]Fehr, C. *Angew. Chem. Int. Ed*. ***1996***, *35*, 2567.
[426]Walborsky, H.M.; Ollman, J.; Hamdouchi, C.; Topolski, M. *Tetrahedron Lett*. ***1992***, *33*, 761.
[427]Brown, H.C.; Murray, K.J. *Tetrahedron* ***1986***, *42*, 5497; Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, ***1988***, pp. 242–244.
[428]For a review of hydro-de-silylation of allylic and vinylic silanes, see Fleming, I.; Dunoguès, J.; Smithers, R. *Org. React*. ***1989***, *37*, 57, see pp. 89–97, 194–243. Also see, **10-12**
[429]For a review, see Makarova, L.G. *Organomet. React*. ***1970***, *1*, 119, see pp. 251–270, 275–300.
[430]For a review of this and other free-radical reactions of organomercury compounds, see Barluenga, J.; Yus, M. *Chem. Rev*. ***1988***, *88*, 487.

bonds can be cleaved by H_2SO_4, for example, $HOOCCH_2CH_2SiMe_3 \rightarrow 2\ CH_4 + (HOOCCH_2CH_2SiMe_2)_2O$.[431]

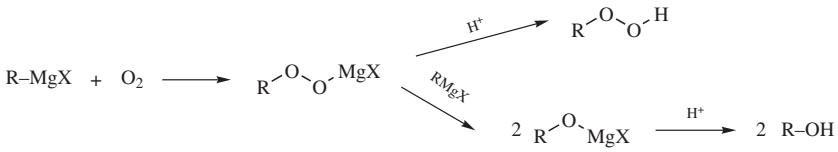
When the hydrogen of the HA is attached to carbon, this reaction is the same as **12-22**.

We do not list the many hydrolyses of sodium or potassium enolates, and so on found in *Organic Syntheses*. The hydrolysis of a Grignard reagent to give an alkane is found at OS **II**, 478; the reduction of a vinylic tin compound at OS **VIII**, 381; and the reduction of an alkynylsilane at OS **VIII**, 281.

B. Oxygen Electrophiles

12-25 The Reaction between Organometallic Reagents and Oxygen[432]

Hydroperoxy-de-metalation; Hydroxy-de-metalation



Oxygen reacts with Grignard reagents to give either hydroperoxides[433] or alcohols. The reaction can be used to convert alkyl halides to alcohols without side reactions. With aryl Grignard reagents yields are lower and only phenols are obtained, not hydroperoxides. Because of this reaction, oxygen should be excluded when Grignard reagents are prepared and used in various reactions.

Most other organometallic compounds also react with oxygen. Trialkylboranes and alkyldichloroboranes $RBCl_2$ can be conveniently converted to hydroperoxides by treatment with oxygen followed by hydrolysis.[434] Dilithiated carboxylic acids (see **10-70**) react with oxygen to give (after hydrolysis) α-hydroxy carboxylic acids.[435] There is evidence that the reaction between Grignard reagents and oxygen involves a free-radical mechanism.[436]

The 1,1-dimetallic compounds $R_2C(SnMe_3)ZnBr$ were oxidized by dry air at -10 to 0°C in the presence of Me_3SiCl to give aldehydes or ketones $R_2C{=}O$.[437]

OS **V**, 918. See also, OS **VIII**, 315.

[431]Sommer, L.H.; Marans, N.S.; Goldberg, G.M.; Rockett, J.; Pioch, R.P. *J. Am. Chem. Soc.* ***1951***, *73*, 882. See also, Abraham, M.H.; Grellier, P.L., in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 2, Wiley, NY, p. 117.

[432]For a monograph, see Brilkina, T.G.; Shushunov, V.A. *Reactions of Organometallic Compounds with Oxygen and Peroxides*, CRC Press, Boca Raton, FL, ***1969***. For a review, see Wardell, J.L.; Paterson, E.S., in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 2, Wiley, NY, ***1985***, pp. 219–338, see pp. 311–316.

[433]For the preparation of propargyl hydroperoxides, see Harada, T.; Kutsuwa, E. *J. Org. Chem.* ***2003***, *68*, 6716.

[434]Brown, H.C.; Midland, M.M. *Tetrahedron* ***1987***, *43*, 4059.

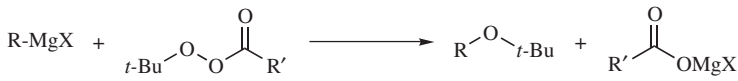
[435]Moersch, G.W.; Zwiesler, M.L. *Synthesis* ***1971***, 647; Adam, W.; Cueto, O. *J. Org. Chem.* ***1977***, *42*, 38.

[436]Davies, A.G.; Roberts, B.P. *J. Chem. Soc. B*, ***1969***, 317; Walling, C.; Cioffari, A. *J. Am. Chem. Soc.* ***1970***, *92*, 6609; Garst, J.F.; Smith, C.D.; Farrar, A.C. *J. Am. Chem. Soc.* ***1972***, *94*, 7707. For a review, see Davies, A.G. *J. Organomet. Chem.* ***1980***, *200*, 87.

[437]Knochel, P.; Xiao, C.; Yeh, M.C.P. *Tetrahedron Lett.* ***1988***, *29*, 6697.

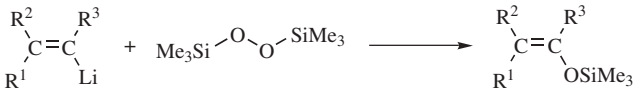
12-26 Reaction between Organometallic Reagents and Peroxides

tert-But**oxy-de-metalation**



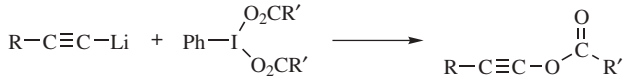
A convenient method of preparation of *tert*-butyl ethers consists of treating Grignard reagents with *tert*-butyl acyl peroxides.[438] Both alkyl and aryl Grignard reagents can be used. The application of this reaction to Grignard reagents prepared from cyclopropyl halides permits cyclopropyl halides to be converted to *tert*-butyl ethers of cyclopropanols,[439] which can then be easily hydrolyzed to the cyclopropanols. The direct conversion of cyclopropyl halides to cyclopropanols by **10-1** is not generally feasible, because cyclopropyl halides do not generally undergo nucleophilic substitutions without ring opening.

Vinylic lithium reagents (**43**) react with silyl peroxides to give high yields of silyl enol ethers with retention of configuration.[440] Since the preparation of **43** from vinylic halides



43

(**12-39**) also proceeds with retention, the overall procedure is a method for the stereospecific conversion of a vinylic halide to a silyl enol ether. In a related reaction, alkynyl esters can be prepared from lithium acetylides and phenyliodine(III) dicarboxylates.[441]



OS **V**, 642, 924.

12-27 Oxidation of Trialkylboranes to Borates

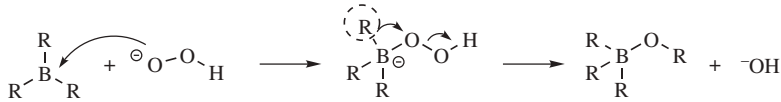
[438]Lawesson, S.; Frisell, C.; Denney, D.B.; Denney, D.Z. *Tetrahedron* ***1963***, *19*, 1229. For a monograph on the reactions of organometallic compounds with peroxides, see Brilkina, T.G.; Shushunov, V.A. *Reactions of Organometallic Compounds with Oxygen and Peroxides*, CRC Press, Boca Raton, FL, ***1969***. For a review, see Razuvaev, G.A.; Shushunov, V.A.; Dodonov, V.A.; Brilkina, T.G., in Swern, D. *Organic Peroxides*, Vol. 3, Wiley, NY, ***1972***, pp. 141–270.

[439]Longone, D.T.; Miller, A.H. *Tetrahedron Lett*. ***1967***, 4941.

[440]Davis, F.A.; Lal, G.S.; Wei, J. *Tetrahedron Lett*. ***1988***, *29*, 4269.

[441]Stang, P.J.; Boehshar, M.; Wingert, H.; Kitamura, T. *J. Am. Chem. Soc*. ***1988***, *110*, 3272.

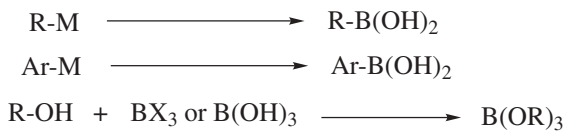
The reaction of alkenes with borane, monoalkyl and dialkylboranes leads to a new organoborane (see **15-16**). Treatment of organoboranes with alkaline H_2O_2 oxidizes trialkylboranes to esters of boric acid.[442] This reaction does not affect double or triple bonds, aldehydes, ketones, halides, or nitriles that may be present elsewhere in the molecule. There is no rearrangement of the R group itself, and this reaction is a step in the hydroboration method of converting alkenes to alcohols (**15-16**). The mechanism has been formulated as involving initial formation of an ate complex when the hydroperoxide anion attacks the electrophilic boron atom. Subsequent rearrangement from boron to oxygen,[442] as shown, leads to the B–O–R unit.



Similar migration of the other two R groups and hydrolysis of the B–O bonds leads to the alcohol and boric acid. Retention of configuration is observed in R. Boranes can also be oxidized to borates in good yields with oxygen,[443] with sodium perborate $NaBO_3$,[444] and with trimethylamine oxide, either anhydrous[445] or in the form of the dihydrate.[446] The reaction with oxygen is free radical in nature.[447]

OS **V**, 918; **VI**, 719, 852, 919.

12-28 Preparation of Borates and Boronic Acids



Alkylboronic acids and arylboronic acids, $RB(OH)_2$, and $ArB(OH)_2$, respectively, are increasingly important in organic chemistry. The palladium catalyzed coupling reaction of aryl halides and aryl triflates with arylboronic acids (the Suzuki–Miyaura

[442]For reviews, see Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Aademic Press, NY, ***1988***, pp. 244–249; Brown, H.C. *Boranes in Organic Chemistry*; Cornell University Press, Ithaca, NY, ***1972***, pp. 321–325; Matteson, D.S., in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 4, Wiley, NY, pp. 307–409, 337–340. See also, Brown, H.C.; Snyder, C.; Subba Rao, B.C.; Zweifel, G. *Tetrahedron* ***1986***, *42*, 5505.

[443]Brown, H.C.; Midland, M.M.; Kabalka, G.W. *J. Am. Chem. Soc*. ***1971***, *93*, 1024; *Tetrahedron* ***1986***, *42*, 5523.

[444]Kabalka, G.W.; Shoup, T.M.; Goudgaon, N.M. *J. Org. Chem*. ***1989***, *54*, 5930.

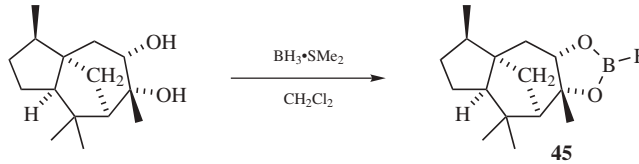
[445]Köster, R.; Arora, S.; Binger, P. *Angew. Chem. Int. Ed*. ***1969***, *8*, 205.

[446]Kabalka, G.W.; Hedgecock, Jr., H.C. *J. Chem. Educ*. ***1975***, *52*, 745; Kabalka, G.W.; Slayden, S.W. *J. Organomet. Chem*. ***1977***, *125*, 273.

[447]Mirviss, S.B. *J. Am. Chem. Soc*. ***1961***, *83*, 3051; *J. Org. Chem*. ***1967***, *32*, 1713; Davies, A.G.; Roberts, B.P. *Chem. Commun*. ***1966***, 298; Midland, M.M.; Brown, H.C. *J. Am. Chem. Soc*. ***1971***, *93*, 1506.

reaction, **13-12**) is probably the most notable example. A simple synthesis involve the reaction of a Grignard reagent, such as phenylmagnesium bromide with an alkyl borate to give phenylboronic acid.[448] Alkylboronic acids are similarly prepared.[449] Note that boronic acids are subject to cyclic trimerization with loss of water to form boroxines. Trimethylborate, $B(OMe)_3$, can be used in place of tri-*n*-butyl borate.[450] Newer methods involve the palladium-mediated borylation of alcohols with bis(pinacolato)diboron[451] or pinacolborane,[452] but deprotection of the boronate esters can be a problem. Diolboranes, such as catecholborane **44**,[453] are prepared by the reaction of a diol with borane. Cedranediolborane (**45**, prepared from the cedrane-8,9-diol[454] by treatment with borane•dimethyl sulfide) can be coupled to aryl iodides with a palladium catalyst, and generates the free boronic acid by treatment with diethanolamine and then aqueous acid.[455] Boronate esters are often prepared as a means to purify the organoboron species, but some of these esters are hydrolytically unstable and difficult to deal with upon completion of the reaction.[456]

44



45

Alkeneboronic esters and acids are also readily available, as in the addition of vinylmagnesium chloride[457] to trimethyl borate below −50°C, followed by hydrolysis.[458]

[448]Bean, F.R.; Johnson, J.R. *J. Am. Chem Soc*. ***1932***, *54*, 4415. For a review, see Lappert, M.F. *Chem. Rev.* ***1956***, *56*, 959.
[449]Khotinsky, E.; Melamed, M. *Chem. Ber.* ***1909***, *42*, 3090.
[450]Soloway, A.H. *J. Am. Chem. Soc*. ***1959***, *81*, 3017.
[451]Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem*. ***1995***, *60*, 7508.
[452]Murata, M.; Oyama, T.; Watanabe, S.; Masuda, Y. *J. Org. Chem*. ***2000***, *65*, 164; Song, Y.L. *Synlett* ***2000***, 1210.
[453]Brown, H.C.; Gupta, S.K. *J. Am. Chem. Soc*. ***1972***, *94*, 4370; Kanth, J. V. B.; Periasamy, M.; Brown, H.C. *Org. Process Res. Dev*. ***2000***, *4*, 550.
[454]Narula, A.S.; Trifilieff, E.; Bang, L.; Ourisson, G. *Tetrahedron Lett*. ***1977***, *18*, 3959; Song, Y.; Ding, Z.; Wang, Q.; Tao, F. *Synth. Commun*. ***1998***, *28*, 3757.
[455]Song, Y.-L.; Morin, C. *Synlett* ***2001***, 266.
[456]Lightfoot, A.P.; Maw, G.; Thirsk, C.; Twiddle, S.J.R.; Whiting, A. *Tetrahedron Lett*. ***2003***, *44*, 7645.
[457]Ramsden, H.E.; Leebrick, J.R.; Rosenberg, S.D.; Miller, E.H.; Walburn, J.J.; Balint, A.E.; Cserr, R. *J. Org, Chem*., ***1957***, *22*, 1602.
[458]D.S. Matteson *J. Am. Chem. Soc*. ***1960***, 82, 4228; Matteson, D.S. *Acc. Chem. Res*. ***1970***, *3*, 186; Matteson, D.S. *Progr. Boron Chem*. ***1970***, *3*, 117.

A nonaqueous workup procedure has been reproted for the preparation of arylboronic esters [ArB(OR'$_2$)].[459] Uncontrollable polymerization or oxidation of much of the boronic acid occurred during the final stages of the isolation procedure, but could be avoided by *in situ* conversion to the dibutyl ester by adding the crude product to 1-butanol. The samarium(III)-catalyzed hydroboration of olefins with catecholborane is a good synthesis of boronate esters.[460]

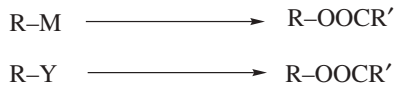
Trialkyl borates (called orthoborates) can be prepared by heating the appropriate alcohol with boron trichloride in a sealed tube, but the procedure works well only for relatively simple alkyl groups.[461] Heating alcohols with boron trioxide (B_2O_3) in an autoclave at 110–170°C give the trialkyl borate.[462] Boric acid can be used for the preparation of orthoborates[463] by heating with alcohols in the presence of either hydrogen chloride or concentrated sulfuric acid. Removal of water as an azeotrope with excess alcohol improves the yield,[464] and good yields can be obtained for trialkyl borates[465] and even for triphenyl borate.[466] This method is unsuccessful for those borates whose parent alcohols do not form azeotropes with water and for the tertiary alkyl borates,[467] impure samples are usually obtained.[468]

Potassium organotrifluoroborates (RBF_3K) are readily prepared by the addition of inexpensive KHF_2 to a variety of organoboron intermediates.[469] They are monomeric, crystalline solids that are readily isolated and indefinitely stable in the air. These reagents can be used in several of the applications where boronic acids or esters are used (**13-10–13-13**).[470] Note that vinylboronic acid and even vinylboronate esters are unstable to polymerization,[471] whereas the analogous vinyltrifluoroborate is readily synthesized and completely stable.[472]

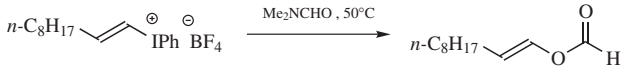
O.S. 13, 16; **81**, 134.

[459]Wong, K.-T.; Chien, Y.-Y.; Liao, Y.-L.; Lin, C.-C.; Chou, M.-Y.; Leung, M.-K. *J. Org. Chem.* ***2002***, *67*, 1041.
[460]Evans, D.A.; Muci, A.R.; Stuermer, R. *J. Org. Chem.*, ***1993***, *58*, 5307.
[461]Councler, C. *Ber.* ***1876***, *9*, 485; ***1877***, *10*, 1655; ***1878***, *11*, 1106.
[462]Schiff, H. *Ann. Suppl.* ***1867***, *6*, 158; Councler, C. *J. Prakt. Chem.* ***1871***, *16*, 371.
[463]Cohn, G. *Pharm. Zentr.* ***1911***, *62*, 479.
[464]Bannister, W.J. U.S. Patent 1,668,797 (*Chem. Abstr.* ***1928***, *22:*2172).
[465]Ballard, S.A, U.S. Patent 2,431,224 (*Chem. Abstr.* ***1948***, *42*:1960); Haider, S.Z.; Khundhar, M.H.; Siddiqulah, Md. *J. Appl. Chem.* ***1954***, *4*, 93; Scattergood, A.; Miller, W.H.; Gammon, J. *J. Am. Chem. Soc.* ***1945***, *67*, 2150; Wuyts, H.; Duquesne, A. *Bull. Soc. Chim. Belg.* ***1939***, *48*, 77.
[466]Colclough, T.; Gerrard, W.; Lappert, M.F. *J. Chem. Soc.* ***1955***, 907.
[467]Haider, S.Z.; Khundhar, M.H.; Siddiqullah, Md. *J. Appl. Chem.* ***1954***, *4*, 93; Scattergood, A., Miller, W.H.; Gammon, J. *J. Am. Chem. Soc.* ***1945***, *67*, 2150.
[468]Ahmad, T.; Khundkar, M.H. *Chem. Ind.* ***1954***, 248.
[469]Vedejs, E.; Chapman, R.W.; Fields, S.C.; Lin, S.; Schrimpf, M.R. *J. Org. Chem.* ***1995***, *60*, 3020; Vedejs, E.; Fields, S.C.; Hayashi, R.; Hitchcock, S.R.; Powell, D.R.; Schrimpf, M.R. *J. Am. Chem. Soc.* ***1999***, *121*, 2460.
[470]Molander, G.A.; Ito, T. *Org. Lett.* ***2001***, *3*, 393; Molander, G.A.; Biolatto, B. *Org. Lett.* ***2002***, *4*, 1867; Molander, G.A.; Biolatto, B. *J. Org. Chem.* ***2003***, *68*, 4302; Molander, G.A.; Katona, B.W.; Machrouhi, F. *J. Org. Chem.* ***2002***, *67*, 8416; Molander, G.A.; Yun, C.; Ribagorda, M.; Biolatto, B. *J. Org. Chem.* ***2003***, *68*, 5534; Molander, G.A.; Ribagorda, M. *J. Am. Chem. Soc.* ***2003***, *125*, 11148.
[471]Matteson, D.S. *J. Am. Chem. Soc.* ***1960***, *82*, 4228.
[472]Molander, G.A.; Felix, L.A. *J. Org. Chem.* ***2005***, *70*, 3950.

12-29 Oxygenation of Organometallic Reagents and Other Substrates to *O*-Esters and Related Compounds

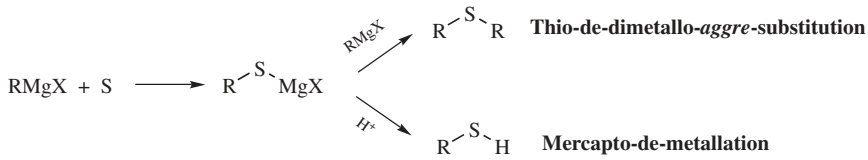


In some cases, it is possible to oxygenated a nonaromatic carbon atom using various reagents, where the product is an *O*- ester rather than an alcohol. In one example, a vinyl iodonium salt was heated with DMF to product the corresponding formate ester.[473]

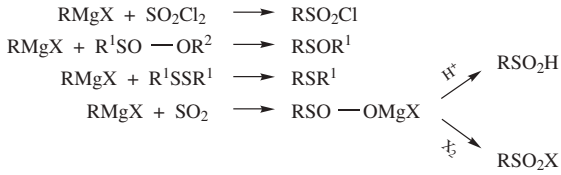


C. Sulfur Electrophiles

12-30 Conversion of Organometallic Reagents to Sulfur Compounds



Thiols and sulfides are occasionally prepared by treatment of Grignard reagents with sulfur.[474] Analogous reactions are known for selenium and tellurium compounds. Grignard reagents and other organometallic



compounds[475] react with sulfuryl chloride to give sulfonyl chlorides,[476] with esters of sulfinic acids to give (stereospecifically) sulfoxides,[477] with disulfides to give

[473]Ochiai, M.; Yamamoto, S.; Sato, K. *Chem. Commun.* ***1999***, 1363.

[474]For reviews of the reactions in this section, see Wardell, J.L.; Paterson, E.S., in Hartley, F.R.; Patai, S. *The Chemistry of the Metal-Carbon Bond*, Vol. 2, Wiley, NY, ***1985***, pp. 316–323; Wardell, J.L., in Patai, S. *The Chemistry of the Thiol Group*, pt. 1, Wiley, NY, ***1974***, pp. 211–215; Wakefield, B.J. *Organolithium Methods*, Academic Press, NY, ***1988***, pp. 135–142.

[475]For a discussion of conversions of organomercury compounds to sulfur-containing compounds, see Larock, R.C. *Organomercury Compounds in Organic Synthesis*, Springer, NY, ***1985***, pp. 210–216.

[476]Bhattacharya, S.N.; Eaborn, C.; Walton, D.R.M. *J. Chem. Soc. C* ***1968***, 1265. For similar reactions with organolithiums, see Quast, H.; Kees, F. *Synthesis* ***1974***, 489; Hamada, T.; Yonemitsu, O. *Synthesis* ***1986***, 852.

[477]Harpp, D.N.; Vines, S.M.; Montillier, J.P.; Chan, T.H. *J. Org. Chem.* ***1976***, *41*, 3987.

sulfides,[478] and with SO_2 to give sulfinic acid salts[479] which can be hydrolyzed to sulfinic acids or treated with halogens to give sulfonyl halides.[480]

OS **III**, 771; **IV**, 667; **VI**, 533, 979.

D. Halogen Electrophiles

12-31 Halo-de-metalation

$$RMgX + I_2 \longrightarrow RI + MgIX$$

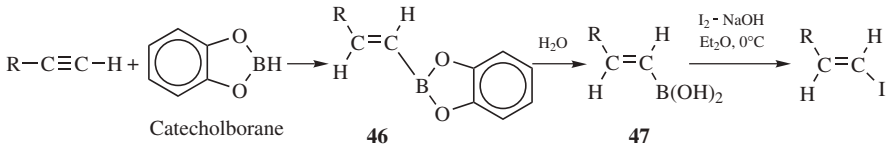
Grignard reagents react with halogens to give alkyl halides. The reaction is useful for the preparation of iodo compounds from the corresponding chloro or bromo compounds. The reaction is not useful for preparing chlorides, since the reagents RMgBr and RMgI react with Cl_2 to give mostly RBr and RI, respectively.[481]

Most organometallic compounds, both alkyl and aryl, also react with halogens to give alkyl or aryl halides.[482] The reaction can be used to convert acetylide ions to 1-haloalkynes.[483] Since acetylide ions are easily prepared from alkynes (**12-23**), this provides a means of accomplishing the conversion RC≡CH → RC≡CX. Vinyliodonium tetrafluoroborates were converted to vinyl fluorides by heating.[484] Similarly, vinyl trifluoroborates were converted to the vinyl iodide with NaI and chloramine-T in aq. THF.[485] The reaction of an alkene with CuO•BF4, iodine and triethylsilane gave the 2-iodo alkane.[486]

Trialkylboranes react rapidly with I_2[487] or Br_2[488] in the presence of NaOMe in methanol, or with $FeCl_3$ or other reagents[489] to give alkyl iodides, bromides, or chlorides, respectively. Combined with the hydroboration reaction (**15-16**), this is an indirect way of adding HBr, HI, or HCl to a double bond to give products with an

[478]For a discussion, see Negishi, E. *Organometallics in Organic Synthesis*, Wiley, NY, ***1980***, pp. 243–247.
[479]For a review of the reactions of organometallic compounds with SO_2, see Kitching, W.; Fong, C.W. *Organomet. Chem. Rev. Sect. A* ***1970***, *5*, 281.
[480]Asinger, F.; Laue, P.; Fell, B.; Gubelt, C. *Chem. Ber.* ***1967***, *100*, 1696.
[481]Zakharkin, L.I.; Gavrilenko, V.V.; Paley, B.A. *J. Organomet. Chem.* ***1970***, *21*, 269.
[482]For a review, see Abraham, M.H.; Grellier, P.L., in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 2, Wiley, NY, pp. 72–105. For reviews with respect to organomercury compounds, see Larock, R.C. *Organomercury Compounds in Organic Synthesis*, Springer, NY, ***1985***, pp. 158–178; Makarova, L.G. *Organomet. React*. ***1970***, *1*, 119, pp. 325–348.
[483]For a review, see Delavarenne, S.Y.; Viehe, H.G., in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 665–688. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 655–656. For an improved procedure, see Brandsma, L.; Verkruijsse, H.D. *Synthesis* ***1990***, 984.
[484]Okuyama, T.; Fujita, M.; Gronheid, R.; Lodder, G. *Tetrahedron Lett.* ***2000***, *41*. 5125.
[485]Kabalka, G.W.; Mereddy, A.R. *Tetrahedron Lett*. ***2004***, *45*, 1417.
[486]Campos, P.J.; García, B.; Rodríguez, M.A. *Tetrahedron Lett*. ***2002***, *43*, 6111.
[487]Brown, H.C.; Rathke, M.W.; Rogić, M.M.; De Lue, N.R. *Tetrahedron* ***1988***, *44*, 2751.
[488]Brown, H.C.; Lane, C.F. *Tetrahedron* ***1988***, *44*, 2763; Brown, H.C.; Lane, C.F.; De Lue, N.R. *Tetrahedron* ***1988***, *44*, 2273. For another reagent, see Nelson, D.J.; Soundararajan, R. *J. Org. Chem.* ***1989***, *54*, 340.
[489]Nelson, D.J.; Soundararajan, R. *J. Org. Chem.* ***1988***, *53*, 5664. For other reagents, see Jigajinni, V.B.; Paget, W.E.; Smith, K. *J. Chem. Res. (S)* ***1981***, 376; Brown, H.C.; De Lue, N.R. *Tetrahedron* ***1988***, *44*, 2785.

anti-Markovnikov orientation (see **15-1**). Trialkylboranes can also be converted to alkyl iodides by treatment with allyl iodide and air in a free-radical process.[490] *trans*-1-Alkenylboronic acids **47**, prepared by hydroboration of terminal alkynes with catecholborane to give **46**[491] (**15-16**), followed by hydrolysis, react with I_2 in the presence of NaOH at 0°C in ethereal solvents to give trans vinylic iodides.[492] Treatment with ICl also gives the vinyl iodide.[493] This is an indirect way of accomplishing the anti-Markovnikov addition of HI to a



terminal triple bond. The reaction cannot be applied to alkenylboronic acids prepared from internal alkynes. However, alkenylboronic acids prepared from both internal and terminal alkynes react with Br_2 (2 equivalents of Br_2 must be used) followed by base to give the corresponding vinylic bromide, but in this case with *inversion* of configuration; so the product is the cis vinylic bromide.[494] Alkenylboronic acids also give vinylic bromides and iodides when treated with a mild oxidizing agent and NaBr or NaI, respectively.[495] Treatment of **47** (prepared from terminal alkynes) with Cl_2 gave vinylic chlorides with inversion.[496] Vinylic boranes can be converted to the corresponding vinylic halide by treatment with NCS or NBS.[497] Vinylic halides can also be prepared from vinylic silanes[498] and from vinylic copper reagents. The latter react with I_2 to give iodides,[499] and with NCS or NBS at −45°C to give chlorides or bromides.[500] T

For the reaction of lithium enolate anions of esters with I_2 or CX_4, see **12-5**.

The conversion of terminal alkynes to 1-iodo-1-alkynes was reported using NaI under electrochemical conditions.[501] The reaction of an aryl alkyne with $HInCl_2/BEt_3$,

[490]Suzuki, A.; Nozawa, S.; Harada, M.; Itoh, M.; Brown, H.C.; Midland, M.M. *J. Am. Chem. Soc.* ***1971***, *93*, 1508. For reviews, see Brown, H.C.; Midland, M.M. *Angew. Chem. Int. Ed.* ***1972***, *11*, 692, pp. 699–700; Brown, H.C. *Boranes in Organic Chemistry*, Cornell Univ. Press, Ithica, NY, ***1972***, pp. 442–446.

[491]For a review of this reagent, see Kabalka, G.W. *Org. Prep. Proced. Int.* ***1977***, *9*, 131.

[492]Brown, H.C.; Hamaoka, T.; Ravindran, N.; Subrahmanyam, C.; Somayaji, V.; Bhat, N.G. *J. Org. Chem.* ***1989***, *54*, 6075. See also, Kabalka, G.W.; Gooch, E.E.; Hsu, H.C. *Synth. Commun.* ***1981***, *11*, 247.

[493]Stewart, S.K.; Whiting, A. *Tetrahedron Lett.* ***1995***, *36*, 3929.

[494]Brown, H.C.; Hamaoka, T.; Ravindran, N. *J. Am. Chem. Soc.* ***1973***, *95*, 6456. See also, Brown, H.C.; Bhat, N.G. *Tetrahedron Lett.* ***1988***, *29*, 21.

[495]See Kabalka, G.W.; Sastry, K.A.R.; Knapp, F.F.; Srivastava, P.C. *Synth. Commun.* ***1983***, *13*, 1027.

[496]Kunda, S.A.; Smith, T.L.; Hylarides, M.D.; Kabalka, G.W. *Tetrahedron Lett.* ***1985***, *26*, 279.

[497]Hoshi, M.; Shirakawa, K. *Tetrahedron Lett.* ***2000***, *41*, 2595.

[498]See, for example, Chou, S.P.; Kuo, H.; Wang, C.; Tsai, C.; Sun, C. *J. Org. Chem.* ***1989***, *54*, 868.

[499]Normant, J.F.; Chaiez, G.; Chuit, C.; Villieras, J. *J. Organomet. Chem.* ***1974***, *77*, 269; *Synthesis* ***1974***, 803.

[500]Westmijze, H.; Meijer, J.; Vermeer, P. *Recl. Trav. Chim. Pays-Bas* ***1977***, *96*, 168; Levy, A.B.; Talley, P.; Dunford, J.A. *Tetrahedron Lett.* ***1977***, 3545.

[501]Nishiguchi, I.; Kanbe, O.; Itoh, K.; Maekawa, H. *Synlett* ***2000***, 89.

and then iodine leads to a *Z*-vinyl iodide with respect to the aryl group and the iodine atom.[502] 1-Bromo-1-alkynes were converted to the 1-iodo-1-alkyne with CuI.[503]

It is unlikely that a single mechanism suffices to cover all conversions of organometallic compounds to alkyl halides.[504] In a number of cases, the reaction has been shown to involve inversion of configuration (see p. 757), indicating an S_E2 (back) mechanism, while in other cases retention of configuration has been shown,[505] implicating an S_E2 (front) or S_Ei mechanism. In still other cases, complete loss of configuration as well as other evidence have demonstrated the presence of a free-radical mechanism.[505,506]

OS **I**, 125, 325, 326; **III**, 774, 813; **V**, 921; **VI**, 709; **VII**, 290; **VIII**, 586; **IX**, 573. Also see, OS **II**, 150.

E. Nitrogen Electrophiles

12-32 The Conversion of Organometallic Compounds to Amines

Amino-de-metalation

$$\mathrm{RLi} \xrightarrow[\mathrm{MeLi}]{\mathrm{CH_3ONH_2}} \mathrm{RNH_2}$$

There are several methods for conversion of alkyl- or aryllithium compounds to primary amines.[507] The two most important are treatment with hydroxylamine derivatives and with certain azides.[508] In the first of these methods, treatment of RLi with methoxyamine and MeLi in ether at −78°C gives RNH_2.[509] Grignard reagents from aliphatic halides give lower yields. The reaction can be extended to give secondary amines by the use of *N*-substituted methoxyamines (CH_3ONHR').[510] There is evidence[511] that the mechanism involves the direct displacement of OCH_3 by R

[502]Takami, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* ***2002***, *4*, 2993.

[503]Abe, H.; Suzuki, H. *Bull. Chem. Soc. Jpn.* ***1999***, *72*, 787.

[504]For reviews of the mechanisms, see Abraham, M.H.; Grellier, P.L., in Hartley, F.R.; Patai, S. *The Chemistry of the Carbon–Metal Bond*, Vol. 2, Wiley, NY, p. 72; Abraham, M.H. *Comprehensive Chemical Kinetics*, Bamford, C.H.; Tipper, C.F.H., Eds., Vol. 12; Elsevier, NY, ***1973***, pp. 135–177; Jensen, F.R.; Rickborn, B. *Electrophilic Substitution of Organomercurials*, McGraw-Hil, NY, ***1968***, pp. 75–97.

[505]For example, see Jensen, F.R.; Gale, L.H. *J. Am. Chem. Soc.* ***1960***, *82*, 148.

[506]See, for example, Beletskaya, I.P.; Reutov, O.A.; Gur'yanova, T.P. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1961***, 1483; Beletskaya, I.P.; Ermanson, A.V.; Reutov, O.A. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1965***, 218; de Ryck, P.H.; Verdonck, L.; Van der Kelen, G.P. *Bull. Soc. Chim. Belg.*, ***1985***, *94*, 621.

[507]For a review of methods for achieving the conversion $RM \rightarrow RNH_2$, see Erdik, E.; Ay, M. *Chem. Rev.* ***1989***, *89*, 1947.

[508]For some other methods of converting organolithium or Grignard reagents to primary amines, see Alvernhe, G.; Laurent, A. *Tetrahedron Lett.* ***1972***, 1007; Hagopian, R.A.; Therien, M.J.; Murdoch, J.R. *J. Am. Chem. Soc.* ***1984***, *106*, 5753; Genet, J.P.; Mallart, S.; Greck, C.; Piveteau, E. *Tetrahedron Lett.* ***1991***, *32*, 2359.

[509]Beak, P.; Kokko, B.J. *J. Org. Chem.* ***1982***, *47*, 2822. For other hydroxylamine derivatives, see Colvin, E.W.; Kirby, G.W.; Wilson, A.C. *Tetrahedron Lett.* ***1982***, *23*, 3835; Boche, G.; Bernheim, M.; Schrott, W. *Tetrahedron Lett.* ***1982***, *23*, 5399; Boche, G.; Schrott, W. *Tetrahedron Lett.* ***1982***, *23*, 5403.

[510]Kokko, B.J.; Beak, P. *Tetrahedron Lett.* ***1983***, *24*, 561.

[511]Beak, P.; Basha, A.; Kokko, B.; Loo, D. *J. Am. Chem. Soc.* ***1986***, *108*, 6016.

on an intermediate $CH_2ONR'^-(CH_3ONR'^-\ Li^+ + RLi \rightarrow CH_3OLi + RNR'^-\ Li^+)$. The most useful azide is tosyl azide TsN_3.[512] The initial product is usually RN_3, but this is easily reducible to the amine (**19-51**). With some azides, such as azidomethyl phenyl sulfide ($PhSCH_2N_3$), the group attached to the N_3 is a poor leaving group, so the initial product is a triazene (in this case $ArNHN{=}NCH_2SPh$ from ArMgX), which can be hydrolyzed to the amine.[513]

$$R_3B \xrightarrow{NH_3-NaOCl} 2\,RNH_2 + RB(OH)_2$$

Organoboranes react with a mixture of aqueous NH_3 and NaOCl to produce primary amines.[514] It is likely that the actual reagent is chloramine (NH_2Cl). Chloramine itself,[515] hydroxylamine-*O*-sulfonic acid in diglyme,[516] and trimethylsilyl azide[517] also give the reaction. Since the boranes can be prepared by the hydroboration of alkenes (**15-16**), this is an indirect method for the addition of NH_3 to a double bond with anti-Markovnikov orientation. Secondary amines can be prepared[518] by the treatment of alkyl- or aryldichloroboranes or dialkylchloroboranes with alkyl or aryl azides.

$$RBCl_2 + R'N_3 \longrightarrow RR'NBCl_2 \xrightarrow[OH^-]{H_2O} RNHR'$$

$$R_2BCl + R'N_3 \xrightarrow[2.H_2O]{1.Et_2O} RNHR'$$

The use of an optically active R^*BCl_2 gave secondary amines of essentially 100% optical purity.[519] Aryllead triacetates, $ArPb(OAc)_3$, give secondary amines ($ArNHAr'$) when treated with primary aromatic amines $Ar'NH_2$ and $Cu(OAc)_2$.[520]

Secondary amines have been converted to tertiary amines by treatment with lithium dialkylcuprate reagents: $R_2CuLi + NHR \rightarrow RNR_2'$.[521] The reaction was also used to convert primary amines to secondary, but yields were lower.[522]

[512]See, for example, Spagnolo, P.; Zanirato, P.; Gronowitz, S. *J. Org. Chem.* ***1982***, *47*, 3177; Reed, J.N.; Snieckus, V. *Tetrahedron Lett.* ***1983***, *24*, 3795. For other azides, see Hassner, A.; Munger, P.; Belinka Jr., B.A. *Tetrahedron Lett.* ***1982***, *23*, 699; Mori, S.; Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* ***1984***, *25*, 429.
[513]Trost, B.M.; Pearson, W.H. *J. Am. Chem. Soc.* ***1981***, *103*, 2483; ***1983***, *105*, 1054.
[514]Kabalka, G.W.; Wang, Z.; Goudgaon, N.M. *Synth. Commun.* ***1989***, *19*, 2409. For the extension of this reaction to the preparation of secondary amines, see Kabalka, G.W.; Wang, Z. *Organometallics* ***1989***, *8*, 1093; *Synth. Commun.* ***1990***, *20*, 231.
[515]Brown, H.C.; Heydkamp, W.R.; Breuer, E.; Murphy, W.S. *J. Am. Chem. Soc.* ***1964***, *86*, 3565.
[516]Brown, H.C.; Kim, K.; Srebnik, M.; Singaram, B. *Tetrahedron* ***1987***, *43*, 4071. For a method of using this reaction to prepare optically pure chiral amines, see Brown, H.C.; Kim, K.; Cole, T.E.; Singaram, B. *J. Am. Chem. Soc.* ***1986***, *106*, 6761.
[517]Kabalka, G.W.; Goudgaon, N.M.; Liang, Y. *Synth. Commun.* ***1988***, *18*, 1363.
[518]Brown, H.C.; Midland, M.M.; Levy, A.B.; Suzuki, A.; Sono, S.; Itoh, M. *Tetrahedron* ***1987***, *43*, 4079; Carboni, B.; Vaultier, M.; Courgeon, T.; Carrié, R. *Bull. Soc. Chim. Fr.* ***1989***, 844.
[519]Brown, H.C.; Salunkhe, A.M.; Singaram, B. *J. Org. Chem.* ***1991***, *56*, 1170.
[520]Barton, D.H.R.; Donnelly, D.M.X.; Finet, J.; Guiry, P.J. *Tetrahedron Lett.* ***1989***, *30*, 1377.
[521]Yamamoto, H.; Maruoka, K. *J. Org. Chem.* ***1980***, *45*, 2739.
[522]Merkushev, E.B. *Synthesis* ***1988***, 923

In the presence of a CuI catalyst, acetamide reacted with vinyl iodides to give the corresponding enamide, where the nitrogen of the amide replaced the iodine atom.[523]

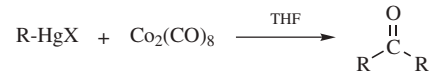
Terminal alkynes reacted with chlorodiphenylphosphine (Ph_2PCl) and a nickel catalyst to give the 1-diphenylphosphino alkyne ($R\text{-}C{\equiv}C\text{-}PPh_2$).[524] Alkynyl halides can be used for a similar reaction. Treatment of methyl carbamates with KHMDS and CuI, followed by two equivalents of 1-bromo phenylacetylene gave the *N*-substituted alkyne, $Ph\text{–}C{\equiv}C\text{–}N(CO_2Me)R$.[525]

OS **VI**, 943.

F. Carbon Electrophiles

12-33 The Conversion of Organometallic Compounds to Ketones, Aldehydes, Carboxylic Esters, or Amides

Acyl-de-metalation, and so on

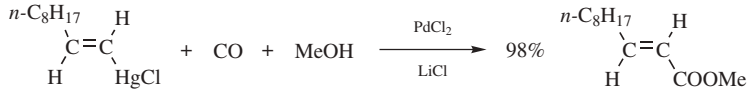


Symmetrical ketones[526] can be prepared in good yields by the reaction of organomercuric halides[527] with dicobalt octacarbonyl in THF,[528] or with nickel carbonyl in DMF or certain other solvents.[529] The R group may be aryl or alkyl. However, when R is alkyl, rearrangements may intervene in the $Co_2(CO)_8$ reaction, although the $Ni(CO)_4$ reaction seems to be free from such rearrangements.[530] Divinylic ketones (useful in the Nazarov cyclization, **15-20**) have been prepared in high yields by treatment of vinylic mercuric halides with CO and a rhodium catalyst.[530] In a more general synthesis of unsymmetrical ketones, tetraalkyltin compounds (R_4Sn) are treated with a halide R′X (R′ = aryl, vinylic, benzylic), CO, and a Pd complex catalyst.[531] Similar reactions use Grignard reagents, $Fe(CO)_5$, and an alkyl halide.[532] Cyclobutanone derivatives were prepared by carbonylation (treatment with CO) of a cyclic titanium compound.[533]

Grignard reagents react with formic acid to give good yields of aldehydes. Two equivalents of RMgX are used; the first converts HCOOH to HCOO–, which reacts

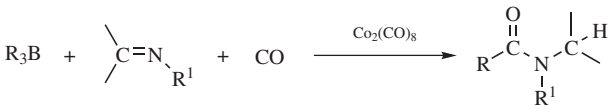
[523]Jiang, L.; Job, G.E.; Klapars, A.; Buchwald, S.L. *Org. Lett.* ***2003***, *5*, 3667.
[524]Beletskaya, I.P.; Affanasiev, V.V.; Kazankova, M.A.; Efimova, I.V. *Org. Lett.* ***2003***, *5*, 4309.
[525]Dunetz, J.R.; Danheiser, R.L. *Org. Lett.* ***2003***, *5*, 4011.
[526]For reviews of the reactions in this section, and related reactions, see Narayana, C.; Periasamy, M. *Synthesis* ***1985***, 253; Gulevich, Yu.V.; Bumagin, N.A.; Beletskaya, I.P. *Russ. Chem. Rev.* ***1988***, *57*, 299.
[527]For a monograph on the synthetic uses of organomercury compounds, see Larock, R.C. *Organomercury Compounds in Organic Synthesis*, Springer, NY, ***1985***. For reviews, see Larock, R.C. *Tetrahedron* ***1982***, *38*, 1713; *Angew. Chem. Int. Ed.* ***1978***, *17*, 27.
[528]Seyferth, D.; Spohn, R.J. *J. Am. Chem. Soc.* ***1969***, *91*, 3037.
[529]Ryu, I.; Ryang, M.; Rhee, I.; Omura, H.; Murai, S.; Sonoda, N. *Synth. Commun.* ***1984***, *14*, 1175 and references cited therein. For another method, see Hatanaka, Y.; Hiyama, T. *Chem. Lett.* ***1989***, 2049.
[530]Larock, R.C.; Hershberger, S.S. *J. Org. Chem.* ***1980***, *45*, 3840.
[531]Tanaka, M. *Tetrahedron Lett.* ***1979***, 2601.
[532]Yamashita, M.; Suemitsu, R. *Tetrahedron Lett.* ***1978***, 761. See also, Vitale, A.A.; Doctorovich, F.; Nudelman, N.S. *J. Organomet. Chem.* ***1987***, *332*, 9.
[533]Carter, C.A.G.; Greidanus, G.; Chen, J.-x.; Stryker, J.M. *J. Am. Chem. Soc.* ***2001***, *123*, 8872.

with the second equivalent to give RCHO.[534] Alkyllithium reagents and Grignard reagents react with CO to give symmetrical ketones.[535] An interesting variation reacts CO_2 with an organolithium, which is then treated with a different organolithium reagent to give the unsymmetrical ketone.[536] α,β-Unsaturated aldehydes can be prepared by treatment of vinylic silanes with dichloromethyl methyl ether and $TiCl_4$ at −90°C.[537] α,β-Unsaturated esters can be prepared by treating boronic esters **27** with CO, $PdCl_2$, and NaOAc in MeOH.[538] The synthesis of α,β-unsaturated esters has also been accomplished by treatment of vinylic mercuric chlorides with CO at atmospheric pressure and a Pd catalyst in an alcohol as solvent, for example,[539]



Alkyl and aryl Grignard reagents can be converted to carboxylic esters with $Fe(CO)_5$ instead of CO.[540]

Amides have been prepared by the treatment of trialkyl or triarylboranes with CO and an imine, in the presence of catalytic amounts of cobalt carbonyl:[541]



In another method for the conversion RM → RCONR, Grignard reagents, and organolithium compounds are treated with a formamide ($HCONR_2'$) to give the intermediate $RCH(OM)NR_2'$, which is not isolated, but treated with PhCHO or Ph_2CO to give the product $RCONR_2'$.[542]

Direct conversion of a hydrocarbon to an aldehyde (R–H → R–CHO) was reported by treatment of the hydrocarbon with $GaCl_3$ and CO.[543]

See also, reactions **10-76**, **15-32**, and **18-23–18-24**.

OS **VIII**, 97.

[534]Sato, F.; Oguro, K.; Watanabe, H.; Sato, M. *Tetrahedron Lett*. ***1980***, *21*, 2869. For another method of converting RMgX to RCHO, see Meyers, A.I.; Comins, D.L. *Tetrahedron Lett*. ***1978***, 5179; Comins, D.L.; Meyers, A.I. *Synthesis* ***1978***, 403; Amaratunga, W.; Fréchet, J.M.J. *Tetrahedron Lett*. ***1983***, *24*, 1143.

[535]Ryang, M.; Sawa, Y.; Hasimoto, T.; Tsutsumi, S. *Bull. Chem. Soc. Jpn*. ***1964***, *37*, 1704; Trzupek, L.S.; Newirth, T.L.; Kelly, E.G.; Sbarbati, N.E.; Whitesides, G.M. *J. Am. Chem. Soc*. ***1973***, *95*, 8118.

[536]Zadel, G.; Breitmaier, E. *Angew. Chem. Int. Ed*. ***1992***, *31*, 1035.

[537]Yamamoto, K.; Yohitake, J.; Qui, N.T.; Tsuji, J. *Chem. Lett*. ***1978***, 859.

[538]Miyaura, N.; Suzuki, A. *Chem. Lett*. ***1981***, 879. See also Yamashina, N.; Hyuga, S.; Hara, S.; Suzuki, A. *Tetrahedron Lett*. ***1989***, *30*, 6555.

[539]Larock, R.C. *J. Org. Chem*. ***1975***, *40*, 3237.

[540]Yamashita, M.; Suemitsu, R. *Tetrahedron Lett*. ***1978***, 1477.

[541]Alper, H.; Amaratunga, S. *J. Org. Chem*. ***1982***, *47*, 3593.

[542]Screttas, C.G.; Steele, B.R. *J. Org. Chem*. ***1988***, *53*, 5151.

[543]Oshita, M.; Chatani, N. *Org. Lett*. ***2004***, *6*, 4323.

12-34 Cyano-de-metalation

$$\text{R-M} + \text{CuCN} \longrightarrow \text{R-CN}$$

Vinylic copper reagents react with ClCN to give vinyl cyanides, although BrCN and ICN give the vinylic halide instead.[544] Vinylic cyanides have also been prepared by the reaction between vinylic lithium compounds and phenyl cyanate (PhOCN).[545] Alkyl nitriles (RCN) have been prepared, in varying yields, by treatment of sodium trialkylcyanoborates with NaCN and lead tetraacetate.[546] Vinyl bromides reacted with KCN, in the presence of a nickel complex and zinc metal to give the vinyl nitrile.[547] Vinyl triflates react with LiCN, in the presence of a palladium catalyst, to give the vinyl nitrile.[548]

For other electrophilic substitutions of the type RM → RC, which are discussed under nucleophilic substitutions in Chapter 10. See also, **16-81–16-85** and **16-99**.

OS IX, 548

G. Metal Electrophiles

12-35 Transmetallation With a Metal

Metalo-de-metalation

$$\text{RM} + \text{M}' \rightleftharpoons \text{RM}' + \text{M}$$

Many organometallic compounds are best prepared by this reaction, which involves replacement of a metal in an organometallic compound by another metal. The RM' compound can be successfully prepared only when M' is above M in the electromotive series, unless some other way is found to shift the equilibrium. That is, RM is usually an unreactive compound and M' is a metal more active than M. Most often, RM is R_2Hg, since mercury alkyls[527] are easy to prepare and mercury is far down in the electromotive series.[549] Alkyls of Li, Na, K, Be, Mg, Al, Ga, Zn, Cd, Te, Sn, and so on have been prepared this way. An important advantage of this method over **12-38** is that it ensures that the organometallic compound will be prepared free of any possible halide. This method can be used for the isolation of solid sodium and potassium alkyls.[550] If the metals lie too close together in the series, it may not be possible to shift the equilibrium. For example, alkylbismuth compounds cannot be prepared in this way from alkylmercury compounds.

OS **V**, 1116.

[544]Westmijze, H.; Vermeer, P. *Synthesis* ***1977***, 784.
[545]Murray, R.E.; Zweifel, G. *Synthesis* ***1980***, 150.
[546]Masuda, Y.; Hoshi, M.; Yamada, T.; Arase, A. *J. Chem. Soc. Chem. Commun.* ***1984***, 398.
[547]Sakakibara, Y.; Enami, H.; Ogawa, H.; Fujimoto, S.; Kato, H.; Kunitake, K.; Sasaki, K.; Sakai, M. *Bull. Chem. Soc. Jpn.* ***1995***, *68*, 3137.
[548]Piers, E.; Fleming, F.F. *Can. J. Chem.* ***1993***, *71*, 1867.
[549]For a review of the reaction when M is Hg, see Makarova, L.G. *Organomet. React.* ***1970***, *1*, 119, pp. 190–226. For a review where M' is Li, see Wardell, J.L., in Zuckerman, J.J. *Inorganic Reactions and Methods*, Vol. 11, VCH, NY, ***1988***, pp. 31–44.
[550]BuNa and BuK have also been prepared by exchange of BuLi with *t*-BuONa or *t*-AmOK: Pi, R.; Bauer, W.; Brix, B.; Schade, C.; Schleyer, P.v.R. *J. Organomet. Chem.* ***1986***, *306*, C1.

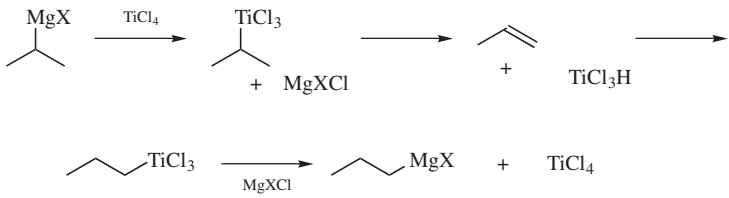
12-36 Transmetallation With a Metal Halide

Metalo-de-metalation

$$RM + M'X \rightleftharpoons RM' + MX$$

In contrast to **12-35**, the reaction between an organometallic compound and a metal *halide* is successful only when M' is *below* M in the electromotive series.[551] The two reactions considered together therefore constitute a powerful tool for preparing all kinds of organometallic compounds. In this reaction, the most common substrates are Grignard reagents and organolithium compounds.[552]

The MgX of Grignard reagents[553] can migrate to terminal positions in the presence of small amounts of $TiCl_4$.[554] The proposed mechanism consists of metal exchange (**12-36**), elimination–addition, and metal exchange:



The addition step is similar to **15-16** or **15-17** and follows Markovnikov's rule, so the positive titanium goes to the terminal carbon.

Among others, alkyls of Be, Zn,[555] Cd, Hg, Al, Sn, Pb, Co, Pt, and Au have been prepared by treatment of Grignard reagents with the appropriate halide.[556] The reaction has been used to prepare alkyls of almost all nontransition metals and even of some transition metals. Alkyls of metalloids and of nonmetals, including

[551]For reviews of the mechanism, see Abraham, M.H.; Grellier, P.L. in Hartley, F.R.; Patai, S. *The Chemistry of the Carbon–Metal Bond*, Vol. 2, Wiley, NY, pp. 25–149; Abraham, M.H. *Comprehensive Chemical Kinetics*, Bamford, C.H.; Tipper, C.F.H., Eds., Vol. 12; Elsevier, NY, ***1973***, pp. 39–106; Jensen, F.R.; Rickborn, B. *Electrophilic Substituton of Organomercurials*, McGraw-Hill, NY, ***1968***, pp. 100–192. Also see Schlosser, M. *Angew. Chem. Int. Ed.* ***1964***, *3*, 287, 362; *Newer Methods Prep. Org. Chem.* ***1968***, *5*, 238.

[552]For monographs on organolithium compounds, see Wakefield, B.J. *Organolithium Methods*, Academic Press, NY, ***1988***; Wakefield, B.J. *The Chemistry of Organolithium Compounds*, Pergamon: Elmsford, NY, ***1974***.

[553]For reviews of rearrangements in organomagnesium chemistry, see Hill, E.A. *Adv. Organomet. Chem.* ***1977***, *16*, 131; *J. Organomet. Chem.* ***1975***, *91*, 123.

[554]Cooper, G.D.; Finkbeiner, H.L. *J. Org. Chem.* ***1962***, *27*, 1493; Fell, B.; Asinger, F.; Sulzbach, R.A. *Chem. Ber.* ***1970***, *103*, 3830. See also, Ashby, E.C.; Ainslie, R.D. *J. Organomet. Chem.* ***1983***, *250*, 1.

[555]For a review of the use of activated zinc, see Erdik, E. *Tetrahedron* ***1987***, *43*, 2203.

[556]For a review, see Noltes, J.G. *Bull. Soc. Chim. Fr.* ***1972***, 2151.

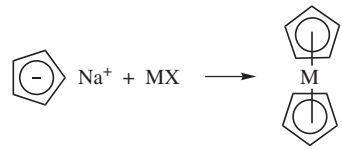
Si, B,[557] Ge, P, As, Sb, and Bi, can also be prepared in this manner.[558] Except for alkali-metal alkyls and Grignard reagents, the reaction between RM and M′X is the most common method for the preparation of organometallic compounds.[559]

Lithium dialkylcopper reagents can be prepared by mixing 2 equivalents of RLi with 1 equivalent of a cuprous halide in ether at low temperatures:[560]

$$2\ RLi + CuX \longrightarrow R_2CuLi + LiX$$

Another way is to dissolve an alkylcopper compound in an alkyllithium solution. Higher order cuprates can also be prepared, as well as "non-ate" copper reagents.[561]

Metallocenes (**48**, see p. 66) are usually made by this method:



48

Among others, metallocenes of Sc, Ti, V, Cr, Mn, Fe, Co, and Ni have been prepared in this manner.[562]

Metal nitrates are sometimes used instead of halides.

In a related reaction sulfurated boranes ($R_2B–SSiR'_2$) react with Grignard reagents, such as methylmagneisum bromide to give the B-alkyl borane (e.g., $R_2B–Me$) upon heating *in vacuo*.[563]

OS **I**, 231, 550; **III**, 601; **IV**, 258, 473, 881; **V**, 211, 496, 727, 918, 1001; **VI**, 776, 875, 1033; **VII**, 236, 290, 524; **VIII**, 23, 57, 268, 474, 586, 606, 609. Also see, OS **IV**, 476

[557]For a method of preparing organoboranes from RMgX and BF_3, where the RMgX is present only *in situ*, see Brown, H.C.; Racherla, U.S. *Tetrahedron Lett*. ***1985***, *26*, 4311.

[558]For reviews as applied to Si, B, and P, see Wakefield, B.J. *Organolithium Methods*, Academic Press, NY, ***1988***, pp. 149–158; Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*; Prentice-Hall: Englewood Cliffs, NJ, ***1954***, pp. 1306–1345.

[559]For a review with respect to Al, see Mole, T. *Organomet. React*. ***1970***, *1*, 1, pp. 31–43; to Hg, see Larock, R.C. *Organomercury Compounds in Organic Synthesis*, Springer, NY, ***1985***, pp. 9–26; Makarova, L.G. *Organomet. React*. ***1970***, *1*, 119, pp. 129–178, 227–240; to Cu, Ag, or Au, see van Koten, G., in Zuckerman, J.J. *Inorganic Reactions and Methods*, Vol. 11, VCH, NY, ***1988***, pp. 219–232; to Zn, Cd, or Hg, see Wardell, J.L. in Zuckerman, J.J. *Inorganic Reactions and Methods*, Vol. 11, VCH, NY, ***1988***, pp. 248–270.

[560]House, H.O.; Chu, C.; Wilkins, J.M.; Umen, M.J. *J. Org. Chem*. ***1975***, *40*, 1460. But see also, Lipshutz, B.H.; Whitney, S.; Kozlowski, J.A.; Breneman, C.M. *Tetrahedron Lett*. ***1986***, *27*, 4273; Bertz, S.H.; Dabbagh, G. *Tetrahedron* ***1989***, *45*, 425.

[561]Stack, D.E.; Klein, W.R.; Rieke, R.D. *Tetrahedron Lett*. ***1993***, *34*, 3063.

[562]For reviews of the preparation of metallocenes, see Bublitz, D.E.; Rinehart, Jr., K.L. *Org. React*. ***1969***, *17*, 1; Birmingham, J.M. *Adv. Organomet. Chem*. ***1965***, *2*, 365, p. 375.

[563]Soderquist, J.A.; DePomar, J.C.J. *Tetrahedron Lett*. ***2000***, *41*, 3537.

12-37 Transmetalation With an Organometallic Compound

Metalo-de-metalation

$$RM + R'M' \rightleftharpoons RM' + R'M$$

This type of metallic exchange is used much less often than **12-35** and **12-36**. It is an equilibrium reaction and is useful only if the equilibrium lies in the desired direction. Usually the goal is to prepare a lithium compound that is not prepared easily in other ways,[564] for example, a vinylic or an allylic lithium, most commonly from an organotin substrate. Examples are the preparation of vinyllithium from phenyllithium and tetravinyltin and the formation of α-dialkylamino organolithium compounds from the corresponding organotin compounds[565]

$$RR'NCH_2SnBu_3 + BuLi \xrightarrow{0^\circ C} RR'NCH_2Li + Bu_4Sn$$

The reaction has also been used to prepare 1,3-dilithiopropanes[566] and 1,1-dilithiomethylenecyclohexane[567] from the corresponding mercury compounds. In general, the equilibrium lies in the direction in which the more electropositive metal is bonded to that alkyl or aryl group that is the more stable carbanion (p. 250). The reaction proceeds with retention of configuration;[568] an S_Ei mechanism is likely.[569]

"Higher order" cuprates[570] (see **10-58**) have been produced by this reaction starting with a vinylic tin compound:[571]

$$RSnR'_3 + Me_2Cu(CN)Li_2 \longrightarrow RCuMe(CN)Li_2 + MeSnR'_{3-} \quad R = \text{a vinylic group}$$

[564]For reviews, see Wardell, J.L. in Hartley, F.R; Patai, S. *The Chemistry of the Carbon-Metal Bond*, Vol. 4, Wiley, NY, pp. 1–157, see pp. 81–89; Kauffmann, T. *Top. Curr. Chem.* ***1980***, *92*, 109, p. 130.

[565]Peterson, D.J.; Ward, J.F. *J. Organomet. Chem.* ***1974***, *66*, 209; Pearson, W.H.; Lindbeck, A.C. *J. Org. Chem.* ***1989***, *54*, 5651.

[566]Seetz, J.W.F.L.; Schat, G.; Akkerman, O.S.; Bickelhaupt, F. *J. Am. Chem. Soc.* ***1982***, *104*, 6848.

[567]Maercker, A.; Dujardin, R. *Angew. Chem. Int. Ed.* ***1984***, *23*, 224.

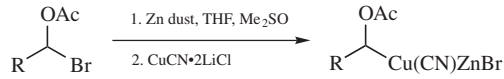
[568]Seyferth, D.; Vaughan, L.G. *J. Am. Chem. Soc.* ***1964***, *86*, 883; Sawyer, J.S.; Kucerovy, A.; Macdonald, T.L.; McGarvey, G.J. *J. Am. Chem. Soc.* ***1988***, *110*, 842.

[569]Dessy, R.E.; Kaplan, F.; Coe, G.R.; Salinger, R.M. *J. Am. Chem. Soc.* ***1963***, *85*, 1191.

[570]For reviews of these and other "higher order" organocuprates, see Lipshutz, B.H.; Wilhelm, R.S.; Kozlowski, J.A. *Tetrahedron* ***1984***, *40*, 5005; Lipshutz, B.H. *Synthesis* ***1987***, 325; *Synlett*, ***1990***, 119. See also, Bertz, S.H. *J. Am. Chem. Soc.* ***1990***, *112*, 4031; Lipshutz, B.H.; Sharma, S.; Ellsworth, E.L. *J. Am. Chem. Soc.* ***1990***, *112*, 4032.

[571]Behling, J.R.; Babiak, K.A.; Ng, J.S.; Campbell, A.L.; Moretti, R.; Koerner, M.; Lipshutz, B.H. *J. Am. Chem. Soc.* ***1988***, *110*, 2641.

These compounds are not isolated, but used directly *in situ* for conjugate addition reactions (**15-25**). Another method for the preparation of such reagents (but with Zn instead of Li) allows them to be made from α-acetoxy halides:[572]



OS **V**, 452; **VI**, 815; **VIII**, 97.

HALOGEN AS LEAVING GROUP

The reduction of alkyl halides can proceed by an electrophilic substitution mechanism, but it is considered in Chapter 19 (**19-53**).

12-38 Metalo-de-halogenation

$$RX + M \longrightarrow RM$$

Alkyl halides react directly with certain metals to give organometallic compounds.[573] The most common metal is magnesium, and of course this is by far the most common method for the preparation of Grignard reagents.[574] The order of halide activity is I > Br > Cl. The reaction can be applied to many alkyl halides primary, secondary, and tertiary and to aryl halides, although aryl *chlorides* require the use of THF or another higher boiling solvent instead of the usual ether, or special entrainment methods.[575] Aryl iodides and bromides can be treated in the usual manner. Allylic Grignard reagents can also be prepared in the usual manner (or in THF),[576] although in the presence of excess halide these may give Wurtz-type coupling products (see **10-56**).[577] Like aryl chlorides, vinylic halides require higher boiling solvents (see OS **IV**, 258). A good procedure for benzylic and allylic halides is to use magnesium anthracene (prepared from Mg and anthracene in THF)[578]

[572]Chou, T.; Knochel, P. *J. Org. Chem.* ***1990***, *55*, 4791.

[573]For reviews, see Massey, A.G.; Humphries, R.E. *Aldrichimica Acta* ***1989***, *22*, 31; Negishi, E. *Organometallics in Organic Synthesis*, Wiley, NY, ***1980***, pp. 30–37; Rochow, E.G. *J. Chem. Educ.* ***1966***, *43*, 58.

[574]For reviews, see Raston, C.L.; Salem, G., in Hartley, F.R.; Patai, S. *The Chemistry of the Carbon–Metal Bond*, Vol. 4, Wiley, NY, pp. 159–306, 162–175; Kharasch, M.S.; Reinmuth, O. *Grignard Reactions of Monmetallic Substances*, Prentice-Hall, Englewood Cliffs, NJ, ***1954***, pp. 5–91.

[575]Pearson, D.E.; Cowan, D.; Beckler, J.D. *J. Org. Chem.* ***1959***, *24*, 504.

[576]For a review of allyl and crotyl Grignard reagents, see Benkeser, R.A. *Synthesis* ***1971***, 347.

[577]For a method of reducing coupling in the formation of allylic Grignard reagents, see Oppolzer, W.; Schneider, P. *Tetrahedron Lett.* ***1984***, *25*, 3305.

[578]Freeman, P.K.; Hutchinson, L.L. *J. Org. Chem.* ***1983***, *48*, 879; Bogdanović, B.; Janke, N.; Kinzelmann, H. *Chem. Ber.* ***1990***, *123*, 1507, and other papers in this series.

instead of ordinary magnesium,[579] although activated magnesium turnings have also been used.[580] Alkynyl Grignard reagents are not generally prepared by this method at all. For these, **12-22** is used. Grignard reagents can also be formed from an alkyl halide and 1,2-dibromoethane with iodine as an initiator.[581]

Dihalides[582] can be converted to Grignard reagents if the halogens are different and are at least three carbons apart. If the halogens are the same, it is possible to obtain dimagnesium compounds (e.g., $BrMg(CH_2)_4MgBr$).[583] 1,2-Dihalides give elimination[584] instead of Grignard reagent formation (**17-22**), and the reaction is seldom successful with 1,1-dihalides, although the preparation of *gem*-disubstituted compounds, such as $CH_2(MgBr)_2$, has been accomplished with these substrates.[585] α-halo Grignard reagents and α-halolithium reagents can be prepared by the method given in **12-39**.[586] Alkylmagnesium fluorides can be prepared by refluxing alkyl fluorides with Mg in the presence of appropriate catalysts (e.g., I_2 or EtBr) in THF for several days.[587] Nitrogen-containing Grignard reagents have been prepared.[588]

The presence of other functional groups in the halide usually affects the preparation of the Grignard reagent. Groups that contain active hydrogen (defined as any hydrogen that will react with a Grignard reagent), such as OH, NH_2, and COOH, can be present in the molecule, but only if they are converted to the salt form (O^-, NH^-, COO^-, respectively). Groups that react with Grignard reagents, such as C=O, C≡N, NO_2, COOR, inhibit Grignard formation entirely. In general, the only functional groups that may be present in the halide molecule without any interference at all are double and triple bonds (except terminal triple bonds) and OR and NR_2 groups. However, β-halo ethers generally give β elimination when treated with

[579]Gallagher, M.J.; Harvey, S.; Raston, C.L.; Sue, R.E. *J. Chem. Soc. Chem. Commun*. ***1988***, 289.

[580]Baker, K.V.; Brown, J.M.; Hughes, N.; Skarnulis, A.J.; Sexton, A. *J. Org. Chem*. ***1991***, *56*, 698. For a review of the use of activated magnesium, see Lai, Y. *Synthesis* ***1981***, 585.

[581]Li, J.; Liao, X.; Liu, H.; Xie, Q.; Liu, Z.; He, X. *Synth. Commun*. ***1999***, *29*, 1037.

[582]For reviews of the preparation of Grignard reagents from dihalides, see Raston, C.L.; Salem, G. in Hartley, F.R.; Patai, S. *The Chemistry of the Carbon–Metal Bond*, Vol. 4, Wiley, NY, pp. 187–193; Heaney, H. *Organomet. Chem. Rev.* ***1966***, *1*, 27. For a review of di-Grignard reagents, see Bickelhaupt, F. *Angew. Chem. Int. Ed*. ***1987***, *26*, 990.

[583]For example, see Denise, B.; Ducom, J.; Fauvarque, J. *Bull. Soc. Chim. Fr.* ***1972***, 990; Seetz, J.W.F.L.; Hartog, F.A.; Böhm, H.P.; Blomberg, C.; Akkerman, O.S.; Bickelhaupt, F. *Tetrahedron Lett*. ***1982***, *23*, 1497.

[584]For formation of 1,2-dilithio compounds and 1,2-di-Grignard reagents, but not by this method, see van Eikkema Hommes, N.J.R.; Bickelhaupt, F.; Klumpp, G.W. *Recl. Trav. Chim. Pays-Bas* ***1988***, *107*, 393; *Angew. Chem. Int. Ed*. ***1988***, *27*, 1083.

[585]For example, see Bertini, F.; Grasselli, P.; Zubiani, G.; Cainelli, G. *Tetrahedron* ***1970***, *26*, 1281; Bruin, J.W.; Schat, G.; Akkerman, O.S.; Bickelhaupt, F. *J. Organomet. Chem*. ***1985***, *288*, 13. For the synthesis of *gem*-dilithio and 1,1,1-trilithio compounds, see Baran, Jr., J.R.; Lagow, R. *J. Am. Chem. Soc*. ***1990***, *112*, 9415.

[586]For a review of compounds containing both carbon–halogen and carbon-metal bonds, see Chivers, T. *Organomet. Chem. Rev. Sect. A* ***1970***, *6*, 1.

[587]Yu, S.H.; Ashby, E.C. *J. Org. Chem*. ***1971***, *36*, 2123.

[588]Sugimoto, O.; Yamada, S.; Tanji, K. *J. Org. Chem*. ***2003***, *68*, 2054.

magnesium (see **17-24**), and Grignard reagents from α-halo ethers[589] can only be formed in THF or dimethoxymethane at a low temperature, for example,[590]

$$EtOCH_2Cl + Mg \xrightarrow[-30^\circ C]{THF \text{ or } CH_2(OMe)_2} EtOCH_2MgCl$$

because such reagents immediately undergo a elimination (see **12-39**) at room temperature in ether solution.

Because Grignard reagents react with water (**12-24**) and with oxygen (**12-25**), it is generally best to prepare them in an anhydrous nitrogen atmosphere. Grignard reagents are generally neither isolated nor stored; solutions of Grignard reagents are used directly for the required synthesis. Grignard reagents can also be prepared in benzene or toluene, if a tertiary amine is added to complex with the RMgX.[591] This method eliminates the need for an ether solvent. With certain primary alkyl halides it is even possible to prepare alkylmagnesium compounds in hydrocarbon solvents in the absence of an organic base.[592] It is also possible to obtain Grignard reagents in powdered form, by complexing them with the chelating agent tris(3,6-dioxaheptyl)amine, $N(CH_2CH_2OCH_2CH_2OCH_3)_3$.[593]

Next to the formation of Grignard reagents, the most important application of this reaction is the conversion of alkyl and aryl halides to organolithium compounds,[594] but it has also been carried out with many other metals (e.g., Na, Be, Zn, Hg, As, Sb, and Sn). With sodium, the Wurtz reaction (**10-56**) is an important side reaction. In some cases where the reaction between a halide and a metal is too slow, an alloy of the metal with potassium or sodium can be used instead. The most important example is the preparation of tetraethyl lead from ethyl bromide and a Pb–Na alloy.

The efficiency of the reaction can often be improved by use of the metal in its powdered[595] or vapor[596] form. These techniques have permitted the preparation of some organometallic compounds that cannot be prepared by the standard

[589]For a review of organometallic compounds containing a hetero atom (N, O, P, S, or Si), see Peterson, D.J. *Organomet. Chem. Rev. Sect. A* ***1972***, *7*, 295.

[590]For example, see Normant, H.; Castro, B. *C. R. Acad. Sci*. ***1963***, *257*, 2115; ***1964***, *259*, 830; Castro, B. *Bull. Soc. Chim. Fr.* ***1967***, 1533, 1540, 1547; Taeger, E.; Kahlert, E.; Walter, H. *J. Prakt. Chem*. ***1965***, *[4] 28*, 13.

[591]Ashby, E.C.; Reed, R. *J. Org. Chem.* ***1966***, *31*, 971; Gitlitz, M.H.; Considine, W.J. *J. Organomet. Chem.* ***1970***, *23*, 291.

[592]Smith Jr., W.N. *J. Organomet. Chem.* ***1974***, *64*, 25.

[593]Boudin, A.; Cerveau, G.; Chuit, C.; Corriu, R.J.P.; Reye, C. *Tetrahedron* ***1989***, *45*, 171.

[594]For reviews, see Wakefield, B.J. *Organolithium Methods*, Academic Press, NY, ***1988***, pp. 21–32; Wardell, J.L., in Hartley, F.R.; Patai, S. Vol. 4, pp. 1–157, 5–27; Newcomb, M.E., in Zuckerman, J.J. *Inorganic Reactions and Methods*, Vol. 11, VCH, NY, ***1988***, pp. 3–14.

[595]For a review, see Rieke, R.D. *Science* ***1989***, *246*, 1260.

[596]For reviews, see Klabunde, K.J. *React. Intermed*. (*Plenum*) ***1980***, *1*, 37; *Acc. Chem. Res.*; ***1975***, *8*, 393; Skell, P.S. Havel, J.J.; McGlinchey, M.J. *Acc. Chem. Res*. ***1973***, *6*, 97; Timms, P.L. *Adv. Inorg. Radiochem*. ***1972***, *14*, 121.

procedures. Among the metals produced in an activated form are Mg,[597] Ca,[598] Zn,[599] Al, Sn, Cd,[600] Ni, Fe, Ti, Cu,[601] Pd, and Pt.[602]

The mechanism of Grignard reagent formation involves free radicals,[603] and there is much evidence for this, from CIDNP[604] (p. 269) and from stereochemical, rate, and product studies.[605] Further evidence is that free radicals have been trapped,[606] and that experiments that studied the intrinsic reactivity of MeBr on a magnesium single-crystal surface showed that Grignard reagent formation does not take place by a single-step insertion mechanism.[607] The following SET mechanism has been proposed:[604]

$$\mathrm{R{-}X} + \overline{\mathrm{M}}\mathrm{g} \longrightarrow \mathrm{R{-}X}^{\bullet -} + \mathrm{Mg}_{\mathrm{s}}^{\bullet +}$$

$$\mathrm{R{-}X}^{\bullet -} \longrightarrow \mathrm{R}^{\bullet} + \mathrm{X}^{-}$$

$$\mathrm{X}^{-} + \mathrm{Mg}_{\mathrm{s}}^{\bullet +} \longrightarrow \mathrm{XMg}_{\mathrm{s}}^{\bullet}$$

$$\mathrm{R}^{\bullet} + \mathrm{XMg}_{\mathrm{s}}^{\bullet} \longrightarrow \mathrm{RMgX}$$

Other evidence has been offered to support a SET-initiated radical process for the second step of this mechanism.[608] The species $\mathrm{R{-}X}^{\bullet -}$ and $\mathrm{Mg}^{\bullet +}$ are radical ions.[609] The subscript "s" is meant to indicate that the species so marked are bound to the surface of the magnesium. It is known that this is a surface reaction.[610] It has been suggested that some of the $\mathrm{R}^{\bullet}$ radicals diffuse from the magnesium surface into the solution and then return to the surface to react with the $\mathrm{XMg}^{\bullet}$. There is evidence

[597]Ebert, G.W.; Rieke, R.D. *J. Org. Chem.* ***1988***, *53*, 4482. See also, Baker, K.V.; Brown, J.M.; Hughes, N.; Skarnulis, A.J.; Sexton, A. *J. Org. Chem.* ***1991***, *56*, 698.

[598]Wu, T.; Xiong, H.; Rieke, R.D. *J. Org. Chem.* ***1990***, *55*, 5045.

[599]Rieke, R.D.; Li, P.T.; Burns, T.P.; Uhm, S.T. *J. Org. Chem.* ***1981***, *46*, 4323. See also, Grondin, J.; Sebban, M.; Vottero, G.P.; Blancou, H.; Commeyras, A. *J. Organomet. Chem.* ***1989***, *362*, 237; Berk, S.C.; Yeh, M.C.P.; Jeong, N.; Knochel, P. *Organometallics* ***1990***, *9*, 3053; Zhu, L.; Wehmeyer, R.M.; Rieke, R.D. *J. Org. Chem.* ***1991***, *56*, 1445.

[600]Burkhardt, E.R.; Rieke, R.D. *J. Org. Chem.* ***1985***, *50*, 416.

[601]Stack, D.E.; Dawson, B.T.; Rieke, R.D. *J. Am. Chem. Soc.* ***1991***, *113*, 4672, and references cited therein.

[602]For reviews, see Lai, Y. *Synthesis* ***1981***, 585; Rieke, R.D. *Acc. Chem. Res.* ***1977***, *10*, 301; *Top. Curr. Chem.* ***1975***, *59*, 1.

[603]For a review, see Blomberg, C. *Bull. Soc. Chim. Fr.* ***1972***, 2143.

[604]Bodewitz, H.W.H.J.; Blomberg, C.; Bickelhaupt, F. *Tetrahedron Lett.* ***1975***, 2003; *Tetrahedron* ***1975***, *31*, 1053. See also, Lawler, R.G.; Livant, P. *J. Am. Chem. Soc.* ***1976***, *98*, 3710; Schaart, B.J.; Blomberg, C.; Akkerman, O.S.; Bickelhaupt, F. *Can. J. Chem.* ***1980***, *58*, 932.

[605]See, for example, Walborsky, H.M.; Aronoff, M.S. *J. Organomet. Chem.* ***1973***, *51*, 31; Czernecki, S.; Georgoulis, C.; Gross, B.; Prevost, C. *Bull. Soc. Chim. Fr.* ***1968***, 3720; Rogers, H.R.; Hill, C.L.; Fujiwara, Y.; Rogers, R.J.; Mitchell, H.L.; Whitesides, G.M. *J. Am. Chem. Soc.* ***1980***, *102*, 217; Barber, J.J.; Whitesides, G.M. *J. Am. Chem. Soc.* ***1980***, *102*, 239.

[606]Root, K.S.; Hill, C.L.; Lawrence, L.M.; Whitesides, G.M. *J. Am. Chem. Soc.* ***1989***, *111*, 5405.

[607]Nuzzo, R.G.; Dubois, L.H. *J. Am. Chem. Soc.* ***1986***, *108*, 2881.

[608]Hoffmann, R. W.; Brönstrup, M.; Müller, M. *Org. Lett.* ***2003***, *5*, 313.

[609]For additional evidence for this mechanism, see Vogler, E.A.; Stein, R.L.; Hayes, J.M. *J. Am. Chem. Soc.* ***1978***, *100*, 3163; Sergeev, G.B.; Zagorsky, V.V.; Badaev, F.Z. *J. Organomet. Chem.* ***1983***, *243*, 123. However, there is evidence that the mechanism may be more complicated: de Souza-Barboza, J.C.; Luche, J.; Pétrier, C. *Tetrahedron Lett.* ***1987***, *28*, 2013.

[610]Walborsky, H.M.; Topolski, M. *J. Am. Chem. Soc.* ***1992***, *114*, 3455; Walborsky, H.M.; Zimmermann, C. *J. Am. Chem. Soc.* ***1992***, *114*, 4996; Walborsky, H.M. *Accts. Chem. Res.* ***1990***, *23*, 286.

both for[611] and against[612] this suggestion. Another proposal is that the fourth step is not the one shown here, but that the R• is reduced by Mg^+ to the carbanion R^-, which combines with MgX^+ to give RMgX.[613]

There are too many preparations of Grignard reagents in *Organic Syntheses* for us to list here. Chiral Grignard reagents are rare, since they are configurationally unstable in most cases. However, a few chiral Grignard reagents are known.[614] Use of the reaction to prepare other organometallic compounds can be found in OS **I**, 228; **II**, 184, 517, 607; **III**, 413, 757; **VI**, 240; **VII**, 346; **VIII**, 505. The preparation of unsolvated butylmagnesium bromide is described at OS **V**, 1141. The preparation of highly reactive (powdered) magnesium is given at OS **VI**, 845.

12-39 Replacement of a Halogen by a Metal from an Organometallic Compound

Metalo-de-halogenation

$$RX + R'M \longrightarrow RM + R'X$$

The exchange reaction between halides and organometallic compounds occurs most readily when M is lithium and X is bromide or iodide,[615] although it has been shown to occur with magnesium.[616] The R' group is usually, although not always, alkyl, and often butyl; R is usually aromatic.[617] Alkyl halides are generally not reactive enough, while allylic and benzylic halides usually give Wurtz coupling. Of course, the R that becomes bonded to the halogen is the one for which RH is the weaker acid. Despite the preponderance of reactions with bromides and iodides, it is noted that the reaction of 1-fluorooctane with 4–10 equivalents of lithium powder and 2–4 equivalents of DTBB (4,4′-di-*tert*-butylbiphenyl) in THP at 0°C for 5 min, was shown to give a solution of the corresponding 1-octyllithium.[618] Vinylic halides react with retention of configuration.[619] The

[611]Garst, J.F.; Deutch, J.E.; Whitesides, G.M. *J. Am. Chem. Soc*. ***1986***, *108*, 2490; Ashby, E.C.; Oswald, J. *J. Org. Chem*. ***1988***, *53*, 6068; Garst, J.F. *Acc. Chem. Res*. ***1991***, *24*, 95; Garst, J.F.; Ungváry, F.; Batlaw, R.; Lawrence, K.E. *J. Am. Chem. Soc*. ***1991***, *113*, 5392.

[612]Walborsky, H.M.; Rachon, J. *J. Am. Chem. Soc*. ***1989***, *111*, 1896; Rachon, J.; Walborsky, H.M. *Tetrahedron Lett*. ***1989***, *30*, 7345; Walborsky, H.M. *Acc. Chem. Res*. ***1990***, *23*, 286.

[613]de Boer, H.J.R.; Akkerman, O.S.; Bickelhaupt, F. *Angew. Chem. Int. Ed*. ***1988***, *27*, 687.

[614]See Hölzer, B.; Hoffmann, R.W. *Chem. Commun*. ***2003***, 732; Walborsky, H.M.; Impastato, F.J.; Young, A.E. *J. Am. Chem. Soc*. ***1964***, *86*, 3283; Tanaka, M.; Ogata, I. *Bull. Chem. Soc. Jpn*. ***1975***, *48*, 1094; Schumann, H.; Wassermann, B.C.; Hahn, F.E. *Organometallics* ***1992***, *11*, 2803; Dakternieks, D.; Dunn, K.; Henry, D.J.; Schiesser, C.H.; Tiekink, E.R. *Organometallics* ***1999***, *18*, 3342.

[615]For reviews, see Wardell, J.L., in Zuckerman, J.J. *Inorganic Reactions and Methods*, Vol. 11, VCH, NY, ***1988***, pp. 107–129; Parham, W.E.; Bradsher, C.K. *Acc. Chem. Res*. ***1982***, *15*, 300.

[616]See, for example, Zakharkin, L.I.; Okhlobystin, O.Yu.; Bilevitch, K.A. *J. Organomet. Chem*. ***1964***, *2*, 309; Tamborski, C.; Moore, G.J. *J. Organomet. Chem*. ***1971***, *26*, 153.

[617]For the preparation of primary alkyllithiums by this reaction, see Bailey, W.F.; Punzalan, E.R. *J. Org. Chem*. ***1990***, *55*, 5404; Negishi, E.; Swanson, D.R.; Rousset, C.J. *J. Org. Chem*. ***1990***, *55*, 5406.

[618]Yus, M.; Herrera, R.P.; Guijarro, A. *Tetrahedron Lett*., ***2003***, *44*, 5025.

[619]For examples of exchange where R = vinylic, see Neumann, H.; Seebach, D. *Chem. Ber*. ***1978***, *111*, 2785; Miller, R.B.; McGarvey, G. *Synth. Commun*. ***1979***, *9*, 831; Sugita, T.; Sakabe, Y.; Sasahara, T.; Tsukuda, M.; Ichikawa, K. *Bull. Chem. Soc. Jpn*. ***1984***, *57*, 2319.

reaction can be used to prepare α-halo organolithium and α-halo organomagnesium compounds,[620] for example,[621]

$$CCl_4 + BuLi \xrightarrow[-105^\circ C]{THF} Cl_3C{-}Li$$

Such compounds can also be prepared by hydrogen–metal exchange, for example,[622]

$$Br_3CH + i\text{PrMgCl} \xrightarrow[-95^\circ C]{THF-HMPA} Br_3C{-}MgCl + C_3H_8$$

This is an example of **12-22**. However, these α-halo organometallic compounds are stable (and configurationally stable as well[623]) only at low temperatures (ca. −100°C) and only in THF or mixtures of THF and other solvents (e.g., HMPA). At ordinary temperatures they lose MX (α elimination) to give carbenes (which then react further) or carbenoid reactions. The α-chloro-α-magnesio sulfones $ArSO_2CH(Cl)MgBr$ are exceptions, being stable in solution at room temperature and even under reflux.[624] Compounds in which a halogen and a transition metal are on the same carbon can be more stable than the ones with lithium.[625]

There is evidence that the mechanism[626] of the reaction of alkyllithium compounds with alkyl and aryl iodides involves free radicals.[627]

$$RX + R'M \rightleftharpoons \underbrace{[R\bullet, X, M, R'\bullet]}_{\text{Solvent cage}} \rightleftharpoons RM + R'X$$

Among the evidence is the fact that coupling and disproportionation products are obtained from R• and R′• and the observation of CIDNP.[627,628] However, in the degenerate exchange between PhI and PhLi the ate complex $Ph_2I^-\ Li^+$ has been

[620]For reviews of such compounds, see Siegel, H. *Top. Curr. Chem.* ***1982***, *106*, 55; Negishi, E. *Organometallics in Organic Synthesis*, Wiley, NY, ***1980***, pp. 136–151; Köbrich, G. *Angew. Chem. Int. Ed.* ***1972***, *11*, 473; ***1967***, *6*, 41; *Bull. Soc. Chim. Fr.* ***1969***, 2712; Villieras, J. *Organomet. Chem. Rev. Sect. A* ***1971***, *7*, 81. For related reviews, see Krief, A. *Tetrahedron* ***1980***, *36*, 2531; Normant, H. *J. Organomet. Chem.* ***1975***, *100*, 189; Zhil'tsov, S.F.; Druzhkov, O.N. *Russ. Chem. Rev.* ***1971***, *40*, 126.

[621]Hoeg, D.F.; Lusk, D.I.; Crumbliss, A.L. *J. Am. Chem. Soc.* ***1965***, *87*, 4147. See also, Villieras, J.; Tarhouni, R.; Kirschleger, B.; Rambaud, M. *Bull. Soc. Chim. Fr.* ***1985***, 825.

[622]Villieras, J. *Bull. Soc. Chim. Fr.* ***1967***, 1520.

[623]Schmidt, A.; Köbrich, G.; Hoffmann, R.W. *Chem. Ber.* ***1991***, *124*, 1253; Hoffmann, R.W.; Bewersdorf, M. *Chem. Ber.* ***1991***, *124*, 1259.

[624]Stetter, H.; Steinbeck, K. *Liebigs Ann. Chem.* ***1972***, *766*, 89.

[625]Kauffmann, T.; Fobker, R.; Wensing, M. *Angew. Chem. Int. Ed.* ***1988***, *27*, 943.

[626]For reviews of the mechanism, see Bailey, W.F.; Patricia, J.J. *J. Organomet. Chem.* ***1988***, *352*, 1; Beletskaya, I.P.; Artamkina, G.A.; Reutov, O.A. *Russ. Chem. Rev.* ***1976***, *45*, 330.

[627]Ward, H.R.; Lawler, R.G.; Cooper, R.A. *J. Am. Chem. Soc.* ***1969***, *91*, 746; Lepley, A.R.; Landau, R.L. *J. Am. Chem. Soc.* ***1969***, *91*, 748; Ashby, E.C.; Pham, T.N. *J. Org. Chem.* ***1987***, *52*, 1291. See also, Bailey, W.F.; Patricia, J.J.; Nurmi, T.T.; Wang, W. *Tetrahedron Lett.* ***1986***, *27*, 1861.

[628]Ward, H.R.; Lawler, R.G.; Loken, H.Y. *J. Am. Chem. Soc.* ***1968***, *90*, 7359.

shown to be an intermediate,[629] and there is other evidence that radicals are not involved in all instances of this reaction.[630]

In a completely different kind of process, alkyl halides can be converted to certain organometallic compounds by treatment with organometalate ions, for example,

$$RX + R'_3SnLi \longrightarrow RSnR'_3 + LiX$$

Most of the evidence is in accord with a free-radical mechanism involving electron transfer, although an S_N2 mechanism can compete under some conditions.[631]

OS **VI**, 82; **VII**, 271, 326, 495; **VIII**, 430. See also, OS **VII**, 512; **VIII**, 479.

CARBON LEAVING GROUPS

In these reactions (**12-40–12-48**), a carbon–carbon bond cleaves. We regard as the substrate the side that retains the electron pair; hence the reactions are considered electrophilic substitutions. The incoming group is hydrogen in all but one (**12-42**) of the cases. The reactions in groups A and B are sometimes called *anionic cleavages*,[632] although they do not always occur by mechanisms involving free carbanions (S_E1). When they do, the reactions are facilitated by increasing stability of the carbanion.

A. Carbonyl-Forming Cleavages

These reactions follow the pattern

The leaving group is stabilized because the electron deficiency at its carbon is satisfied by a pair of electrons from the oxygen. With respect to the leaving group the reaction is elimination to form a C=O bond. Retrograde aldol reactions (**16-34**) and cleavage of cyanohydrins (**16-52**) belong to this classification but are treated in Chapter 16 under their more important reverse reactions. Other eliminations to form C=O bonds are discussed in Chapter 17 (**17-32**).

12-40 Decarboxylation of Aliphatic Acids

Hydro-de-carboxylation

$$RCOOH \longrightarrow RH + CO_2$$

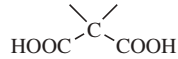
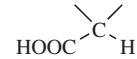
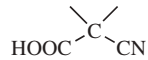
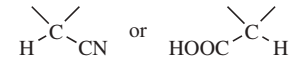
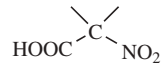
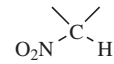
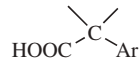
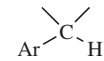
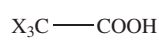
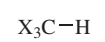
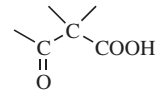
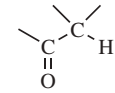
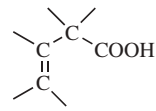
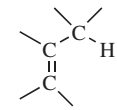
[629]See Farnham, W.B.; Calabrese, J.C. *J. Am. Chem. Soc.* ***1986***, *108*, 2449; Reich, H.J.; Green, D.P.; Phillips, N.H. *J. Am. Chem. Soc.* ***1989***, *111*, 3444.

[630]Rogers, H.R.; Houk, J. *J. Am. Chem. Soc.* ***1982***, *104*, 522; Beak, P.; Allen, D.J.; Lee, W.K. *J. Am. Chem. Soc.* ***1990***, *112*, 1629.

[631]See San Filippo, Jr., J.; Silbermann, J. *J. Am. Chem. Soc.* ***1982***, *104*, 2831; Ashby, E.C.; Su, W.; Pham, T.N. *Organometallics* ***1985***, *4*, 1493; Alnajjar, M.S.; Kuivila, H.G. *J. Am. Chem. Soc.* ***1985***, *107*, 416.

[632]For a review, see Artamkina, G.A.; Beletskaya, I.P. *Russ. Chem. Rev.* ***1987***, *56*, 983.

TABLE 12.2. Some Acids that Undergo Decarboxylation Fairly Readily[a]

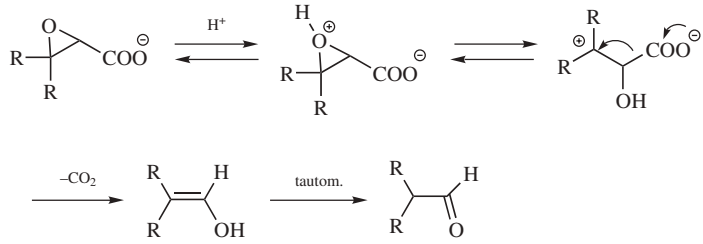
	Acid Type	Decarboxylation Product
Malonic		
α-Cyano		
α-Nitro		
α-Aryl		
α,α,α-Trihalo		
β-Keto		
β,γ-Unsaturated		

[a]Others are described in the text.

Many carboxylic acids can be successfully decarboxylated, either as the free acid or in the salt form, but not simple fatty acids.[633] An exception is acetic acid, which as the acetate, heated with base, gives good yields of methane. Malonic acid derivatives are the most common substrates for decarboxylation, giving the corresponding monocarboxylic acid. Decarboxylation of 2-substituted malonic acids has been reported using microwave irradiation.[634] Aliphatic acids that do undergo successful decarboxylation have certain functional groups or double or triple bonds in the α or β position. Some of these are shown in Table 12.2. For decarboxylation of aromatic acids, see **11-35**. Decarboxylation of an α-cyano acid can give a nitrile or a carboxylic acid, since the cyano group may or may not be hydrolyzed in the course of the reaction. In addition to the compounds listed in Table 12.2, decarboxylation can also be carried out on α,β-unsaturated and α,β-acetylenic acids. α,β-Unsaturated acids can also be decarboxylated[635] with copper

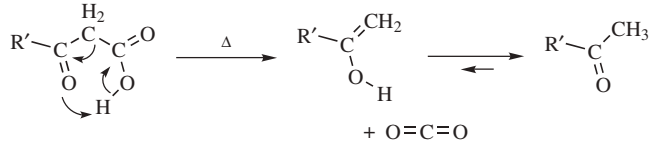
[633]March, J. *J. Chem. Educ*. ***1963***, *40*, 212.
[634]Zara, C.L.; Jin, T.; Giguere, R.J. *Synth. Commun*. ***2000***, *30*, 2099.
[635]For an example involving the conversion of C=C-COOH to C=C-Br with LiBr and ceric ammonium nitrate in aqueous acetonitrile, see Roy, S.C.; Guin, C.; Maiti, G. *Tetrahedron Lett*. ***2001***, *42*, 9253.

and quinoline in a manner similar to that discussed in **11-35**. Glycidic acids give aldehydes on decarboxylation. The following mechanism has been suggested:[636]



The direct product is an enol that tautomerizes to the aldehyde.[637] This is the usual last step in the Darzens reaction (**16-40**).

Decarboxylations can be regarded as reversals of the addition of carbanions to carbon dioxide (**16-82**), but free carbanions are not always involved.[638] When the carboxylate *ion* is decarboxylated, the mechanism can be either S_E1 or S_E2. In the case of the S_E1 mechanism, the reaction is of course aided by the presence of electron-withdrawing groups, which stabilize the carbanion.[639] Decarboxylations of carboxylate ions can be accelerated by the addition of a suitable crown ether, which in effect removes the metallic ion.[640] The reaction without the metallic ion has also been performed in the gas phase.[641] But some acids can also be decarboxylated directly and, in most of these cases, there is a cyclic, six-center mechanism:



Here too there is an enol that tautomerizes to the product. The mechanism is illustrated for the case of β-keto acids,[642] but it is likely that malonic acids, α-cyano acids, α-nitro acids, and β,γ-unsaturated acids[643] behave similarly,

[636]Singh, S.P.; Kagan, J. *J. Org. Chem.* ***1970***, *35*, 2203.

[637]Shiner, Jr., V.J.; Martin, B. *J. Am. Chem. Soc.* ***1962***, *84*, 4824.

[638]For reviews of the mechanism, see Richardson, W.H.; O'Neal, H.E., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 5, Elsevier, NY, ***1972***, pp. 447–482; Clark, L.W., in Patai, S. *The Chemistry of Carboxylic Acids and Esters*; Wiley, NY, ***1969***, pp. 589–622. For a review of carbon isotope effect studies, see Dunn, G.E. *Isot. Org. Chem.* ***1977***, *3*, 1.

[639]See, for example, Oae, S.; Tagaki, W.; Uneyama, K.; Minamida, I. *Tetrahedron* ***1968***, *24*, 5283; Buncel, E.; Venkatachalam, T.K.; Menon, B.C. *J. Org. Chem.* ***1984***, *49*, 413.

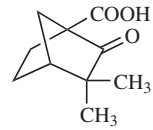
[640]Hunter, D.H.; Patel, V.; Perry, R.A. *Can. J. Chem.* ***1980***, *58*, 2271, and references cited therein.

[641]Graul, S.T.; Squires, R.R. *J. Am. Chem. Soc.* ***1988***, *110*, 607.

[642]For a review of the mechanism of the decarboxylation of β-keto acids, see Jencks, W.P. *Catalysis in Chemistry and Enzmology*; McGraw-Hill, NY, ***1969***, pp. 116–120.

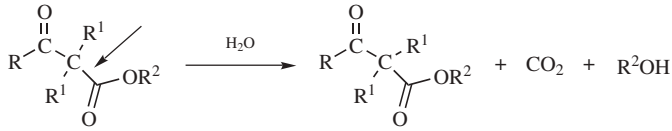
[643]Bigley, D.B.; Clarke, M.J. *J. Chem. Soc. Perkin Trans. 2* ***1982***, 1, and references cited therein. For a review, see Smith, G.G.; Kelly, F.W. *Prog. Phys. Org. Chem.* ***1971***, *8*, 75, pp. 150–153.

since similar six-membered transition states can be written for them. Some α,β-unsaturated acids are also decarboxylated by this mechanism by isomerizing to the β,γ-isomers before they



49

actually decarboxylate.[644] Evidence is that **49** and similar bicyclic β-keto acids resist decarboxylation.[645] In such compounds, the six-membered cyclic transition state cannot form for steric reasons, and if it could, formation of the intermediate enol would violate Bredt's rule (p. 229).[646] Some carboxylic acids that cannot form a six-membered transition state can still be decarboxylated, and these presumably react through an S_E1 or S_E2 mechanism.[647] Further evidence for the cyclic mechanism is that the reaction rate varies very little with a change from a nonpolar to a polar solvent (even from benzene to water[648]), and is not subject to acid catalysis.[649] The rate of decarboxylation of a β,γ-unsaturated acid was increased $\sim 10^5$–10^6 times by introduction of a β-methoxy group, indicating that the cyclic transition state has dipolar character.[650]



β-Keto acids[651] are easily decarboxylated, but such acids are usually prepared from β-keto esters, and the esters are easily decarboxylated themselves on hydrolysis without isolation of the acids.[652] This decarboxylation of β-keto esters

[644]Bigley, D.B. *J. Chem. Soc.* ***1964***, 3897.

[645]Wasserman, H.H., in Newman *Steric Effects in Organic Chemistry*, Wiley, NY, ***1956***, p. 352. See also, Buchanan, G.L.; Kean, N.B.; Taylor, R. *Tetrahedron* ***1975***, *31*, 1583.

[646]Sterically hindered β-keto acids decarboxylate more slowly: Meier, H.; Wengenroth, H.; Lauer, W.; Krause, V. *Tetrahedron Lett.* ***1989***, *30*, 5253.

[647]For example, see Ferris, J.P.; Miller, N.C. *J. Am. Chem. Soc.* ***1966***, *88*, 3522.

[648]Westheimer, F.H.; Jones, W.A. *J. Am. Chem. Soc.* ***1941***, *63*, 3283; Swain, C.G.; Bader, R.F.W.; Esteve Jr., R.M.; Griffin, R.N. *J. Am. Chem. Soc.* ***1961***, *83*, 1951.

[649]Pedersen, K.J. *Acta Chem. Scand.* ***1961***, *15*, 1718; Noyce, D.S.; Metesich, M.A. *J. Org. Chem.* ***1967***, *32*, 3243.

[650]Bigley, D.B.; Al-Borno, A. *J. Chem. Soc. Perkin Trans. 2* ***1982***, 15.

[651]For a review of β-keto acids, see Oshry, L.; Rosenfeld, S.M. *Org. Prep. Proced. Int.* ***1982***, *14*, 249.

[652]For a list examples, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1542–1543. For an example of decarboxylation of the β-keto ester with Cp2TiCl2 and *i*-PrMgBr, followed by treatment with 2*N* HCl, see Yu, Y.; Zhang, Y. *Synth. Commun.* ***1999***, *29*, 243.

involving cleavage on the carboxyl side of the substituted methylene group (arrow) is carried out under acidic, neutral, or slightly basic conditions to yield a ketone. When strongly basic conditions are used, cleavage occurs on the other side of the CR_2 group (**12-43**). β-Keto esters can be decarbalkoxylated without passing through the free-acid stage by treatment with boric anhydride (B_2O_3) at 150°C.[653] The alkyl portion of the ester (R') is converted to an alkene or, if it lacks a β hydrogen, to an ether R'OR'. Another method for the decarbalkoxylation of β-keto esters, malonic esters, and α-cyano esters consists of heating the substrate in wet DMSO containing NaCl, Na_3PO_4, or some other simple salt.[654] In this method too, the free acid is probably not an intermediate, but here the alkyl portion of the substrate is converted to the corresponding alcohol. Ordinary carboxylic acids, containing no activating groups, can be decarboxylated by conversion to esters of *N*-hydroxypyridine-2-thione and treatment of these with Bu_3SnH.[655] A free-radical mechanism is likely. α-Amino acids have been decarboxylated by treatment with a catalytic amount of 2-cyclohexenone.[656] Amino acids are decarboxylated by sequential treatment with NBS at pH 5 followed by $NaBH_4$ and $NiCl_2$.[657] Certain decarboxylations can also be accomplished photochemically.[658] See also, the decarbonylation of acyl halides, mentioned in **14-32**. In some cases, decarboxylations can give organometallic compounds: $RCOOM \rightarrow RM + CO_2$.[659]

Some of the decarboxylations listed in *Organic Syntheses* are performed with concomitant ester or nitrile hydrolysis and others are simple decarboxylations.

With ester or nitrile hydrolysis: OS **I**, 290, 451, 523; **II**, 200, 391; **III**, 281, 286, 313, 326, 510, 513, 591; **IV**, 55, 93, 176, 441, 664, 708, 790, 804; **V**, 76, 288, 572, 687, 989; **VI**, 615, 781, 873, 932; **VII**, 50, 210, 319; **VIII**, 263.

Simple decarboxylations: OS **I**, 351, 401, 440, 473, 475; **II**, 21, 61, 93, 229, 302, 333, 368, 416, 474, 512, 523; **III**, 213, 425, 495, 705, 733, 783; **IV**, 234, 254, 278, 337, 555, 560, 597, 630, 731, 857; **V**, 251, 585; **VI**, 271, 965; **VII**, 249, 359; **VIII**, 235, 444, 536; **75**, 195. Also see, OS **IV**, 633.

[653]Lalancette, J.M.; Lachance, A. *Tetrahedron Lett*. ***1970***, 3903.

[654]For a review of the synthetic applications of this method, see Krapcho, A.P. *Synthesis* ***1982***, 805, 893. For other methods, see Aneja, R.; Hollis, W.M.; Davies, A.P.; Eaton, G. *Tetrahedron Lett*. ***1983***, *24*, 4641; Brown, R.T.; Jones, M.F. *J. Chem. Res. (S)* ***1984***, 332; Dehmlow, E.V.; Kunesch, E. *Synthesis* ***1985***, 320; Taber, D.F.; Amedio, Jr., J.C.; Gulino, F. *J. Org. Chem*. ***1989***, *54*, 3474.

[655]Barton, D.H.R.; Crich, D.; Motherwell, W.B. *Tetrahedron* ***1985***, *41*, 3901; Della, E.W.; Tsanaktsidis, J. *Aust. J. Chem*. ***1987***, *39*, 2061. For another method of more limited scope, see Maier, W.F.; Roth, W.; Thies, I.; Schleyer, P.v.R. *Chem. Ber*. ***1982***, *115*, 808.

[656]Hashimoto, M.; Eda, Y.; Osanai, Y.; Iwai, T.; Aoki, S. *Chem. Lett*. ***1986***, 893.

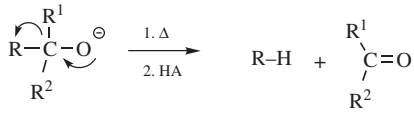
[657]Laval, G.; Golding, B.T. *Synlett* ***2003***, 542.

[658]See Davidson, R.S.; Steiner, P.R. *J. Chem. Soc. Perkin Trans. 2* ***1972***, 1357; Kraeutler, B.; Bard, A.J. *J. Am. Chem. Soc*. ***1978***, *100*, 5985; Hasebe, M.; Tsuchiya, T. *Tetrahedron Lett. 1987, 28*, 6207; Okada, K.; Okubo, K.; Oda, M. *Tetrahedron Lett. 1989, 30*, 6733.

[659]For reviews, see Deacon, G.B. *Organomet. Chem. Rev. A* ***1970***, 355; Deacon, G.B.; Faulks, S.J.; Pain, G.N. *Adv. Organomet. Chem*. ***1986***, *25*, 237.

12-41 Cleavage of Alkoxides

Hydro-de-(α-oxidoalkyl)-substitution



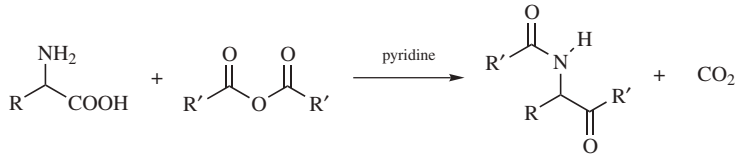
Alkoxides of tertiary alcohols can be cleaved in a reaction that is essentially the reverse of addition of carbanions to ketones (**16-24**).[660] The reaction is unsuccessful when the R groups are simple unbranched alkyl groups, for example, the alkoxide of triethylcarbinol. Cleavage is accomplished with branched alkoxides, such as the alkoxides of diisopropylneopentylcarbinol or tri-*tert*-butylcarbinol.[661] Allylic,[662] benzylic,[663] and aryl groups also cleave; for example, the alkoxide of triphenylcarbinol gives benzene and benzophenone. Studies in the gas phase show that the cleavage is a simple one, giving the carbanion and ketone directly in one step.[664] However, with some substrates in solution, substantial amounts of dimer R–R have been found, indicating a radical pathway.[665] Hindered alcohols (not the alkoxides) also lose one R group by cleavage, also by a radical pathway.[666]

The reaction has been used for extensive mechanistic studies (see p. 758).

OS **VI**, 268.

12-42 Replacement of a Carboxyl Group by an Acyl Group

Acyl-de-carboxylation



[660]Zook, H.D.; March, J.; Smith, D.F. *J. Am. Chem. Soc.* ***1959***, *81*, 1617; Barbot, F.; Miginiac, P. *J. Organomet. Chem.* ***1977***, *132*, 445; Benkeser, R.A.; Siklosi, M.P.; Mozdzen, E.C. *J. Am. Chem. Soc.* ***1978***, *100*, 2134.

[661]Arnett, E.M.; Small, L.E.; McIver Jr., R.T.; Miller, J.S. *J. Org. Chem.* ***1978***, *43*, 815. See also Lomas, J.S.; Dubois, J.E. *J. Org. Chem.* ***1984***, *49*, 2067.

[662]See Snowden, R.L.; Linder, S.M.; Muller, B.L.; Schulte-Elte, K.H. *Helv. Chim. Acta* ***1987***, *70*, 1858, 1879.

[663]Partington, S.M.; Watt, C.I.F. *J. Chem. Soc. Perkin Trans. 2* ***1988***, 983.

[664]Tumas, W.; Foster, R.F.; Brauman, J.I. *J. Am. Chem. Soc.* ***1988***, *110*, 2714; Ibrahim, S.; Watt, C.I.F.; Wilson, J.M.; Moore, C. *J. Chem. Soc. Chem. Commun.* ***1989***, 161.

[665]Paquette, L.A.; Gilday, J.P.; Maynard, G.D. *J. Org. Chem.* ***1989***, *54*, 5044; Paquette, L.A.; Maynard, G.D. *J. Org. Chem.* ***1989***, *54*, 5054.

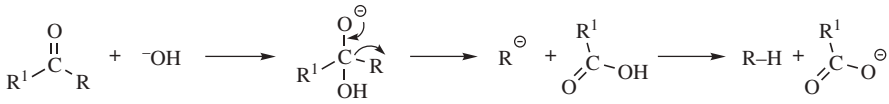
[666]See Lomas, J.S.; Fain, D.; Briand, S. *J. Org. Chem.* ***1990***, *55*, 1052, and references cited therein.

When an α-amino acid is treated with an anhydride in the presence of pyridine, the carboxyl group is replaced by an acyl group and the NH_2 becomes acylated. This is called the *Dakin–West reaction*.[667] The mechanism involves formation of an oxazolone.[668] The reaction sometimes takes place on carboxylic acids even when an a amino group is not present. A number of *N*-substituted amino acids, RCH(NHR′)COOH, give the corresponding *N*-alkylated products.

OS **IV**, 5; **V**, 27.

B. Acyl Cleavages

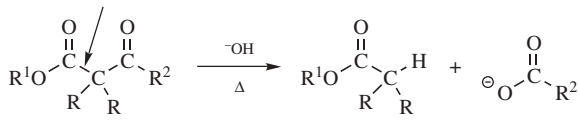
In these reactions (**12-43–12-46**), a carbonyl group is attacked by a hydroxide ion (or amide ion), giving an intermediate that undergoes cleavage to a carboxylic acid (or an amide). With respect to the leaving group, this is nucleophilic substitution at a carbonyl group and the mechanism is the tetrahedral one discussed in Chapter 10.



With respect to R this is of course electrophilic substitution. The mechanism is usually S_E1.

12-43 Basic Cleavage of β-Keto Esters and β-Diketones

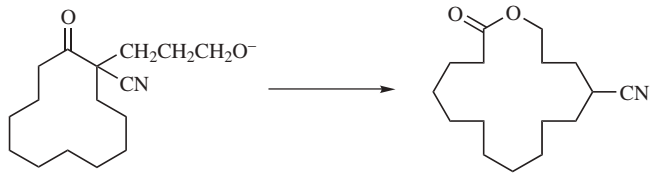
Hydro-de-acylation



When β-keto esters are treated with concentrated base, cleavage occurs, but is on the keto side of the CR_2 group (arrow) in contrast to the acid cleavage mentioned on page 838. The products are a carboxylic ester and the salt of an acid. However, the utility of the reaction is somewhat limited by the fact that decarboxylation is a side reaction, even under basic conditions. β-Diketones behave similarly to give a ketone and the salt of a carboxylic acid. With both β-keto esters and β-diketones, $^-$OEt can be used instead of $^-$OH, in which case the ethyl esters of the corresponding acids are obtained instead of the salts. In the case of β-keto esters, this is the reverse of Claisen condensation (**16-85**). The similar cleavage of cyclic α-cyano

[667]For a review, see Buchanan, G.L. *Chem. Soc. Rev.* ***1988***, *17*, 91.
[668]Allinger, N.L.; Wang, G.L.; Dewhurst, B.B. *J. Org. Chem.* ***1974***, *39*, 1730.

ketones, in an intramolecular fashion, has been used to effect a synthesis of macrocyclic lactones such as **50**.[669]

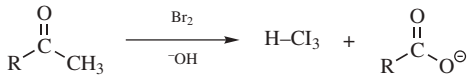


50

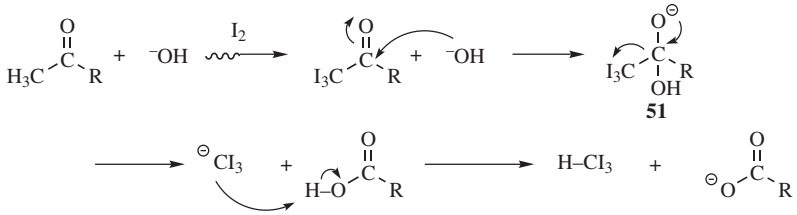
Activated F^- (from KF and a crown ether) has been used as the base to cleave an α-cyano ketone.[670]

OS **II**, 266, 531; **III**, 379; **IV**, 415, 957; **V**, 179, 187, 277, 533, 747, 767.

12-44 Haloform Reaction



In the *haloform reaction*, methyl ketones (and the only methyl aldehyde, acetaldehyde) are cleaved with halogen and a base.[671] The halogen can be bromine, chlorine, or iodine. What takes place is actually a combination of two reactions. The first is an example of **12-4**, in which, under the basic conditions employed, the methyl group is trihalogenated. Then the resulting trihalo ketone is attacked by hydroxide ion to give tetrahedral intermediate **51**.[672] The X_3C^- group is a sufficiently good leaving group (not HX_2C^- or H_2XC^-) that a carboxylic acid is formed, with quickly reacts with the carbanion to give the final products. Primary or secondary methylcarbinols also give the reaction, because they are oxidized to the carbonyl compounds under the conditions employed.



51

[669]Milenkov, B.; Hesse, M. *Helv. Chim. Acta* ***1987***, *70*, 308. For a similar preparation of lactams, see Wälchli, R.; Bienz, S.; Hesse, M. *Helv. Chim. Acta* ***1985***, *68*, 484.

[670]Beletskaya, I.P.; Gulyukina, N.S.; Borodkin, V.S.; Solov'yanov, A.A.; Reutov, O.A. *Doklad. Chem.* ***1984***, *276*, 202. See also, Mignani, G.; Morel, D.; Grass, F. *Tetrahedron Lett*. ***1987***, *28*, 5505.

[671]For a review of this and related reactions, see Chakrabartty, S.K., in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. C, Academic Press, NY, ***1978***, pp. 343–370.

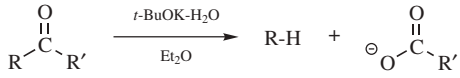
[672]For a complete kinetic analysis of the chlorination of acetone, see Guthrie, J.P.; Cossar, J. *Can. J. Chem.* ***1986***, *64*, 1250. For a discussion of the mechanism of the cleavage step, see Zucco, C.; Lima, C.F.; Rezende, M.C.; Vianna, J.F.; Nome, F. *J. Org. Chem.* ***1987***, *52*, 5356.

As with **12-4**, the rate-determining step is the preliminary enolization of the methyl ketone.[673] A side reaction is α halogenation of the non-methyl R group. Sometimes these groups are also cleaved.[674] The reaction cannot be applied to F_2, but ketones of the form $RCOCF_3$ (R = alkyl or aryl) give fluoroform and $RCOO^-$ when treated with base.[675] Rate constants for cleavage of X_3CCOPh (X = F, Cl, Br) were found to be in the ratio $1 : 5.3 \times 10^{10} : 2.2 \times 10^{13}$, showing that an F_3C^- group cleaves much more slowly than the others.[676] The haloform reaction is often used as a test for methylcarbinols and methyl ketones. Iodine is most often used as the test reagent, since iodoform (HCI_3) is an easily identifiable yellow solid. The reaction is also frequently used for synthetic purposes. Methyl ketones $RCOCH_3$ can be converted directly to methyl esters $RCOOCH_3$ by an electrochemical reaction.[677] Trifluoromethyl ketones have been converted to ethyl esters via treatment with NaH in aqueous DMF followed by reaction with bromoethane.[678]

OS **I**, 526; **II**, 428; **III**, 302; **IV**, 345; **V**, 8. Also see, OS **VI**, 618.

12-45 Cleavage of Nonenolizable Ketones

Hydro-de-acylation



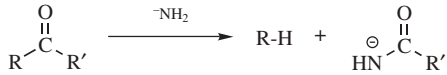
Ordinary ketones are generally much more difficult to cleave than trihalo ketones or β-diketones, because the carbanion intermediates in these cases are more stable than simple carbanions. However, nonenolizable ketones can be cleaved by treatment with a 10:3 mixture of *t*-BuOK–H_2O in an aprotic solvent, such as ether, DMSO, 1,2-dimethoxyethane (glyme),[679] or with solid *t*-BuOK in the absence of a solvent.[680] When the reaction is applied to monosubstituted diaryl ketones, that aryl group preferentially cleaves that comes off as the more stable carbanion, except that aryl groups substituted in the ortho position are more readily cleaved than otherwise because of the steric effect (relief of strain).[680,681] In certain cases, cyclic ketones can be cleaved by base treatment, even if they are enolizable.[682]

OS **VI**, 625. See also, OS **VII**, 297.

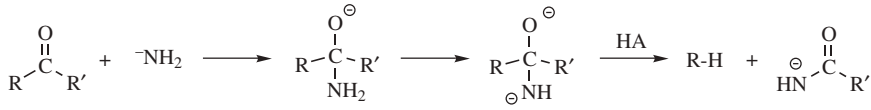
[673]Pocker, Y. *Chem. Ind.* (*London*) ***1959***, 1383.
[674]Levine, R.; Stephens, J.R. *J. Am. Chem. Soc.* ***1950***, *72*, 1642.
[675]See Hudlicky, M. *Chemistry of Organic Fluorine Compounds*, 2nd ed.; Ellis Horwood: Chichester, ***1976***, pp. 276–278.
[676]Guthrie, J.P.; Cossar, J. *Can. J. Chem.* ***1990***, *68*, 1640.
[677]Nikishin, G.I.; Elinson, M.N.; Makhova, I.V. *Tetrahedron* ***1991***, *47*, 895.
[678]Delgado, A.; Clardy, J. *Tetrahedron Lett.* ***1992***, *33*, 2789.
[679]Swan, G.A. *J. Chem. Soc.* ***1948***, 1408; Gassman, P.G.; Lumb, J.T.; Zalar, F.V. *J. Am. Chem. Soc.* ***1967***, *89*, 946.
[680]March, J.; Plankl, W. *J. Chem. Soc. Perkin Trans. 1* ***1977***, 460.
[681]Davies, D.G.; Derenberg, M.; Hodge, P. *J. Chem. Soc. C* ***1971***, 455.
[682]For example, see Swaminathan, S.; Newman, M.S. *Tetrahedron* ***1958***, *2*, 88; Hoffman, T.D.; Cram, D.J. *J. Am. Chem. Soc.* ***1969***, *91*, 1009.

12-46 The Haller–Bauer Reaction

Hydro-de-acylation



Cleavage of ketones with sodium amide is called the *Haller–Bauer reaction*.[683] As with **12-45**, which is exactly analogous, the reaction is usually applied only to non-enolizable ketones, most often to ketones of the form $ArCOCR_3$, where the products R_3CCONH_2 are not easily attainable by other methods. However, many other ketones have been used, although benzophenone is virtually unaffected. It has been shown that the configuration of optically active alkyl groups (R) is retained.[684] The NH_2 loses its proton from the tetrahedral intermediate **52** before the R group is cleaved.[685]



52

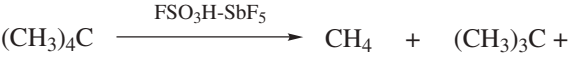
An extension of this cleavage process involves the reaction of α-nitro ketones ($O{=}C\text{-}CHRNO_2$) with a primary amine, neat, to give the corresponding amide ($O{=}C\text{-}NHR'$).[686]

OS **V**, 384, 1074.

C. Other Cleavages

12-47 The Cleavage of Alkanes

Hydro-de-*tert*-butylation, and so on



The C–C bonds of alkanes can be cleaved by treatment with superacids[48] (p. 236). For example, neopentane in FSO_3H–SbF_5 can cleave to give methane and the *tert*-butyl cation. The C–H cleavage (see **12-1**) is a competing reaction and, for example, neopentane can give H_2 and the *tert*-pentyl cation (formed by rearrangement of the initially formed neopentyl cation) by this pathway. In general, the order of reactivity is tertiary C–H > C–C > secondary C–H ≫ primary C–H,

[683]For a review, see Gilday, J.P.; Paquette, L.A. *Org. Prep. Proced. Int.* ***1990***, *22*, 167. For an improved procedure, see Kaiser, E.M.; Warner, C.D. *Synthesis* ***1975***, 395.
[684]Impastato, F.J.; Walborsky, H.M. *J. Am. Chem. Soc.* ***1962***, *84*, 4838; Paquette, L.A.; Gilday, J.P. *J. Org. Chem.* ***1988***, *53*, 4972; Paquette, L.A.; Ra, C.S. *J. Org. Chem.* ***1988***, *53*, 4978.
[685]Bunnett, J.F.; Hrutfiord, B.F. *J. Org. Chem.* ***1962***, *27*, 4152.
[686]Ballini, R.; Bosica, G.; Fiorini, D. *Tetrahedron* ***2003***, *59*, 1143.

although steric factors cause a shift in favor of C–C cleavage in such a hindered compound as tri-*tert*-butylmethane. The mechanism is similar to that shown in **12-1** and **12-20** and involves attack by H^+ on the C–C bond to give a pentavalent cation.

Catalytic hydrogenation seldom breaks unactivated C–C bonds (i.e., $R–R' + H_2 \rightarrow RH + R'H$), but methyl and ethyl groups have been cleaved from substituted adamantanes by hydrogenation with a $Ni–Al_2O_3$ catalyst at about 250°C.[687] Certain C–C bonds have been cleaved by alkali metals.[688]

The C–C bond of 2-allyl-2-arylmalonate derivatives was cleaved, with loss of the allylic group to give the 2-arylmalonate, by treatment with a nickel catalyst.[689]

12-48 Decyanation or Hydro-de-cyanation

$$RCN \xrightarrow{Na\text{-}NH_3 \text{ or } Na\text{-}Fe(acac)_3} RH$$

The cyano group of alkyl nitriles can be removed[690] by treatment with metallic sodium, either in liquid ammonia,[691] or together with tris(acetylacetonato)iron(III) [$Fe(acac)_3$][692] or, with lower yields, titanocene. The two procedures are complementary. Although both can be used to decyanate many kinds of nitriles, the $Na–NH_3$ method gives high yields with R groups, such as trityl, benzyl, phenyl, and tertiary alkyl, but lower yields (~35–50%) when R = primary or secondary alkyl. On the other hand, primary and secondary alkyl nitriles are decyanated in high yields by the $Na–Fe(acac)_3$ procedure. Sodium in liquid ammonia is known to be a source of solvated electrons, and the reaction may proceed through the free radical R• that would then be reduced to the carbanion R^-, which by abstraction of a proton from the solvent, would give RH. The mechanism with $Fe(acac)_3$ is presumably different. Another procedure,[693] which is successful for R = primary, secondary, or tertiary, involves the use of potassium metal and the crown ether dicyclohexano-18-crown-6 in toluene.[694]

[687]Grubmüller, P.; Schleyer, P.v.R.; McKervey, M.A. *Tetrahedron Lett.* ***1979***, 181.

[688]For examples and references, see Grovenstein, Jr., E.; Bhatti, A.M.; Quest, D.E.; Sengupta, D.; VanDerveer, D. *J. Am. Chem. Soc.* ***1983***, *105*, 6290.

[689]Nečas, D.; Turský, M.; Kotora, M. *J. Am. Chem. Soc.* ***2004***, *126*, 10222.

[690]For a list of procedures, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, p. 75.

[691]Büchner, W.; Dufaux, R. *Helv. Chim. Acta* ***1966***, *49*, 1145; Arapakos, P.G.; Scott, M.K.; Huber, Jr., F.E. *J. Am. Chem. Soc.* ***1969***, *91*, 2059; Birch, A.J.; Hutchinson, E.G. *J. Chem. Soc. Perkin Trans. 1* ***1972***, 1546; Yamada, S.; Tomioka, K.; Koga, K. *Tetrahedron Lett.* ***1976***, 61.

[692]Van Tamelen, E.E.; Rudler, H.; Bjorklund, C. *J. Am. Chem. Soc.* ***1971***, *93*, 7113.

[693]For other procedures, see Cuvigny, T.; Larcheveque, M.; Normant, H. *Bull. Soc. Chim. Fr.* ***1973***, 1174; Berkoff, C.E.; Rivard, D.E.; Kirkpatrick, D.; Ives, J.L. *Synth. Commun.* ***1980***, *10*, 939; Savoia, D.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Org. Chem.* ***1980***, *45*, 3227; Ozawa, F.; Iri, K.; Yamamoto, A. *Chem. Lett.* ***1982***, 1707.

[694]Ohsawa, T.; Kobayashi, T.; Mizuguchi, Y.; Saitoh, T.; Oishi, T. *Tetrahedron Lett.* ***1985***, *26*, 6103.

α-Amino and α-amido nitriles $RCH(CN)NR'_2$ and RCH(CN)NHCOR' can be decyanated in high yield by treatment with $NaBH_4$.[695]

ELECTROPHILIC SUBSTITUTION AT NITROGEN

In most of the reactions in this section, an electrophile bonds with the unshared pair of a nitrogen atom. The electrophile may be a free positive ion or a positive species attached to a carrier that breaks off in the course of the attack or shortly after:

53

Further reaction of **53** depends on the nature of Y and of the other groups attached to the nitrogen.

12-49 The Conversion of Hydrazines to Azides

Hydrazine–azide transformation

Monosubstituted hydrazines treated with nitrous acid give azides in a reaction exactly analogous to the formation of aliphatic diazo compounds mentioned in **13-19**. Among other reagents used for this conversion have been N_2O_4[696] and nitrosyl tetrafluoroborate ($NOBF_4$).[697]

OS **III**, 710; **IV**, 819; **V**, 157.

12-50 *N*-Nitrosation

***N*-Nitroso-de-hydrogenation**

When secondary amines are treated with nitrous acid (typically formed from sodium nitrite and a mineral acid),[698] *N*-nitroso compounds (also called

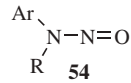
[695]Yamada, S.; Akimoto, H. *Tetrahedron Lett*. ***1969***, 3105; Fabre, C.; Hadj Ali Salem, M.; Welvart, Z. *Bull. Soc. Chim. Fr.* ***1975***, 178. See also Ogura, K.; Shimamura, Y.; Fujita, M. *J. Org. Chem*. ***1991***, *56*, 2920.

[696]Kim, Y.H.; Kim, K.; Shim, S.B. *Tetrahedron Lett*. ***1986***, *27*, 4749.

[697]Pozsgay, V.; Jennings, H.J. *Tetrahedron Lett*. ***1987***, *28*, 5091.

[698]From $NaNO_2$/oxalic acid: Zolfigol, M.A. *Synth. Commun.* ***1999***, *29*, 905. From $NaNO_2$ on wet silica: Zolfigol, M.A.; Ghaemi, E.; Madrikian, E.; Kiany-Burazjani, *M. Synth. Commun.* ***2000***, *30*, 2057.

nitrosamines) are formed.[699] The reaction can be accomplished with dialkyl-, diaryl-, or alkylarylamines, and even with mono-*N*-substituted amides: RCONHR' + HONO → RCON(NO)R'.[700] Tertiary amines have also been *N*-nitrosated, but in these cases one group cleaves, so that the product is the nitroso derivative of a secondary amine.[701] The group that cleaves appears as an aldehyde or ketone. Other reagents have also been used, for example, NOCl, which is useful for amines or amides that are not soluble in an acidic aqueous solution or where the *N*-nitroso compounds are highly reactive. *N*-Nitroso compounds can be prepared in basic solution by treatment of secondary amines with gaseous N_2O_3, N_2O_4,[702] or alkyl nitrites,[703] and, in aqueous or organic solvents, by treatment with $BrCH_2NO_2$.[704] Secondary amines are converted to the *N*-nitroso compound with H_5IO_6 on wet silica.[705]



54

The mechanism of nitrosation is essentially the same as in **13-19** up to the point where **54** is formed. Since this species cannot lose a proton, it is stable and the reaction ends there. The attacking entity can be any of those mentioned in **13-19**. The following has been suggested as the mechanism for the reaction with tertiary amines:[706]

[699]For reviews, see Williams, D.L.H. Williams, D.L.H. *Nitrosation*; Cambridge University Press, Cambridge, ***1988***, pp. 95–109; Kostyukovskii, Ya.L.; Melamed, D.B. *Russ. Chem. Rev.* ***1988***, *57*, 350; Saavedra, J.E. *Org. Prep. Proced. Int.* ***1987***, *19*, 83; Williams, D.L.H. *Adv. Phys. Org. Chem.* ***1983***, *19*, 381; Challis, B.C.; Challis, J.A. in Patai, S.; Rappoport, Z. *The Chemistry of the Functional Groups Supplement F*, pt. 2, Wiley, NY, ***1982***, pp. 1151–1223; Ridd, J.H. *Q. Rev. Chem. Soc.* ***1961***, *15*, 418. For a review of the chemistry of aliphatic *N*-nitroso compounds, including methods of synthesis see Fridman, A.L.; Mukhametshin, F.M.; Novikov, S.S. *Russ. Chem. Rev.* ***1971***, *40*, 34. For a discussion of encapsulated reagents used for nitrosation, see Zyranov, G.V.; Rudkevich, D.M. *Org. Lett.* ***2003***, *5*, 1253.

[700]For a discussion of the mechanism with amides, see Castro, A.; Iglesias, E.; Leis, J.R.; Peña, M.E.; Tato, J.V. *J. Chem. Soc. Perkin Trans. 2* ***1986***, 1725.

[701]Hein, G.E. *J. Chem. Educ.* ***1963***, *40*, 181. See also, Verardo, G.; Giumanini, A.G.; Strazzolini, P. *Tetrahedron* ***1990***, *46*, 4303.

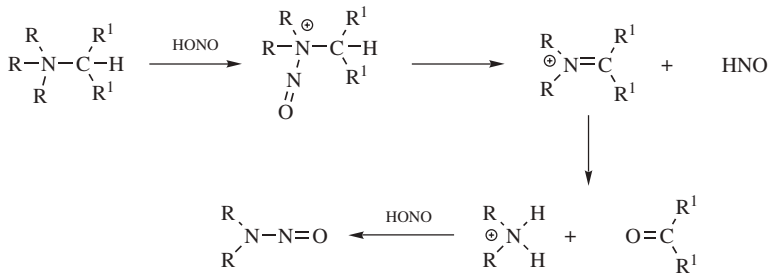
[702]Challis, B.C.; Kyrtopoulos, S.A. *J. Chem. Soc. Perkin Trans. 1* ***1979***, 299.

[703]Casado, J.; Castro, A.; Lorenzo, F.M.; Meijide, F. *Monatsh. Chem.* ***1986***, *117*, 335.

[704]Challis, B.C.; Yousaf, T.I. *J. Chem. Soc. Chem. Commun.* ***1990***, 1598.

[705]Zolfigol, M.A.; Choghamarani, A.G.; Shivini, F.; Keypour, H.; Salehzadeh, S. *Synth. Commun.* ***2001***, *31*, 359. Also with $KHSO_5$ on wet silica, see Zolfigol, M.A.; Bagherzadeh, M.; Choghamarani, A.G.; Keypour, H.; Salehzadeh, S. *Synth. Commun.* ***2001***, *31*, 1161.

[706]Smith, P.A.S.; Loeppky, R.N. *J. Am. Chem. Soc.* ***1967***, *89*, 1147; Smith, P.A.S.; Pars, H.G. *J. Org. Chem.* ***1959***, *24*, 1324; Gowenlock, B.G.; Hutchison, R.J.; Little, J.; Pfab, J. *J. Chem. Soc. Perkin Trans. 2* ***1979***, 1110. See also, Loeppky, R.N.; Outram, J.R.; Tomasik, W.; Faulconer, J.M. *Tetrahedron Lett.* ***1983***, *24*, 4271.



The evidence for this mechanism includes the facts that nitrous oxide is a product (formed by 2 HNO $\rightarrow H_2O + N_2O$) and that quinuclidine, where the nitrogen is at a bridgehead, and therefore cannot give elimination, does not react. Tertiary amines have also been converted to nitrosamines with nitric acid in Ac_2O[707] and with N_2O_4.[708]

Amines and amides can be *N*-nitrated[709] with nitric acid,[710] or NO_2^+,[711] and aromatic amines can be converted to triazenes with diazonium salts. Aliphatic primary amines can also be converted to triazenes if the diazonium salts contain electron-withdrawing groups.[712] C-Nitrosation is discussed at **11-3** and **12-8**.

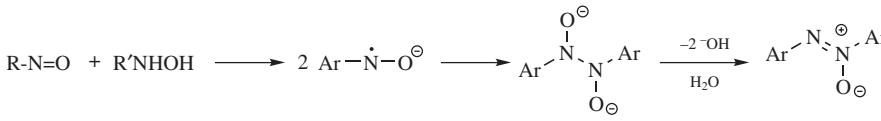
OS **I**, 177, 399, 417; **II**, 163, 211, 290, 460, 461, 462, 464 (also see **V**, 842); **III**, 106, 244; **IV**, 718, 780, 943; **V**, 336, 650, 797, 839, 962; **VI**, 542, 981. Also see, OS **III**, 711.

12-51 Conversion of Nitroso Compounds to Azoxy Compounds

In a reaction similar to **13-24**, azoxy compounds can be prepared by the condensation of a nitroso compound with a hydroxylamine.[713] The position of the oxygen in the final product is determined by the nature of the R groups, not by which R groups came from which starting compound. Both R and R' can be alkyl or aryl, but when two different aryl groups are involved, mixtures of azoxy compounds

[707]Boyer, J.H.; Pillai, T.P.; Ramakrishnan, V.T. *Synthesis* ***1985***, 677.
[708]Boyer, J.H.; Kumar, G.; Pillai, T.P. *J. Chem. Soc. Perkin Trans. 1* ***1986***, 1751.
[709]For other reagents, see Mayants, A.G.; Pyreseva, K.G.; Gordeichuk, S.S. *J. Org. Chem. USSR* ***1986***, *22*, 1900; Bottaro, J.C.; Schmitt, R.J.; Bedford, C.D. *J. Org. Chem.* ***1987***, *52*, 2292; Suri, S.C.; Chapman, R.D. *Synthesis* ***1988***, 743; Carvalho, E.; Iley, J.; Norberto, F.; Rosa, E. *J. Chem. Res. (S)* ***1989***, 260.
[710]Cherednichenko, L.V.; Dmitrieva, L.G.; Kuznetsov, L.L.; Gidaspov, B.V. *J. Org. Chem. USSR* ***1976***, *12*, 2101, 2105.
[711]Ilyushin, M.A.; Golod, E.L.; Gidaspov, B.V. *J. Org. Chem. USSR* ***1977***, *13*, 8; Andreev, S.A.; Lededev, B.A.; Tselinskii, I.V. *J. Org. Chem. USSR* ***1980***, *16*, 1166, 1170, 1175, 1179.
[712]For a review of alkyl traizenes, see Vaughan, K.; Stevens, M.F.G. *Chem. Soc. Rev.* ***1978***, *7*, 377.
[713]Boyer, J.H., in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, pt. 1, Wiley, NY, ***1969***, pp. 278–283.

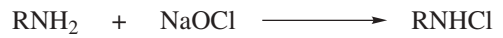
(ArNONAr, ArNONAr′, and Ar′NONAr′) are obtained[714] and the unsymmetrical product (ArNONAr′) is likely to be formed in the smallest amount. This behavior is probably caused by an equilibration between the starting compounds prior to the actual reaction ($ArNO + Ar'NHOH \rightarrow Ar'NO + ArNHOH$).[715] The mechanism[716] has been investigated in the presence of base. Under these conditions both reactants are converted to radical anions, which couple:



These radical anions have been detected by esr.[717] This mechanism is consistent with the following result: when nitrosobenzene and phenylhydroxylamine are coupled, ^{18}O and ^{15}N labeling show that the two nitrogens and the two oxygens become equivalent.[718] Unsymmetrical azoxy compounds can be prepared[719] by combination of a nitroso compound with an *N,N*-dibromoamine. Symmetrical and unsymmetrical azo and azoxy compounds are produced when aromatic nitro compounds react with aryliminodimagnesium reagents $ArN(MgBr)_2$.[720]

12-52 *N*-Halogenation

N-Halo-de-hydrogenation



Treatment with sodium hypochlorite or hypobromite converts primary amines into *N*-halo- or *N,N*-dihaloamines. Secondary amines can be converted to *N*-halo secondary amines. Similar reactions can be carried out on unsubstituted and *N*-substituted amides and on sulfonamides. With unsubstituted amides the *N*-halogen product is seldom isolated but usually rearranges (see **18-13**); however, *N*-halo-*N*-alkyl amides and *N*-halo imides are quite stable. The important reagents NBS and NCS are made in this manner. *N*-Halogenation has also been accomplished with other

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[715]Knight, G.T.; Saville, B. *J. Chem. Soc. Perkin Trans. 2* ***1973***, 1550.
[716]For discussions of the mechanism in the absence of base, see Darchen, A.; Moinet, C. *Bull. Soc. Chim. Fr.* ***1976***, 812; Becker, A.R.; Sternson, L.A. *J. Org. Chem*. ***1980***, *45*, 1708. See also, Pizzolatti, M.G.; Yunes, R.A. *J. Chem. Soc. Perkin Trans. 1* ***1990***, 759.
[717]Russell, G.A.; Geels, E.J.; Smentowski, F.J.; Chang, K.; Reynolds, J.; Kaupp, G. *J. Am. Chem. Soc*. ***1967***, *89*, 3821.
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[719]Zawalski, R.C.; Kovacic, P. *J. Org. Chem*. ***1979***, *44*, 2130. For another method, see Moriarty, R.M.; Hopkins, T.E.; Prakash, I.; Vaid, B.K.; Vaid, R.K. *Synth. Commun*. ***1990***, *20*, 2353.
[720]O kubo, M.; Matsuo, K.; Yamauchi, A. *Bull. Chem. Soc. Jpn*. ***1989***, *62*, 915, and other papers in this series.

reagents (e.g., sodium bromite $NaBrO_2$),[721] benzyltrimethylammonium tribromide ($PhCH_2NMe_3^+$ Br_3-),[722] NaCl with Oxone®,[723] and *N*-chlorosuccinimide.[724] The mechanisms of these reactions[725] involve attack by a positive halogen and are probably similar to those of **13-19** and **12-50**.[726] *N*-Fluorination can be accomplished by direct treatment of amines[727] or amides[728] with F_2. Fluorination of *N*-alkyl-*N*-fluoro amides (RRN(F)COR') results in cleavage to *N,N*-difluoroamines (RNF_2).[728,729] Trichloroisocyanuric acid converts primary amines to the *N,N*-dichloroamine.[730]

OS **III**, 159; **IV**, 104, 157; **V**, 208, 663, 909; **VI**, 968; **VII**, 223; **VIII**, 167, 427.

12-53 The Reaction of Amines With Carbon Monoxide or Carbon Dioxide

N-**Formylation** or *N*-**Formyl-de-hydrogenation**, and so on

Three types of product can be obtained from the reaction of amines with carbon monoxide, depending on the catalyst. (*1*) Both primary and secondary amines react with CO in the presence of various catalysts [e.g., $Cu(CN)_2$, $Me_3N–H_2Se$, rhodium or ruthenium complexes] to give *N*-substituted and *N,N*-disubstituted formamides, respectively.[731] Primary aromatic amines react with ammonium formate to give the formamide.[732] Tertiary amines react with CO and a palladium catalyst to give an amide.[733] (*2*) Symmetrically substituted ureas can be prepared by treatment of a primary amine (or ammonia) with CO[734] in the presence of selenium[735] or

[721]Kajigaeshi, S.; Nakagawa, T.; Fujisaki, S. *Chem. Lett*. ***1984***, 2045.
[722]Kajigaeshi, S.; Murakawa, K.; Asano, K.; Fujisaki, S.; Kakinami, T. *J. Chem. Soc. Perkin Trans. 1* ***1989***, 1702.
[723]Curini, M.; Epifano, F.; Marcotullio, M.C.; Rosati, O.; Tsadjout, A. *Synlett* ***2000***, 813.
[724]See Deno, N.C.; Fishbein, R.; Wyckoff, J.C. *J. Am. Chem. Soc*. ***1971***, *93*, 2065; Guillemin, J.; Denis, J.N. *Synthesis* ***1985***, 1131.
[725]For a study of the mechanism, see Matte, D.; Solastiouk, B.; Merlin, A.; Deglise, X. *Can. J. Chem*. ***1989***, *67*, 786.
[726]For studies of reactivity in this reaction, see Thomm, E.W.C.W.; Wayman, M. *Can. J. Chem*. ***1969***, *47*, 3289; Higuchi, T.; Hussain, A.; Pitman, I.H. *J. Chem. Soc. B*, ***1969***, 626.
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[729]See Barton, D.H.R.; Hesse, R.H.; Klose, T.R.; Pechet, M.M. *J. Chem. Soc. Chem. Commun*. ***1975***, 97.
[730]DeLuca, L.; Giacomelli, G. *Synlett* ***2004***, 2180.
[731]See Saegusa, T.; Kobayashi, S.; Hirota, K.; Ito, Y. *Bull. Chem. Soc. Jpn*. ***1969***, *42*, 2610; Nefedov, B.K.; Sergeeva, N.S.; Éidus, Ya.T. *Bull. Acad. Sci. USSR Div. Chem. Sci*. ***1973***, *22*, 784; Yoshida, Y.; Asano, S.; Inoue, S. *Chem. Lett*. ***1984***, 1073; Bitsi, G.; Jenner, G. *J. Organomet. Chem*. ***1987***, *330*, 429.
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[733]Murahashi, S.-I.; Imada, Y.; Nishimura, K. *Tetrahedron*, ***1994***, *50*, 453.
[734]For a synthesis involving a palladium catalyst, see Gabriele, B.; Salerno, G.; Mancuso, R.; Costa, M. *J. Org. Chem*. ***2004***, *69*, 4741.
[735]Sonoda, N.; Yasuhara, T.; Kondo, K.; Ikeda, T.; Tsutsumi, S. *J. Am. Chem. Soc*. ***1971***, *93*, 6344.

sulfur.[736] R can be alkyl or aryl. The same thing can be done with secondary amines, by using $Pd(OAc)_2$–I_2–K_2CO_3.[737] Primary aromatic amines react with β-keto esters and a Mo–ZrO_2 catalyst to give the symmetrical urea.[738] Treatment of a secondary amine with nitrobenzene, selenium, and carbon monoxide leads to the unsymmetrical urea.[739] (*3*) When $PdCl_2$ is the catalyst, primary amines yield isocyanates.[740] Isocyanates can also be obtained by treatment of CO with azides: $RN_3 + CO \rightarrow RNCO$,[741] or with an aromatic nitroso or nitro compound and a rhodium complex catalyst.[742] Primary amines react with di-*tert*-butyltricarbonate to give the isocyanate.[743] Lactams are converted to the corresponding *N*-chloro lactam with $Ca(OCl)_2$ with moist alumina in dichloromethane.[744]

A fourth type of product, a carbamate RNHCOOR', can be obtained from primary or secondary amines, if these are treated with CO, O_2, and an alcohol R'OH in the presence of a catalyst.[745] Primary amines react with dimethyl carbonate in supercritical CO_2 (see p. 414) to give a carbamate.[746] Carbamates can also be obtained from nitroso compounds, by treatment with CO, R'OH, $Pd(OAc)_2$, and $Cu(OAc)_2$,[747] and from nitro compounds.[748] When allylic amines ($R_2C{=}CHRCHRNR'_2$) are treated with CO and a palladium–phosphine catalyst, the CO inserts to produce the β,γ-unsaturated amides ($R_2C{=}CHRCHRCONR'_2$) in good yields.[749] Ring-expanded lactams are obtained from cyclic amines via a similar reaction[750] (see also, **16-22**). Silyloxy carbamates ($RNHCO_2SiR'_3$) can be prepared by the reaction of a primary amine with carbon dioxide and triethylamine, followed by reaction with triisopropylsilyl triflate and tetrabutylammonium fluoride.[751]

Carbon dioxide reacts with amines ($ArNH_2$) and alkyl halides, under electrolysis conditions, to give the corresponding carbamate ($ArNHCO_2Et$).[752] Secondary

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[744]Larionov, O.V.; Kozhushkov, S.I.; de Meijere, A. *Synthesis* ***2003***, 1916.
[745]Fukuoka, S.; Chono, M.; Kohno, M. *J. Org. Chem.* ***1984***, *49*, 1458; *J. Chem. Soc. Chem. Commun.* ***1984***, 399; Feroci, M.; Inesi, A.; Rossi, L. *Tetrahedron Lett.* ***2000***, *41*, 963.
[746]Selva, M.; Tundo, P.; Perosa, A. *Tetrahedron Lett.* ***2002***, *43*, 1217.
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[750]Wang, M.D.; Alper, H. *J. Am. Chem. Soc.* ***1992***, *114*, 7018.
[751]Lipshutz, B.H.; Papa, P.; Keith, J.M. *J. Org. Chem.* ***1999***, *64, 3* 792.
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amines react with all halides and an onium salt in supercritical CO_2 (see p. 414) to give the carbamate.[753] *N*-phenylthioamines react with CO and a palladium catalyst to give a thiocarbamate ($ArSCO_2NR'_2$).[754] Urea derivatives were obtained from amines, CO_2, and an antimony catalyst.[755]

Aziridines can be converted to cyclic carbamates (oxazolidinones) by heating with carbon dioxide and a chromium–salen catalyst.[756] The reaction of aziridines with LiI, and then CO_2 also generates oxazolidinones.[757]

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