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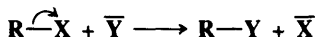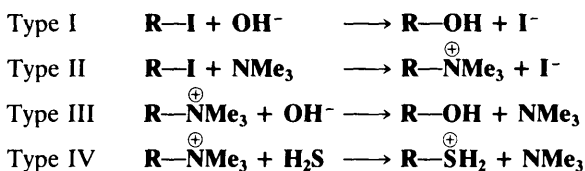
ALIPHATIC NUCLEOPHILIC SUBSTITUTION

In nucleophilic substitution the attacking 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:

$$R \overset{\frown}{-} X + \overline{Y} \longrightarrow R{-}Y + \overline{X}$$

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

Type I	$R{-}I + OH^-$	$\longrightarrow R{-}OH + I^-$
Type II	$R{-}I + NMe_3$	$\longrightarrow R{-}\overset{\oplus}{N}Me_3 + I^-$
Type III	$R{-}\overset{\oplus}{N}Me_3 + OH^-$	$\longrightarrow R{-}OH + NMe_3$
Type IV	$R{-}\overset{\oplus}{N}Me_3 + H_2S$	$\longrightarrow R{-}\overset{\oplus}{S}H_2 + NMe_3$

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 NMe₃ is an *alkylation* of trimethylamine. Similarly, nucleophilic substitution at an acyl carbon is an *acylation* of the nucleophile.

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 SN1 and SN2 mechanisms.

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[1]For a monograph on this subject, see Hartshorn *Aliphatic Nucleophilic Substitution*; Cambridge University Press: Cambridge, 1973. For reviews, see Katritzky; Brycki *Chem. Soc. Rev.* **1990**, *19*, 83-105; Richard *Adv. Carbocation Chem.* **1989**, *1*, 121-169; Bazilevskii; Koldobskii; Tikhomirov *Russ. Chem. Rev.* **1986**, *55*, 948-965; de la Mare; Swedlund, in Patai *The Chemistry of the Carbon–Halogen Bond*, pt. 1; Wiley: New York, 1973, pp. 409-490. For some older books, see Thornton *Solvolysis Mechanisms*; Ronald Press: New York, 1964; Bunton *Nucleophilic Substitution at a Saturated Carbon Atom*; American Elsevier: New York, 1963; Streitwieser *Solvolytic Displacement Reactions*; McGraw-Hill: New York, 1962.

The SN2 Mechanism

SN2 stands for *substitution nucleophilic bimolecular*. The IUPAC designation (p. 290) is A_ND_N. In this mechanism there is *backside attack*: 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. 297-298 and 305). The C—Y bond is formed as the C—X bond is broken:

$$\overline{Y} + \overset{}{C}{-}X \longrightarrow Y\cdots\overset{}{C}\cdots X \longrightarrow Y{-}\overset{}{C}{-} + \overline{X}$$

1
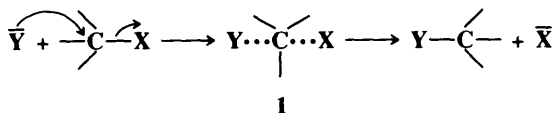
The energy necessary to break the C—X bond is supplied by simultaneous formation of the C—Y bond. The position of the atoms at the top of the curve of free energy of activation can be represented as **1**. Of course the reaction does not stop here: this is the transition state. The group X must leave 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 SN2 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.

There is a large amount of evidence for the SN2 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

$$\text{Rate} = k[\mathbf{RX}][\mathbf{Y}] \tag{1}$$

This rate law has been found to apply. It has been noted that the 2 in SN2 stands for bimolecular. It must be remembered that this is not always the same as second order (see p. 221). If a large excess of nucleophile is present—for example, if it is the solvent—the mechanism may still be bimolecular, though the experimentally determined kinetics will be first order:
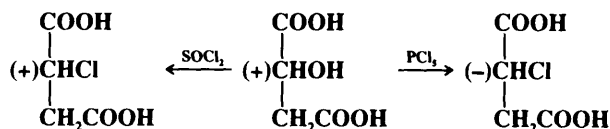
$$\text{Rate} = k[\mathbf{RX}] \tag{2}$$

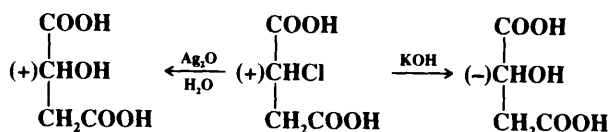As previously mentioned (p. 223), such kinetics are called *pseudo-first order*.

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. 111) is called the *Walden inversion* and was observed long before the SN2 mechanism was formulated by Hughes and Ingold.[2]

[2]Cowdrey; Hughes; Ingold; Masterman; Scott *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 in *Valence and the Structure of Atoms and Molecules;* Chemical Catalog Company: New York, 1923, p. 113. The idea that a one-step substitution leads to inversion was proposed by Olsen *J. Chem. Phys.* **1933**, *1*, 418.

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[3] in which inversion *must* have taken place. For example, (+)-malic acid could be converted to (+)-chlorosuccinic acid by thionyl chloride and to (−)-chlorosuccinic acid by phosphorus pentachloride:

$$
\begin{array}{ccc}
\text{COOH} & \text{COOH} & \text{COOH} \\
| & | & | \\
\text{(+)CHCl} \xleftarrow{\text{SOCl}_2} & \text{(+)CHOH} \xrightarrow{\text{PCl}_5} & \text{(−)CHCl} \\
| & | & | \\
\text{CH}_2\text{COOH} & \text{CH}_2\text{COOH} & \text{CH}_2\text{COOH}
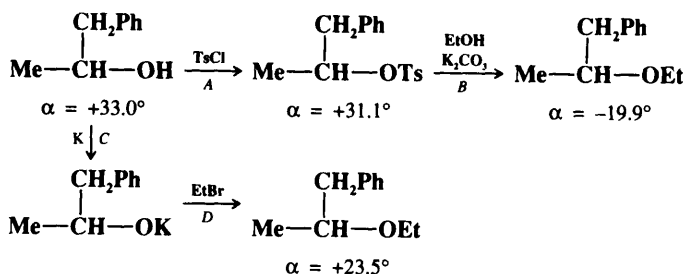\end{array}
$$

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. 108), rotation need not be related to configuration. Another example discovered by Walden is

$$
\begin{array}{ccc}
\text{COOH} & \text{COOH} & \text{COOH} \\
| & | & | \\
\text{(+)CHOH} \xleftarrow[\text{H}_2\text{O}]{\text{Ag}_2\text{O}} & \text{(+)CHCl} \xrightarrow{\text{KOH}} & \text{(−)CHOH} \\
| & | & | \\
\text{CH}_2\text{COOH} & \text{CH}_2\text{COOH} & \text{CH}_2\text{COOH}
\end{array}
$$

Once again, one reaction and only one must be an inversion, but which?[4] It may also be noticed [illustrated by the use of thionyl chloride on (+)-malic acid and treatment of the product with KOH] that it is possible to convert an optically active compound into its enantiomer.[5]

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:[6]

$$
\begin{array}{ccc}
\text{CH}_2\text{Ph} & \text{CH}_2\text{Ph} & \text{CH}_2\text{Ph} \\
| & | & | \\
\text{Me—CH—OH} \xrightarrow[A]{\text{TsCl}} & \text{Me—CH—OTs} \xrightarrow[B]{\overset{\text{EtOH}}{\text{K}_2\text{CO}_3}} & \text{Me—CH—OEt} \\
\alpha = +33.0° & \alpha = +31.1° & \alpha = -19.9°
\end{array}
$$

$$
\text{K} \downarrow C
$$

$$
\begin{array}{cc}
\text{CH}_2\text{Ph} & \text{CH}_2\text{Ph} \\
| & | \\
\text{Me—CH—OK} \xrightarrow[D]{\text{EtBr}} & \text{Me—CH—OEt} \\
& \alpha = +23.5°
\end{array}
$$

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*,

[3]Walden *Ber.* **1893**, *26*, 210, **1896**, *29*, 133, **1899**, *32*, 1855.

[4]For a discussion of these cycles, see Kryger; Rasmussen *Acta Chem. Scand.* **1972**, *26*, 2349.

[5]The student may wonder just what the mechanism is in cases where retention of configuration is involved since it certainly is not simple S$_N$2. As we shall see later, the reaction between malic acid and thionyl chloride is an S$_N$i process (p. 326), while a neighboring-group mechanism (p. 308) is involved in the treatment of chlorosuccinic acid with silver oxide.

[6]Phillips *J. Chem. Soc.* **1923**, *123*, 44. For analyses of such cycles and general descriptions of more complex ones, see Garwood; Cram *J. Am. Chem. Soc.* **1970**, *92*, 4575; Cram; Cram *Fortschr. Chem. Forsch.* **1972**, *31*, 1-43.

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 leaving group.[8] Inversion of configuration has also been found for SN2 reactions proceeding in the gas phase.[9]

Another kind of evidence for the SN2 mechanism comes from compounds with potential leaving groups at bridgehead carbons. If the SN2 mechanism is correct, these compounds should not be able to react by this mechanism, since the nucleophile cannot approach from the rear. Among the many known examples of unsuccessful reaction attempts at bridgeheads

2   **3**
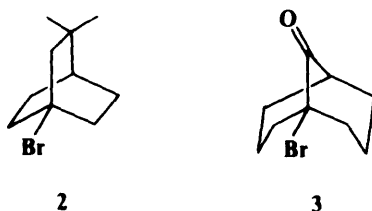
under SN2 conditions[10] are treatment of the [2.2.2] system **2** with ethoxide ion[11] and treatment of the [3.3.1] system **3** with sodium iodide in acetone.[12] In these cases, open-chain analogs underwent the reactions readily. As a final example of evidence for the SN2 mechanism, the reaction between optically active 2-octyl iodide and radioactive iodide ion may be mentioned:

$$C_6H_{13}CHMeI + *I^- \longrightarrow C_6H_{13}CHMe*I + I^-$$
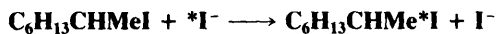
We expect racemization in this reaction, since if we start with the pure *R* isomer, at first each exchange will produce an *S* isomer, but with increasing concentration of *S* isomer, *it* will begin to compete for I⁻ with the *R* isomer, until at the end a racemic mixture is left. The point investigated was a comparison of the rate of inversion with the rate of uptake of radioactive *I . It was found[13] that the rates were identical within experimental error:

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

[7]For example, see Kenyon; Phillips; Turley *J. Chem. Soc.* **1925**, *127*, 399; Kenyon; Phillips; Taylor *J. Chem. Soc.* **1933**, 173; Kenyon; Phillips; Shutt *J. Chem. Soc.* **1935**, 1663.

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

[9]Lieder; Brauman *J. Am. Chem. Soc.* **1974**, 96, 4028; Speranza; Angelini *J. Am. Chem. Soc.* **1980**, *102*, 3115. For a review of nucleophilic displacements in the gas phase, see Riveros; José; Takashima *Adv. Phys. Org. Chem.* **1985**, *21*, 197-240.

[10]For a review of bridgehead reactivity in nucleophilic substitution reactions, see Müller; Mareda, in Olah *Cage Hydrocarbons*; Wiley: New York, 1990, pp. 189-217. For a review of reactions at bridgehead carbons, see Fort; Schleyer *Adv. Alicyclic Chem.* **1966**, *1*, 283-370.

[11]Doering; Levitz; Sayigh; Sprecher; Whelan *J. Am. Chem. Soc.* **1953**, 75, 1008. Actually, a slow substitution was observed in this case, but not by an SN2 mechanism.

[12]Cope; Synerholm *J. Am. Chem. Soc.* **1950**, 72, 5228.

[13]Hughes; Juliusburger; Masterman; Topley; Weiss *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 SN2 reaction must be linear.[14] Base treatment of methyl α-tosyl-o-toluenesulfonate (4) gives the o-(1-tosylethyl)benzenesulfonate ion (6). The role of the base is to remove the α
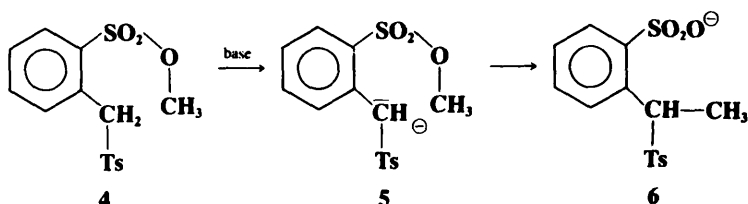
proton to give the ion 5. It might be supposed that the negatively charged carbon of 5 attacks the methyl group in an internal SN2 process:
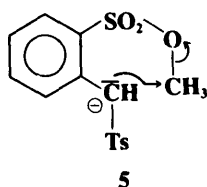
but this is not the case. Crossover experiments[14] (p. 555) have shown that the negatively charged carbon attacks the methyl group of another molecule rather than the nearby one in the same molecule, that is, the reaction is intermolecular and not intramolecular, despite the more favorable entropy of the latter pathway (p. 211). 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. 309), where intramolecular SN2 mechanisms operate freely.

There is evidence, both experimental and theoretical, that there are intermediates in at least some SN2 reactions in the gas phase, in charge type I reactions, where a negative ion nucleophile attacks a neutral substrate. Two energy minima, one before and one after the transition state appear in the reaction coordinate (Figure 10.1).[15] These minima correspond to unsymmetrical ion–dipole complexes.[16] Theoretical calculations also show such minima in certain solvents, e.g., DMF, but not in water.[17]

For a list of some of the more important reactions that operate by the SN2 mechanism, see Table 10.7.

[14]Tenud; Farooq; Seibl; Eschenmoser *Helv. Chim. Acta* **1970**, *53*, 2059. See also King; McGarrity *J. Chem. Soc., Chem. Commun.* **1979**, 1140.

[15]Taken from Chandrasekhar; Smith; Jorgensen, Ref. 16.

[16]Olmstead; Brauman *J. Am. Chem. Soc.* **1977**, *99*, 4219; Pellerite; Brauman *J. Am. Chem. Soc.* **1980**, *102*, 5993; Wolfe; Mitchell; Schlegel *J. Am. Chem. Soc.* **1981**, *103*, 7692; Chandrasekhar; Smith; Jorgensen *J. Am. Chem. Soc.* **1985**, *107*, 154; Evanseck; Blake; Jorgensen *J. Am. Chem. Soc.* **1987**, *109*, 2349; Kozaki; Morihashi; Kikuchi *J. Am. Chem. Soc.* **1989**, *111*, 1547; Jorgensen *Acc. Chem. Res.* **1989**, *22*, 184-189.

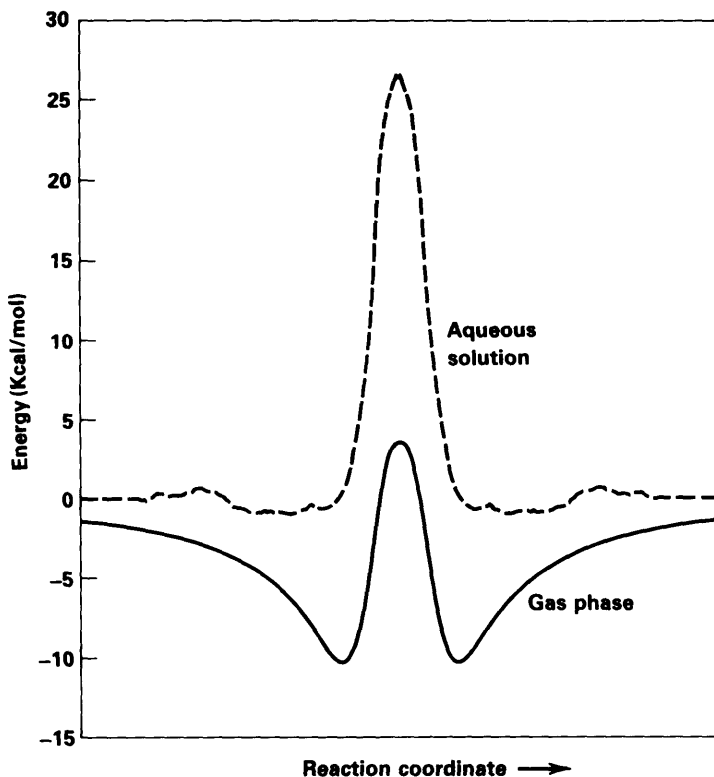[17]Chandrasekhar; Jorgensen *J. Am. Chem. Soc.* **1985**, *107*, 2974.

FIGURE 10.1 Free-energy profile for the gas phase (solid line) and aqueous solution (dashed line) SN2 reaction between CH_3Cl and Cl^-, from molecular orbital calculations.[15]
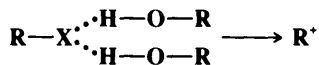
The SN1 Mechanism

The most ideal version of the SN1 mechanism (*substitutional nucleophilic unimolecular*) consists of two steps (once again, possible charges on the substrate and nucleophile are not shown):

Step 1 $$R—X \xrightleftharpoons{slow} R^+ + X$$

Step 2 $$R^+ + Y \xrightarrow{fast} R—Y$$

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 ionization is always assisted by the solvent,[18] 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 (630 kJ/mol). 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 (84 kJ/mol). The difference

[18]For reviews of solvolysis, see Okamoto *Adv. Carbocation Chem.* **1989**, *1*, 171-218; Blandamer; Scott; Robertson *Prog. Phys. Org. Chem.* **1985**, *15*, 149-196; Robertson *Prog. Phys. Org. Chem.* **1967**, *4*, 213-280. For a review of the solvolytic cleavage of *t*-butyl substrates, see Dvorko; Ponomareva; Kulik *Russ. Chem. Rev.* **1984**, *53*, 547-560.

is solvation energy. In 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[19] that in pulling X away from RX, two molecules of a protic solvent form weak hydrogen bonds with X

$$\text{R—X:} \overset{\cdot\text{H—O—R}}{\underset{\cdot\text{H—O—R}}{}} \longrightarrow \text{R}^+$$
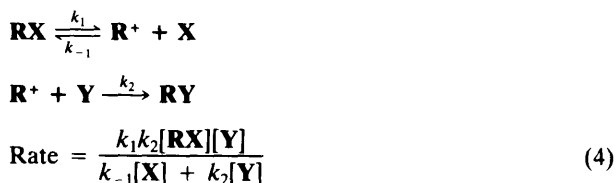
In the IUPAC system the S_N1 mechanism is $D_N + A_N$ or $D_N^{\ddagger} + A_N$ (where $\ddagger$ denotes the rate-determining step). The IUPAC designations for the S_N1 and S_N2 mechanisms thus clearly show the essential differences between them: $A_N D_N$ indicates that bond breaking is concurrent 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

$$\text{Rate} = k[\textbf{RX}] \tag{3}$$

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. (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 follows (see Chapter 6):

$$\textbf{RX} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \textbf{R}^+ + \textbf{X}$$

$$\textbf{R}^+ + \textbf{Y} \xrightarrow{k_2} \textbf{RY}$$

$$\text{Rate} = \frac{k_1 k_2 [\textbf{RX}][\textbf{Y}]}{k_{-1}[\textbf{X}] + k_2[\textbf{Y}]} \tag{4}$$

At the beginning of the reaction, when the concentration of X is very small, $k_{-1}[\text{X}]$ is negligible compared with $k_2[\text{Y}]$ and the rate law is reduced to Eq. (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. (4) predicts that the rate should decrease. This is found to be the case for diarylmethyl halides,[20] though not for *t*-butyl halides, which follow Eq. (3) for the entire reaction.[21] An explanation for this difference is that *t*-butyl cations are less selective than the relatively stable diarylmethyl type (p. 169). Although halide ion is a much more powerful nucleophile than water, there is much more water available since it is the solvent.[22] The selective diphenylmethyl cation survives many collisions with solvent molecules before combining with a reactive halide, but the less selective *t*-butyl ion cannot wait for a reactive but relatively rare halide ion and combines with the solvent.

[19]Blandamer; Burgess; Duce; Symons; Robertson; Scott *J. Chem. Res. (S)* **1982**, 130.
[20]Benfey; Hughes; Ingold *J. Chem. Soc.* **1952**, 2488.
[21]Bateman; Hughes; Ingold *J. Chem. Soc.* **1940**, 960.
[22]In the experiments mentioned, the solvent was actually "70%" or "80%" aqueous acetone. "80%" aqueous acetone consists of 4 vol of dry acetone and 1 vol of water.

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 *t*-butyl halides.

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 SN1 reaction (p. 359). 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 SN1 reactions makes especially impressive the *decrease* in rate caused by the common ion.

It may be noted that the pseudo-first-order rate law for an SN2 reaction in the presence of a large excess of Y [Eq. (2)] is the same as that for an ordinary SN1 reaction [Eq. (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 SN2 reaction beyond the effect caused by other ions. Unfortunately, as we have seen, not all SN1 reactions show the common-ion effect, and this test fails for *t*-butyl and similar cases.

Kinetic studies also provide other evidence for the SN1 mechanism. If this mechanism operates essentially as shown on p. 298, 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.[23] In each case the initial rate of the reaction was approximately the same when 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. 348) as H_2O and OH^-.

It is normally not possible to detect the carbocation intermediate of an SN1 reaction directly, because its lifetime is very short. However, in the case of 3,4'-dimethoxydiphenylmethyl acetate (**7**) and certain other substrates in polar solvents it was possible to initiate


7
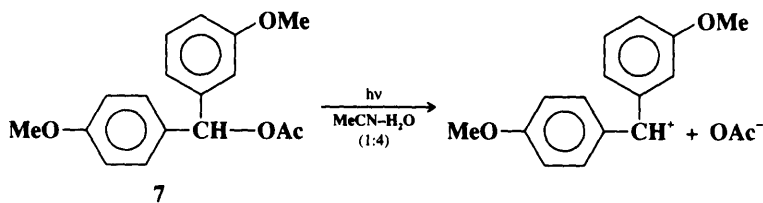
the reaction photolytically, and under these conditions the uv spectra of the intermediate carbocations could be obtained,[24] providing additional evidence for the SN1 mechanism.

Further evidence for the SN1 mechanism is that reactions run under SN1 conditions fail or proceed very slowly at the bridgehead positions[10] of [2.2.1] (norbornyl) systems[25] (e.g. 1-chloroapocamphane, **8**). If SN1 reactions require carbocations and if carbocations must

[23]Bateman; Hughes; Ingold *J. Chem. Soc.* **1940**, 1011.
[24]McClelland; Kanagasabapathy; Steenken *J. Am. Chem. Soc.* **1988**, *110*, 6913.
[25]For a review, see Fort, in Olah; Schleyer *Carbonium Ions*, vol. 4; Wiley: New York, 1973, pp. 1783-1835.

8   **9**   **10**   **11**
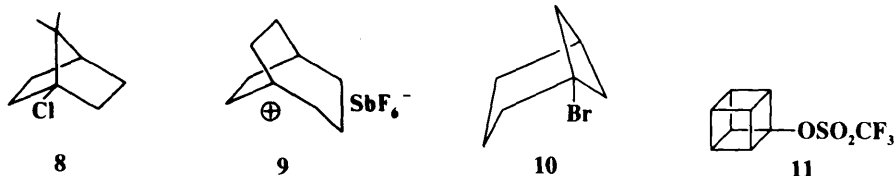
be planar or nearly planar, then it is no surprise that bridgehead 1-norbornyl carbon atoms, which cannot assume planarity, do not become the seat of carbocations. As an example, **8**, boiled 21 hr with 30% KOH in 80% ethanol or 48 hr with aqueous ethanolic silver nitrate, gave no reaction in either case,[26] though analogous open-chain systems reacted readily. According to this theory, SN1 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 SN1 reactions much faster than smaller bicyclic systems, though the reaction is still slower than with open-chain systems.[27] Proceeding to a still larger system, the bridgehead [3.2.2] cation **9** is actually stable enough to be kept in solution in SbF_5–SO_2ClF at temperatures below $-50°C$[28] (see also p. 345). Other small bridgehead systems that undergo SN1 reactions are the [3.1.1] (e.g., **10**)[29] and the cubyl (e.g., **11**)[30] systems. Ab initio calculations show that the cubyl cation, though it cannot be planar, requires less energy to form than the 1-norbornyl cation.[31]

Certain nucleophilic substitution reactions that normally involve carbocations can take place at norbornyl bridgeheads[32] (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, e.g.,
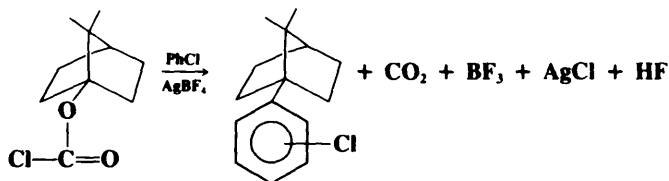
In this example,[33] chlorobenzene is the nucleophile (see **1-12**).

Additional evidence for the SN1 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. 166).[34]

[26]Bartlett; Knox *J. Am. Chem. Soc.* **1939**, *61*, 3184.

[27]For synthetic examples, see Kraus; Hon *J. Org. Chem.* **1985**, *50*, 4605.

[28]Olah; Liang; Wiseman; Chong *J. Am. Chem. Soc.* **1972**, *74*, 4927.

[29]Della; Pigou; Tsanaktsidis *J. Chem. Soc., Chem. Commun.* **1987**, 833.

[30]Eaton; Yang; Xiong *J. Am. Chem. Soc.* **1990**, *112*, 3225; Moriarty; Tuladhar; Penmasta; Awasthi *J. Am. Chem. Soc.* **1990**, *112*, 3228.

[31]Hrovat; Borden *J. Am. Chem. Soc.* **1990**, *112*, 3227.

[32]Ref. 26; Beak; Trancik *J. Am. Chem. Soc.* **1968**, *90*, 2714; Clive; Denyer *Chem. Commun.* **1971**, 1112; White; McGirk; Aufdermarsh; Tiwari; Todd *J. Am. Chem. Soc.* **1973**, *95*, 8107; Beak; Harris *J. Am. Chem. Soc.* **1974**, *96*, 6363.

[33]For a review of reactions with the OCOCl leaving group, see Beak *Acc. Chem. Res.* **1976**, *9*, 230-236.

[34]Arnett; Petro *J. Am. Chem. Soc.* **1978**, *100*, 5408; Arnett; Petro; Schleyer *J. Am. Chem. Soc.* **1979**, *101*, 522; Arnett; Pienta *J. Am. Chem. Soc.* **1980**, *102*, 3329; Arnett; Molter *Acc. Chem. Res.* **1985**, *18*, 339-346.
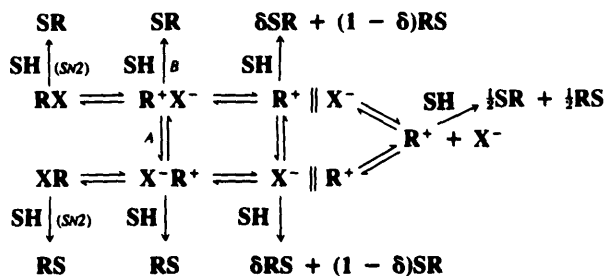
Ion Pairs in the S$_N$1 Mechanism[35]

Like the kinetic evidence, the stereochemical evidence for the S$_N$1 mechanism is less clear-cut than it is for the S$_N$2 mechanism. If there is a free carbocation, it is planar (p. 172), and the nucleophile should attack with equal facility from either side of the plane, resulting in complete racemization. Although many first-order substitutions do give complete racemization, many others do not. Typically there is 5 to 20% inversion, though in a few cases, a small amount of retention of configuration has been found. These and other results have led to the conclusion that in many S$_N$1 reactions at least some of the products are not formed from free carbocations but rather from *ion pairs*. According to this concept,[36] S$_N$1 reactions proceed in this manner:

$$R{-}X \rightleftharpoons R^+X^- \rightleftharpoons R^+ \| X^- \rightleftharpoons R^+ + X^-$$
$$\phantom{R{-}X \rightleftharpoons}\ 12 \ 13 \ 14$$
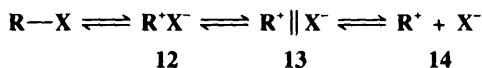
where **12** is an *intimate, contact,* or *tight* ion pair, **13** a *loose,* or *solvent-separated* ion pair, and **14** the dissociated ions (each surrounded by molecules of solvent).[37] The reaction in which the intimate ion pair recombines to give the original substrate is referred to as *internal return*. The reaction products can result from attack by the nucleophile at any stage. In the intimate ion pair **12**, R^+ does not behave like the free cation of **14**. There is probably significant bonding between R^+ and X^- and asymmetry may well be maintained.[38] X^- "solvates" the cation on the side from which it departed, while solvent molecules near **12** can only solvate it from the opposite side. Nucleophilic attack by a solvent molecule on **12** thus leads to inversion.

A complete picture of the possibilities for solvolysis reactions in a solvent SH (ignoring the possibilities of elimination or rearrangement—see Chapters 17 and 18) is the following,[39] though in any particular case it is unlikely that all these reactions occur:

$$
\begin{array}{ccc}
\text{SR} & \text{SR} & \delta\text{SR} + (1-\delta)\text{RS} \\
\text{SH}\uparrow_{(S_N2)} & \text{SH}\uparrow_B & \text{SH}\uparrow \\
\text{RX} \rightleftharpoons & \text{R}^+\text{X}^- \rightleftharpoons & \text{R}^+ \| \text{X}^- \searrow\ \text{SH} \to \tfrac{1}{2}\text{SR} + \tfrac{1}{2}\text{RS} \\
\quad\downarrow_A & \quad\downarrow & \qquad\qquad \text{R}^+ + \text{X}^- \\
\text{XR} \rightleftharpoons & \text{X}^-\text{R}^+ \rightleftharpoons & \text{X}^- \| \text{R}^+ \nearrow \\
\text{SH}\downarrow_{(S_N2)} & \text{SH}\downarrow & \text{SH}\downarrow \\
\text{RS} & \text{RS} & \delta\text{RS} + (1-\delta)\text{SR}
\end{array}
$$

In this scheme RS and SR represent enantiomers, etc., 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$_N$2 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

[35]For reviews of ion pairs in S$_N$ reactions, see Beletskaya *Russ. Chem. Rev.* **1975**, *44*, 1067-1090; Harris *Prog. Phys. Org. Chem.* **1974**, *11*, 89-173; Raber; Harris; Schleyer, in Szwarc *Ions and Ion Pairs in Organic Reactions,* vol. 2; Wiley: New York, 1974, pp. 247-374.

[36]Proposed by Winstein; Clippinger; Fainberg; Heck; Robinson *J. Am. Chem. Soc.* **1956**, *78*, 328.

[37]For a review of the energy factors involved in the recombination of ion pairs, see Kessler; Feigel *Acc. Chem. Res.* **1982**, 15, 2-8.
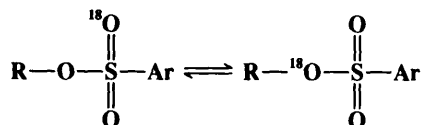
[38]Fry; Lancelot; Lam; Harris; Bingham; Raber; Hall; Schleyer *J. Am. Chem. Soc.* **1970**, *92*, 2538.

[39]Shiner; Fisher *J. Am. Chem. Soc.* **1971**, *93*, 2553.
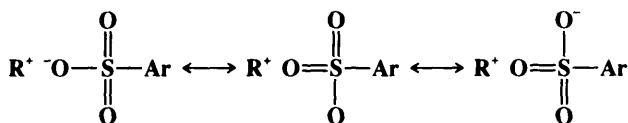
maintained as tightly and more racemization (perhaps total) is expected. (4) Finally, if free R^+ is formed, it is planar, and attack by SH gives complete racemization.

The ion-pair concept thus predicts that SN1 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 SN1 reactions. There is much other evidence for the intervention of ion pairs:[40]

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, though not completely, scrambled:[41]

$$R-O-\overset{\overset{^{18}O}{\parallel}}{\underset{\underset{O}{\parallel}}{S}}-Ar \;\rightleftharpoons\; R-^{18}O-\overset{\overset{O}{\parallel}}{\underset{\underset{O}{\parallel}}{S}}-Ar$$

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

$$R^+\;{}^-O-\overset{\overset{O}{\parallel}}{\underset{\underset{O}{\parallel}}{S}}-Ar \;\longleftrightarrow\; R^+\;O=\overset{\overset{O}{\parallel}}{\underset{\underset{\underline{O}}{\parallel}}{S}}-Ar \;\longleftrightarrow\; R^+\;O=\overset{\overset{O^-}{\mid}}{\underset{\underset{O}{\parallel}}{S}}-Ar$$

Similar results were obtained with several other sulfonate esters.[42] The possibility must be considered that the scrambling resulted from ionization 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 SN2 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 to 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 $R'COO^-$.[43] 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.[44]

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).[45] This is interpreted as follows: the ClO_4^-

[40]For further evidence beyond that given here, see Winstein; Baker; Smith *J. Am. Chem. Soc.* **1964**, *86*, 2072; Streitwieser; Walsh *J. Am. Chem. Soc.* **1965**, *87*, 3686; Sommer; Carey *J. Org. Chem.* **1967**, *32*, 800, 2473; Kwart; Irvine *J. Am. Chem. Soc.* **1969**, *91*, 5541; Harris; Becker; Fagan; Walden *J. Am. Chem. Soc.* **1974**, *96*, 4484; Bunton; Huang; Paik *J. Am. Chem. Soc.* **1975**, *97*, 6262; Humski; Sendijarević; Shiner *J. Am. Chem. Soc.* **1976**, *98*, 2865; Maskill; Thompson; Wilson *J. Chem. Soc., Chem. Commun.* **1981**, 1239; McManus; Safavy; Roberts *J. Org. Chem.* **1982**, *47*, 4388; Ref. 35; McLennan; Stein; Dobson *Can. J. Chem.* **1986**, *64*, 1201; Kinoshita; Komatsu; Ikai; Kashimura; Tanikawa; Hatanaka; Okamoto *J. Chem. Soc., Perkin Trans. 2* **1988**, 1875; Ronco; Petit; Guyon; Villa *Helv. Chim. Acta* **1988**, *71*, 648; Kevill; Kyong; Weitl *J. Org. Chem.* **1990**, *55*, 4304.

[41]Diaz; Lazdins; Winstein *J. Am. Chem. Soc.* **1968**, *90*, 1904.

[42]Goering; Thies *J. Am. Chem. Soc.* **1968**, *90*, 2967, 2968; Goering; Jones *J. Am. Chem. Soc.* **1980**, *102*, 1628; Yukawa; Morisaki; Tsuji; Kim; Ando *Tetrahedron Lett.* **1981**, *22*, 5187; Chang; le Noble *J. Am. Chem. Soc.* **1983**, *105*, 3708; Paradisi; Bunnett *J. Am. Chem. Soc.* **1985**, *107*, 8223; Fujio; Sanematsu; Tsuno; Sawada; Takai *Tetrahedron Lett.* **1988**, *29*, 93.

[43]Goering; Levy *J. Am. Chem. Soc.* **1962**, *84*, 3853, **1964**, *86*, 120; Goering; Hopf *J. Am. Chem. Soc.* **1971**, *93*, 1224.

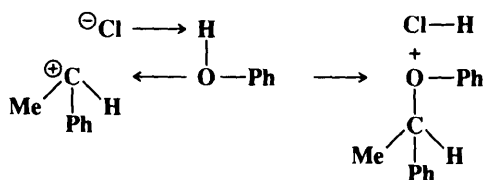[44]Dietze; Wojciechowski *J. Am. Chem. Soc.* **1990**, *112*, 5240.

[45]Ref. 36; Winstein; Klinedinst; Clippinger *J. Am. Chem. Soc.* **1961**, *83*, 4986; Cristol; Noreen; Nachtigall *J. Am. Chem. Soc.* **1972**, *94*, 2187.

(or Br$^-$) traps the solvent-separated ion pair to give R$^+$ ‖ 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.[46]

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,[47] while in other cases partial or complete retention is found, for example, solvolysis in aqueous acetone of *p*-chlorobenzhydryl *p*-nitrobenzoate.[48] Racemization of RX is presumably caused by the pathway: RX $\rightleftarrows$ R$^+$X$^-$ $\rightleftarrows$ X$^-$R$^+$ $\rightleftarrows$ 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 about 30 times faster than it solvolyzes in acetic acid.[49]

Molecular orbital calculations[50] 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 (compare the C—Cl bond length of 1.8 Å).

In a few cases, SN1 reactions have been found to proceed with partial retention (20 to 50%) of configuration. Ion pairs have been invoked to explain some of these.[51] 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.[52] Partial retention can also arise when the ion pair is shielded at the backside by an additive such as acetonitrile, acetone, or aniline.[53]

The difference between the SN1 and SN2 mechanisms is in the timing of the steps. In the SN1 mechanism, first X leaves, then Y attacks. In the SN2 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

[46]Simon; Peters *J. Am. Chem. Soc.* **1982**, *104*, 6142.

[47]Goering; Briody; Sandrock, *J. Am. Chem. Soc.* **1970**, *92*, 7401.

[48]Goering; Briody; Levy *J. Am. Chem. Soc.* **1963**, *85*, 3059.

[49]Winstein; Gall; Hojo; Smith *J. Am. Chem. Soc.* **1960**, *82*, 1010. See also Shiner; Hartshorn; Vogel *J. Org. Chem.* **1973**, *38*, 3604.

[50]Jorgensen; Buckner; Huston; Rossky *J. Am. Chem. Soc.* **1987**, *109*, 1891.

[51]Okamoto; Yamada; Nitta; Shingu *Bull. Chem. Soc. Jpn.* **1966**, *39*, 299; Okamoto; Takeuchi; Inoue *J. Chem. Soc., Perkin Trans. 2* **1980**, 842; Okamoto *Pure Appl. Chem.* **1984**, *56*, 1797-1808. For a similar mechanism with amine nucleophiles, see Lee; Kim; Kang; Lee *J. Org. Chem.* **1988**, *53*, 2678; Lee; Kim; Lee; Kim *J. Phys. Org. Chem.* **1989**, *2*, 35.

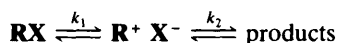[52]Okamoto; Kinoshita; Shingu *Bull. Chem. Soc. Jpn.* **1970**, *43*, 1545.

[53]Okamoto; Nitta; Dohi; Shingu *Bull. Chem. Soc. Jpn.* **1971**, *44*, 3220; Kinoshita; Ueno; Ikai; Fujiwara; Okamoto *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3273; Kinoshita et al., Ref. 40.

eight electrons in the outer shell of carbon. However, this type of mechanism is possible and indeed occurs at other types of substrate (p. 331; Chapter 13).

Mixed SN1 and SN2 Mechanisms

Some reactions of a given substrate under a given set of conditions display all the characteristics of SN2 mechanisms; other reactions seem to proceed by SN1 mechanisms, but cases are found that cannot be characterized so easily. There seems to be something in between, a mechanistic "borderline" region.[54] At least two broad theories have been devised to explain these phenomena. One theory holds that intermediate behavior is caused by a mechanism that is neither "pure" SN1 nor "pure" SN2, 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 SN1 and SN2 mechanisms; that is, some molecules react by the SN1, while others react by the SN2 mechanism.

One formulation of the intermediate-mechanism theory is that of Sneen.[55] The formulation is in fact very broad and applies not only to borderline behavior but to all nucleophilic substitutions at a saturated carbon.[56] According to Sneen, all SN1 and SN2 reactions can be accommodated by one basic mechanism (the *ion-pair mechanism*). The substrate first ionizes to an intermediate ion pair which is then converted to products:

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

The difference between the SN1 and SN2 mechanisms is that in the former case the *formation* of the ion pair (k_1) is rate-determining, while in the SN2 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.[57] However, a number of investigators have asserted that these results could also be explained in other ways.[58]

There is evidence for the Sneen formulation where the leaving group has a positive charge. In this case there is a cation-molecule pair $(RX^+ \rightarrow R^+ X)$[59] instead of the ion pair that would be present if the leaving group were uncharged. Katritzky, le Noble, and coworkers found that when such a reaction was run at varying high pressures, there was a minimum in the plot of rate constant vs. pressure.[60] A minimum of this sort usually indicates a change in mechanism, and the interpretation in this case was that the normal SN2 mechanism operates at higher pressures and the cation–molecule mechanism at lower pressures.

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[54]For an essay on borderline mechanisms in general, see Jencks *Chem. Soc. Rev.* **1982**, *10*, 345-375.

[55]Weiner; Sneen *J. Am. Chem. Soc.* **1965**, *87*, 292; Sneen; Larsen *J. Am. Chem. Soc.* **1969**, *91*, 362, 6031; Sneen; Felt; Dickason *J. Am. Chem. Soc.* **1973**, *95*, 638; Sneen *Acc. Chem. Res.* **1973**, *6*, 46-53.

[56]Including substitution at an allylic carbon; see Sneen; Bradley *J. Am. Chem. Soc.* **1972**, *94*, 6975; Sneen; Carter *J. Am. Chem. Soc.* **1972**, *94*, 6990; Bordwell; Mecca *J. Am. Chem. Soc.* **1975**, *97*, 123, 127; Bordwell; Wiley; Mecca *J. Am. Chem. Soc.* **1975**, *97*, 132; Kevill; Degenhardt *J. Am. Chem. Soc.* **1979**, *101*, 1465.

[57]For evidence for this point of view, see Ref. 55; Sneen; Carter; Kay *J. Am. Chem. Soc.* **1966**, *88*, 2594; Sneen; Robbins *J. Am. Chem. Soc.* **1972**, *94*, 7868; Graczyk; Taylor *J. Am. Chem. Soc.* **1974**, *96*, 3255; Peeters; Anteunis *J. Org. Chem.* **1975**, *40*, 312; Pross; Aronovitch; Koren *J. Chem. Soc., Perkin Trans. 2* **1978**, 197; Blandamer; Robertson; Scott; Vrielink *J. Am. Chem. Soc.* **1980**, *102*, 2585; Stein; Tencer; Moffatt; Dawe; Sweet *J. Org. Chem.* **1980**, *45*, 3539; Stein; Moffatt *Can. J. Chem.* **1985**, *63*, 3433; Stein *Can. J. Chem.* **1987**, *65*, 363.

[58]See, for example, Gregory; Kohnstam; Queen; Reid *Chem. Commun.* **1971**, 797; Kurz; Harris *J. Am. Chem. Soc.* **1970**, *92*, 4117; Raber; Harris; Hall; Schleyer *J. Am. Chem. Soc.* **1971**, *93*, 4821; McLennan *J. Chem. Soc., Perkin Trans. 2* **1972**, 1577, **1974**, 481, *Acc. Chem. Res.* **1976**, 9, 281-287, *Tetrahedron Lett.* **1975**, 4689; McLennan; Martin *Tetrahedron Lett.* **1973**, 4215; Raaen; Juhlke; Brown; Collins *J. Am. Chem. Soc.* **1974**, *96*, 5928; Gregoriou *Tetrahedron Lett.* **1974**, 233, **1976**, 4605, 4767; Queen; Matts *Tetrahedron Lett.* **1975**, 1503; Stein *J. Org. Chem.* **1976**, *41*, 519; Stephan *Bull. Soc. Chim. Fr.* **1977**, 779; Katritzky; Musumarra; Sakizadeh *J. Org. Chem.* **1981**, *46*, 3831. For a reply to some of these objections, see Sneen; Robbins, Ref. 57. For a discussion, see Klumpp *Reactivity in Organic Chemistry*; Wiley: New York, 1982, pp. 442-450.

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

[60]Katritzky; Sakizadeh; Gabrielsen; le Noble *J. Am. Chem. Soc.* **1984**, *106*, 1879.

An alternative view that also favors an intermediate mechanism is that of Schleyer and co-workers,[61] who believe that the key to the problem is varying degrees of nucleophilic solvent assistance to ion-pair formation. They have proposed an SN2 (intermediate) mechanism.[62]

Among the experiments that have been cited for the viewpoint that borderline behavior results from simultaneous SN1 and SN2 mechanisms is the behavior of 4-methoxybenzyl chloride in 70% aqueous acetone.[63] In this solvent, hydrolysis (that is, conversion to 4-methoxybenzyl alcohol) occurs by an SN1 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 SN1 process. However, the rate of ionization is always *less* than the total rate of reaction, so some azide must also form by an SN2 mechanism.[63] Thus, the conclusion is that SN1 and SN2 mechanisms operate simultaneously.[64]

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 SN2 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.[65] When 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 SN2 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 SN2 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 SN1 and SN2 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 SN2. Since methanol and water are more polar than 75% aqueous dioxane and since an increase in polarity of solvent increases the rate of SN1 reactions at the expense of SN2 (p. 356), it is extremely unlikely that any SN1 process could occur in 75% aqueous dioxane. The intermediate in the second process is thus not a carbocation. What it is is suggested by the fact that, in the absence of azide ions, the amount of inverted 2-octanol decreased with an

[61]Bentley; Schleyer *J. Am. Chem. Soc.* **1976**, *98*, 7658; Bentley; Bowen; Morten; Schleyer *J. Am. Chem. Soc.* **1981**, *103*, 5466.
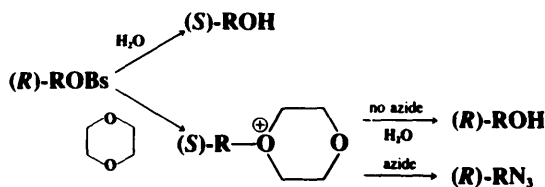
[62]For additional evidence for this view, see Laureillard; Casadevall; Casadevall *Tetrahedron* **1984**, *40*, 4921. *Helv. Chim. Acta* **1984**, *67*, 352; McLennan *J. Chem. Soc., Perkin Trans. 2* **1981**, 1316. For evidence against the SN2(intermediate) mechanism, see Allen; Kanagasabapathy; Tidwell *J. Am. Chem. Soc.* **1985**, *107*, 4513; Fǎrcaşiu; Jähme; Rüchardt *J. Am. Chem. Soc.* **1985**, *107*, 5717; Dietze; Jencks *J. Am. Chem. Soc.* **1986**, *108*, 4549; Dietze; Hariri; Khattak *J. Org. Chem.* **1989**, *54*, 3317; Coles; Maskill *J. Chem. Soc., Perkin Trans. 2* **1987**, 1083; Richard; Amyes; Vontor *J. Am. Chem. Soc.* **1991**, *113*, 5871.

[63]Kohnstam; Queen; Shillaker *Proc. Chem. Soc.* **1959**, 157; Amyes; Richard *J. Am. Chem. Soc.* **1990**, *112*, 9507. For other evidence supporting the concept of simultaneous mechanisms, see Pocker *J. Chem. Soc.* **1959**, 3939, 3944; Casapieri; Swart *J. Chem. Soc.* **1961**, 4342. **1963**, 1254; Ceccon; Papa; Fava *J. Am. Chem. Soc.* **1966**, *88*, 4643; Okamoto; Uchida; Saitô; Shingu *Bull. Chem. Soc. Jpn.* **1966**, *39*, 307; Guinot; Lamaty *Chem. Commun.* **1967**, 960; Queen *Can. J. Chem.* **1979**, *57*, 2646; Katritzky; Musumarra; Sakizadeh; El-Shafie; Jovanovic *Tetrahedron Lett.* **1980**, *21*, 2697; Richard; Rothenberg; Jencks *J. Am. Chem. Soc.* **1984**, *106*, 1361; Richard; Jencks *J. Am. Chem. Soc.* **1984**, *106*, 1373, 1383; Katritzky; Brycki *J. Phys. Org. Chem.* **1988**, *1*, 1; Stein *Can. J. Chem.* **1989**, 67, 297.

[64]These data have also been explained as being in accord with the ion-pair mechanism: Sneen; Larsen *J. Am. Chem. Soc.* **1969**, *91*, 6031.

[65]Weiner; Sneen *J. Am. Chem. Soc.* **1965**, 87, 287.

increasing percentage of dioxane in the solvent. Thus the intermediate is an oxonium ion formed by an SN2 attack *by dioxane*. This ion is not a stable product but reacts with water in another SN2 process to produce 2-octanol with retained configuration. The entire process can be shown as follows:

That part of the original reaction that resulted in retention of configuration[66] is thus seen to stem from two successive SN2 reactions and not from any "borderline" behavior.[67]

SET Mechanisms

In certain reactions where nucleophilic substitutions would seem obviously indicated, there is evidence that radicals and/or radical ions are actually involved.[68] The first step in such a process is transfer of an electron from the nucleophile to the substrate to form a radical anion:
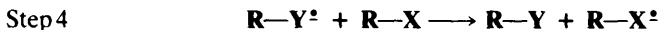
Step 1 $R—X + \overline{Y}^- \longrightarrow R—X^{\cdot} + Y\cdot$

Mechanisms that begin this way are called *SET (single electron transfer) mechanisms*.[69] Once formed, the radical ion cleaves:

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

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 $R\cdot + Y\cdot \longrightarrow R—Y$

or

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

Step 4 $R—Y^{\cdot} + R—X \longrightarrow R—Y + R—X^{\cdot}$

In the latter case, the radical ion R—X$^{\cdot}$ is formed by Step 4 as well as by Step 1, so that a chain reaction (p. 678) can take place.
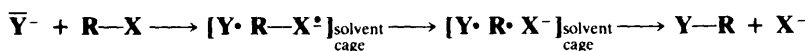
[66]According to this scheme, the configuration of the isolated RN3 should be retained. It was, however, largely inverted, owing to a competing SN2 reaction where N$_3^-$ directly attacks ROBs.

[67]For other examples, see Streitwieser; Walsh; Wolfe *J. Am. Chem. Soc.* **1965**, *87*, 3682; Streitwieser; Walsh *J. Am. Chem. Soc.* **1965**, *87*, 3686; Beronius; Nilsson; Holmgren *Acta Chem. Scand.* **1972**, *26*, 3173. See also Knier; Jencks *J. Am. Chem. Soc.* **1980**, *102*, 6789.

[68]Kerber; Urry; Kornblum *J. Am. Chem. Soc.* **1965**, *87*, 4520; Kornblum; Michel; Kerber *J. Am. Chem. Soc.* **1966**, *88*, 5660, 5662; Russell; Danen *J. Am. Chem. Soc.* **1966**, *88*, 5663; Bank; Noyd *J. Am. Chem. Soc.* **1973**, *95*, 8203; Ashby; Goel; Park *Tetrahedron Lett.* **1981**, *22*, 4209. For discussions of the relationship between SN2 and SET mechanisms, see Lewis *J. Am. Chem. Soc.* **1989**, *111*, 7576; Shaik *Acta Chem. Scand.* **1990**, *44*, 205-221.
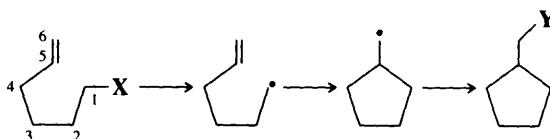
[69]For reviews, see Savéant *Adv. Phys. Org. Chem.* **1990**, *26*, 1-130; Rossi; Pierini; Palacios *J. Chem. Educ.* **1989**, *66*, 720; Ashby *Acc. Chem. Res.* **1988**, *21*, 414-421; Chanon; Tobe *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 1-23 [*Angew. Chem. 94*, 27-49]. See also Pross *Acc. Chem. Res.* **1985**, *18*, 212-219; Chanon *Acc. Chem. Res.* **1987**, *20*, 214-221.

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[70] 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 though 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.

$$\overline{Y}^- \; + \; R{-}X \longrightarrow [Y{\cdot}\;R{-}X^{\bullet}]_{\substack{solvent\\cage}} \longrightarrow [Y{\cdot}\;R{\cdot}\;X^-]_{\substack{solvent\\cage}} \longrightarrow Y{-}R \; + \; X^-$$

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

Other evidence cited[71] for SET mechanisms has been detection of radical or radical ion intermediates by esr[72] or CIDNP; the finding that such reactions can take place at 1-norbornyl bridgeheads;[73] 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. 744).[74]

The SET mechanism is chiefly found where X = I or NO_2 (see **0-94**). A closely related mechanism, the $S_{RN}1$, takes place with aromatic substrates (Chapter 13).[75] In that mechanism the initial attack is by an electron donor, rather than a nucleophile.

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[76]

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

[70]Ashby; Pham *Tetrahedron Lett.* **1987**, *28*, 3183; Daasbjerg; Lund; Lund *Tetrahedron Lett.* **1989**, *30*, 493.

[71]See also Chanon; Tobe, Ref. 69; Fuhlendorff; Lund; Lund; Pedersen *Tetrahedron Lett.* **1987**, *28*, 5335.

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

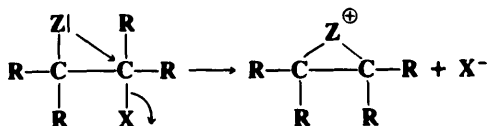[73]Santiago; Morris; Rossi *J. Chem. Soc., Chem. Commun.* **1988**, 220.

[74]For criticisms of this method for demonstrating SET mechanisms, see Newcomb; Kaplan *Tetrahedron Lett.* **1988**, *29*, 3449; Newcomb; Kaplan; Curran *Tetrahedron Lett.* **1988**, *29*, 3451; Newcomb; Curran *Acc. Chem. Res.* **1988**, *21*, 206-214; Newcomb *Acta Chem. Scand.* **1990**, *44*, 299. For replies to the criticism, see Ashby *Acc. Chem. Res.* **1988**, *21*, 414-421; Ashby; Pham; Amrollah-Madjdabadi *J. Org. Chem.* **1991**, *56*, 1596.

[75]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.
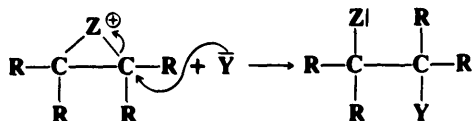
[76]For a monograph, see Capon; McManus *Neighboring Group Participation*, vol. 1; Plenum: New York, 1976.

causing an inversion so the net result is retention of configuration.[77] 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:

Step 1

$$R-\overset{\overset{\displaystyle Z|}{|}}{\underset{\underset{\displaystyle R}{|}}{C}}\overset{\overset{\displaystyle R}{|}}{\underset{\underset{\displaystyle X}{|}}{C}}-R \longrightarrow R-\overset{\overset{\displaystyle Z^{\oplus}}{\diagup}}{\underset{\underset{\displaystyle R}{|}}{C}}\overset{}{\underset{\underset{\displaystyle R}{|}}{C}}-R + X^-$$

Step 2

$$R-\overset{\overset{\displaystyle Z^{\oplus}}{\diagup}}{\underset{\underset{\displaystyle R}{|}}{C}}\overset{}{\underset{\underset{\displaystyle R}{|}}{C}}-R + \bar{Y} \longrightarrow R-\overset{\overset{\displaystyle Z|}{|}}{\underset{\underset{\displaystyle R}{|}}{C}}\overset{\overset{\displaystyle R}{|}}{\underset{\underset{\displaystyle Y}{|}}{C}}-R$$

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. (2) or (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 (ΔS^*), since the reactants are far less free in the transition state than before. Reaction of Z involves a much smaller loss of ΔS^* (see p. 211).[78]

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, $HOCH_2CH_2Br$ vs. 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. Futhermore, 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 more than fiftyfold, 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:[79]

[77]There is evidence that this kind of process can happen intermolecularly (e.g., RX + Z⁻ → RZ + Y⁻). In this case Z⁻ acts as a catalyst for the reaction RX + Y⁻ → RY: McCortney; Jacobson; Vreeke; Lewis *J. Am. Chem. Soc.* **1990**, *112*, 3554.

[78]For a review of the energetics of neighboring-group participation, see Page *Chem. Soc. Rev.* **1973**, *2*, 295-323.

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

threo *dl* pair   *dl* pair

erythro *dl* pair   meso
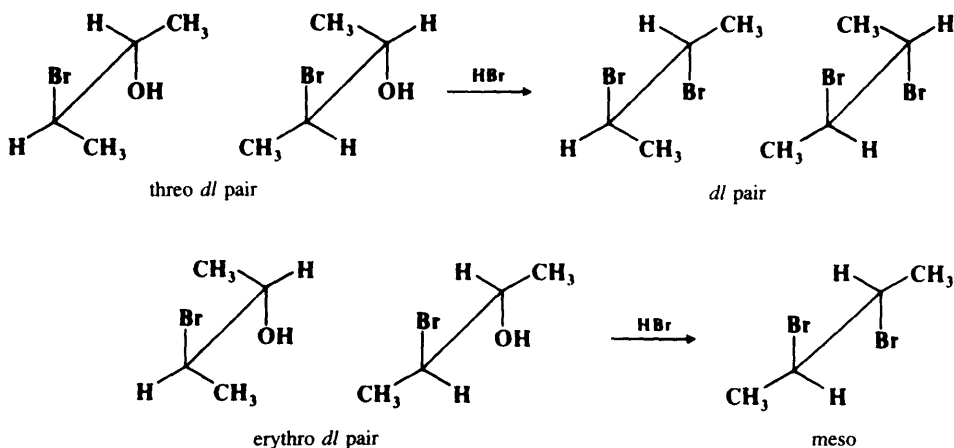
This indicated that retention had taken place. Note that both products are optically inactive and so cannot be told apart by differences in rotation. The meso and *dl* dibromides have different boiling points and indexes of refraction and were identified by these properties. Even more convincing evidence 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 (**15**) is symmetrical, so the external

15
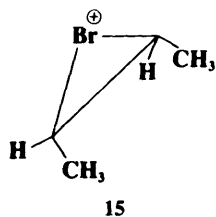
nucleophile Br⁻ can attack both carbon atoms equally well. **15** is a bromonium ion, the existence of which has been demonstrated in several types of reactions.

Although **15** 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:
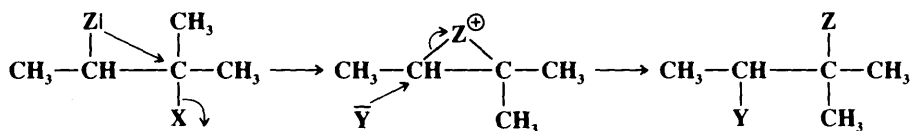
In such cases substitution and rearrangement products are often produced together. For a discussion of rearrangements, see Chapter 18.

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:
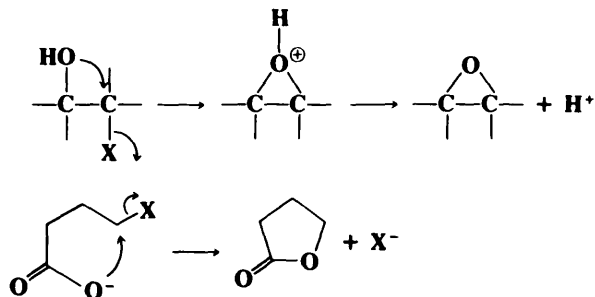
The fact that acetolysis of both 4-methoxy-1-pentyl brosylate (**16**) and 5-methoxy-2-pentyl brosylate (**17**) gave the same mixture of products is further evidence for participation by a
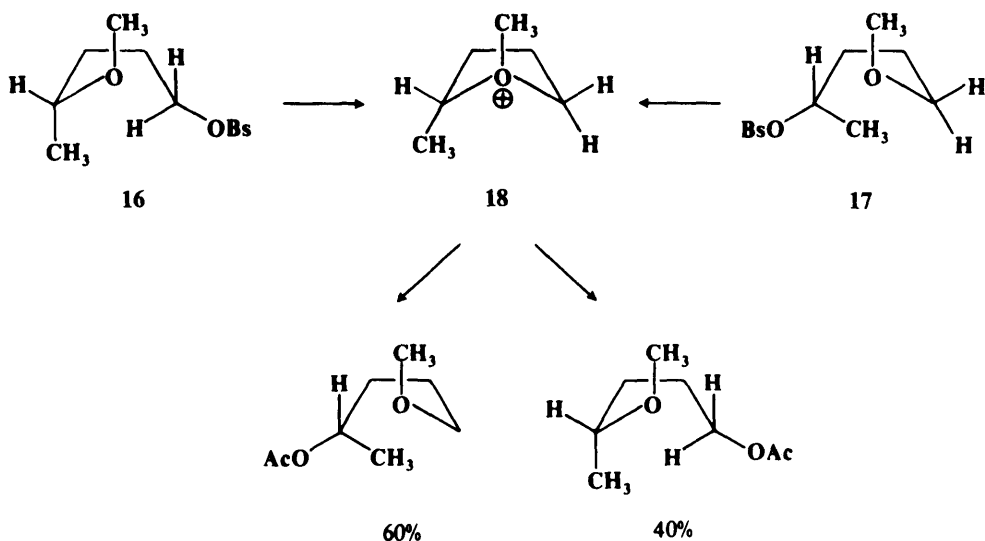
neighboring group.[80] In this case the intermediate **18** is common to both substrates.

The neighboring-group mechanism operates only when the ring size is right for a particular type of Z. For example, for MeO(CH$_2$)$_n$OBs, neighboring-group participation was important for $n = 4$ or 5 (corresponding to a five- or six-membered intermediate) but not for $n = 2$, 3, or 6.[81] 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 α or β to the neighboring group.[82]

The following are some of the more important neighboring groups: COO$^-$ (but not COOH), COOR, COAr, OCOR,[83] OR, OH, O$^-$,[84] NH$_2$, NHR,NR$_2$, NHCOR, SH, SR,

[80]Allred; Winstein *J. Am. Chem. Soc.* **1967**, *89*, 3991, 3998.

[81]Winstein; Allred; Heck; Glick *Tetrahedron* **1958**, *3*, 1; Allred; Winstein *J. Am. Chem. Soc.* **1967**, *89*, 4012.

[82]Eliel; Clawson; Knox *J. Org. Chem.* **1985**, *50*, 2707; Eliel; Knox *J. Am. Chem. Soc.* **1985**, *107*, 2946.

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

[84]For a review of oxygen functions as neighboring groups, see Perst *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; Hansell; Patel; Swindell *J. Am. Chem. Soc.* **1990**, *112*, 3535.

S$^-$,[85] I, Br, and Cl. The effectiveness of halogens as neighboring groups decreases in the order I > Br > Cl.[86] 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.[87] 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. 315).

A number of intermediates of halogen participation (halonium ions),[88] e.g., **19** and **20**, have been prepared as stable salts in SbF$_5$–SO$_2$ or SbF$_5$–SO$_2$ClF solutions.[89] Some have even

19   **20**
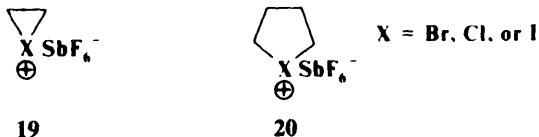
been crystallized. Attempts to prepare four-membered homologs of **19** and **20** were not successful.[90] There is no evidence that F can act as a neighboring group.[86]

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$_2$C$_6$H$_4$SO$_2$O (the nosylate group) is a better leaving group than p-MeC$_6$H$_4$SO$_2$O (the tosylate group). Experiments have shown that the OH group in *trans*-2-hydroxycyclopentyl arenesulfonates:
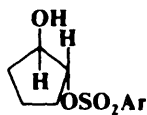
acts as a neighboring group when the leaving group is tosylate but not when it is nosylate, apparently because the nosylate group leaves so rapidly that it does not require assistance.[91]

Neighboring-Group Participation by π and σ Bonds. Nonclassical Carbocations[92]

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-

[85]For a review of sulfur-containing neighboring groups, see Block *Reactions of Organosulfur Compounds*; Academic Press: New York, 1978, pp. 141-145.

[86]Peterson *Acc. Chem. Res.* **1971**, *4*, 407-413, and references cited therein.

[87]Peterson; Bopp; Chevli; Curran; Dillard; Kamat *J. Am. Chem. Soc.* **1967**, *89*, 5902. See also Reich; Reich *J. Am. Chem. Soc.* **1974**, *96*, 2654.

[88]For a monograph, see Olah *Halonium Ions*; Wiley: New York, 1975. For a review, see Koster, in Patai; Rappoport *The Chemistry of Functional Groups, Supplement D*, pt. 2; Wiley: New York, 1983, pp. 1265-1351.

[89]See, for example Olah; Bollinger *J. Am. Chem. Soc.* **1967**, *89*, 4744, **1968**, *90*, 947; Olah; Peterson *J. Am. Chem. Soc.* **1968**, *90*, 4675; Peterson; Clifford; Slama *J. Am. Chem. Soc.* **1970**, *92*, 2840; Bonazza; Peterson *J. Org. Chem.* **1973**, *38*, 1015; Henrichs; Peterson *J. Am. Chem. Soc.* **1973**, *95*, 7449, *J. Org. Chem.* **1976**, *41*, 362; Olah; Liang; Staral *J. Am. Chem. Soc.* **1974**, *96*, 8112; Vančik; Perčač; Sunko *J. Chem. Soc., Chem. Commun.* **1991**, 807.

[90]Olah; Bollinger; Mo; Brinich *J. Am. Chem. Soc.* **1972**, *94*, 1164.

[91]Haupt; Smith *Tetrahedron Lett.* **1974**, 4141.

[92]For monographs, see Olah; Schleyer *Carbonium Ions*, vol. 3; Wiley: New York, 1972; Bartlett *Nonclassical Ions;* W.A. Benjamin: New York, 1965. For reviews, see Barkhash *Top. Curr. Chem.* **1984**, *116/117*, 1-265; Kirmse *Top. Curr. Chem.* **1979**, *80*, 125-311, pp. 196-288; McManus; Pittman, in McManus *Organic Reactive Intermediates*; Academic Press: New York, 1973, pp. 302-321; Bethell; Gold *Carbonium Ions*; Academic Press: New York, 1967; pp. 222-282. For a related review, see Prakash; Iyer *Rev. Chem. Intermed.* **1988**, *9*, 65-116.

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 *non-classical* (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 (**21**), the norbornyl cation (**22**),

| 21a | 21b | 21c | 21d |

| 22a | 22b | 22c |

| 23a | 23b | 23c |
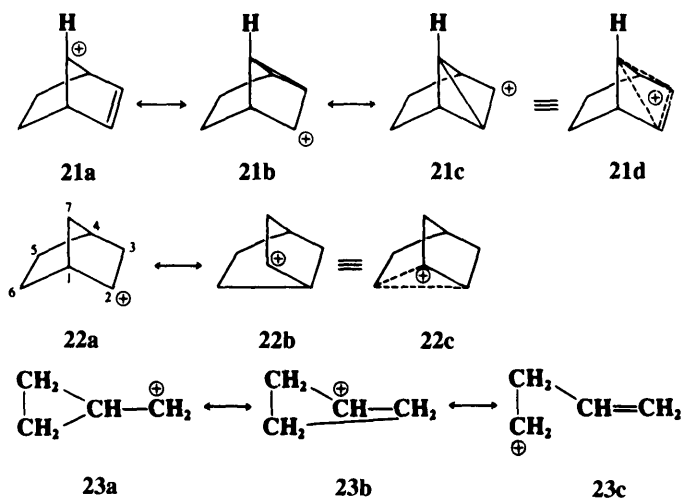
and the cyclopropylmethyl cation (**23**). **21** is called a *homoallylic* carbocation, because in **21a** there is one carbon atom between the positively charged carbon and the double bond. Many of these carbocations can be produced in more than one way if the proper substrates are chosen. For example, **22** can be generated by the departure of a leaving group from **24**

| 24 | 22 | 25 |
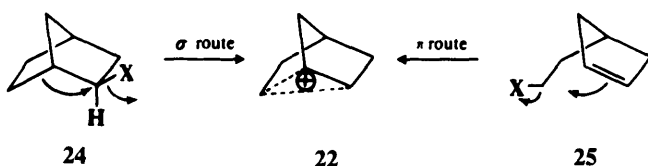
or from **25**.[93] The first of these pathways is called the σ route to a nonclassical carbocation, because participation of a σ bond is involved. The second is called the π route.[94] The argument against the existence of nonclassical carbocations is essentially that the structures **21a, 21b, 21c** (or **22a, 22b**, etc.) are not canonical forms but real structures and that there is rapid equilibration among them.

In discussing nonclassical carbocations we must be careful to make the distinction between neighboring-group participation and the existence of nonclassical carbocations.[95] If a non-classical carbocation exists in any reaction, then an ion with electron delocalization, as shown

[93]Lawton *J. Am. Chem. Soc.* **1961**, *83*, 2399; Bartlett; Bank; Crawford; Schmid *J. Am. Chem. Soc.* **1965**, *88*, 1288.
[94]Winstein; Carter *J. Am. Chem. Soc.* **1961**, *83*, 4485.
[95]This was pointed out by Cram *J. Am. Chem. Soc.* **1964**, *86*, 3767.

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 σ bonds and on the existence of nonclassical carbocations,[96] though a thorough discussion is beyond the scope of this book.[78]

1. C=C *as a neighboring group*.[97] The most striking evidence that C=C can act as a neighboring group is that acetolysis of **26**-OTs is 10^{11} times faster than that of **27**-OTs and *proceeds with retention of configuration*.[98] The rate data alone do not necessarily prove that

| **26** | **27** | **28** |
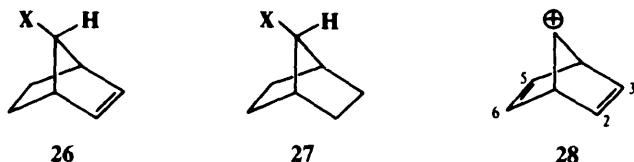
acetolysis of **26**-OTs involves a nonclassical intermediate (**21d**), but it is certainly strong evidence that the C=C group assists in the departure of the OTs. Evidence that **21** is indeed a nonclassical ion comes from an nmr study of the relatively stable norbornadienyl cation (**28**). The spectrum shows that the 2 and 3 protons are not equivalent to the 5 and 6 protons.[99] Thus there is interaction between the charged carbon and one double bond, which is evidence for the existence of **21d**.[100] In the case of **26** 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,[101] as well as in positions farther away,[102] can also lend anchimeric assistance, though generally with much lower rate ratios. One example of the latter is the compound β-(*syn*-7-norbornenyl)ethyl brosylate (**29**) which at 25°C undergoes

| **29** | **30** |
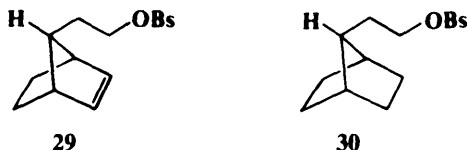
[96]The arguments against nonclassical ions are summed up in Brown *The Nonclassical Ion Problem*; Plenum: New York, 1977. This book also includes rebuttals by Schleyer. See also Brown *Pure Appl. Chem.* **1982**, *54*, 1783-1796.

[97]For reviews, see Story; Clark, in Olah; Schleyer, Ref. 92, vol. 3, 1972, pp. 1007-1060; Richey, in Zabicky *The Chemistry of Alkenes*, vol. 2; Wiley: New York, 1970, pp. 77-101.

[98]Winstein; Shatavsky *J. Am. Chem. Soc.* **1956**, *78*, 592.

[99]Story; Saunders *J. Am. Chem. Soc.* **1962**, *84*, 4876; Story; Snyder; Douglass; Anderson; Kornegay *J. Am. Chem. Soc.* **1963**, *85*, 3630. For a discussion, see Story; Clark, Ref. 97, pp. 1026-1041. See also Lustgarten; Brookhart; Winstein *J. Am. Chem. Soc.* **1972**, *94*, 2347.
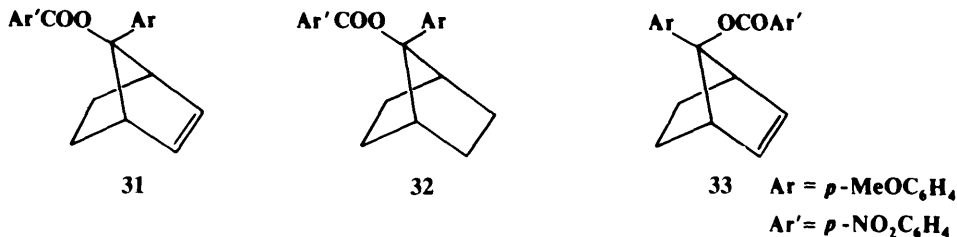
[100]For further evidence for the nonclassical nature of **21**, see Winstein; Ordronneau *J. Am. Chem. Soc.* **1960**, *82*, 2084; Brookhart; Diaz; Winstein *J. Am. Chem. Soc.* **1966**, *88*, 3135; Richey; Lustgarten *J. Am. Chem. Soc.* **1966**, *88*, 3136; Gassman; Patton *J. Am. Chem. Soc.* **1969**, *91*, 2160; Richey; Nichols; Gassman; Fentiman; Winstein; Brookhart; Lustgarten *J. Am. Chem. Soc.* **1970**, *92*, 3783; Gassman; Doherty *J. Am. Chem. Soc.* **1982**, *104*, 3742; Laube *J. Am. Chem. Soc.* **1989**, *111*, 9224.

[101]For examples, see Shoppee *J. Chem. Soc.* **1946**, 1147; LeBel; Huber *J. Am. Chem. Soc.* **1963**, *85*, 3193; Closson; Kwiatkowski *Tetrahedron* **1965**, *21*, 2779; Cristol; Nachtigall *J. Am. Chem. Soc.* **1968**, *90*, 7132; Masamune; Takada; Nakatsuka; Vukov; Cain *J. Am. Chem. Soc.* **1969**, *91*, 4322; Hess *J. Am. Chem. Soc.* **1969**, *91*, 5657; Brown; Peters; Ravindranathan *J. Am. Chem. Soc.* **1975**, *97*, 7449; Lambert; Finzel *J. Am. Chem. Soc.* **1983**, *105*, 1954; Schleyer; Bentley; Koch; Kos; Schwarz *J. Am. Chem. Soc.* **1987**, *109*, 6953.

[102]For examples, see LeNy *C. R. Acad. Sci.* **1960**, *251*, 1526; Goering; Closson *J. Am. Chem. Soc.* **1961**, *83*, 3511; Bartlett; Trahanovsky; Bolon; Schmid *J. Am. Chem. Soc.* **1965**, *87*, 1314; Bly; Swindell *J. Org. Chem.* **1965**, *30*, 10; Marvell; Sturmer; Knutson *J. Org. Chem.* **1968**, *33*, 2991; Cogdell *J. Org. Chem.* **1972**, *37*, 2541; Ferber; Gream *Aust. J. Chem.* **1981**, *34*, 1051; Kronja; Polla; Borčić *J. Chem. Soc., Chem. Commun.* **1983**, 1044; Orlović; Borčić; Humski; Kronja; Imper; Polla; Shiner *J. Org. Chem.* **1991**, *56*, 1874; Ref. 94.

acetolysis about 140,000 times faster than the saturated analog **30**.[103] Triple bonds[104] and allenes[105] can also act as neighboring groups.

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. 312), or if a sufficiently good leaving group is present (p. 312). 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 **26** and **27** exerts a powerful leveling effect on the rate differences. Thus, solvolysis in acetone–water at 85°C of **31** was only about 2.5 times


Ar'COO   Ar   Ar'COO   Ar   Ar   OCOAr'

31   **32**   **33**   Ar = *p*-MeOC$_6$H$_4$

                                                          Ar'= *p* -NO$_2$C$_6$H$_4$

faster than that of the saturated compound **32**.[106] Furthermore, both **31** and its stereoisomer **33** gave the same mixture of solvolysis products, showing that the stereoselectivity in the solvolysis of **26** is not present here. The difference between **31** and **26** is that in the case of **31** 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 participation by the C=C bond is not needed.[107] The use of a phenyl instead of a *p*-anisyl group is not sufficient to stop participation by the double bond completely, though it does reduce it.[108] These results permit us to emphasize our previous conclusion that *a neighboring group lends anchimeric assistance only when there is sufficient demand for it.*[109]

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 **34**, the solvolysis rate was lowered by a factor of about 10^6.[110] A second CF$_3$ group had

MosO   H
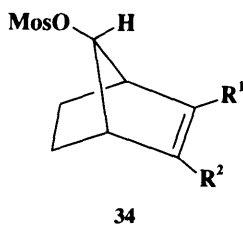
Relative Rates

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

Mos = MeO—⟨◯⟩—SO$_2$—

34
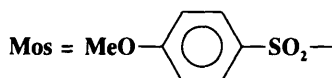
[103]Bly; Bly; Bedenbaugh; Vail *J. Am. Chem. Soc.* **1967**, *89*, 880.

[104]See, for example, Closson; Roman *Tetrahedron Lett.* **1966**, 6015; Hanack; Herterich; Vött *Tetrahedron Lett.* **1967**, 3871; Lambert; Papay; Mark *J. Org. Chem.* **1975**, *40*, 633; Peterson; Vidrine *J. Org. Chem.* **1979**, *44*, 891. For a review of participation by triple bonds and allylic groups, see Rappoport *React. Intermed. (Plenum)* **1983**, *3*, 440-453.

[105]Jacobs; Macomber *Tetrahedron Lett.* **1967**, 4877; Bly; Koock *J. Am. Chem. Soc.* **1969**, *91*, 3292, 3299; Von Lehman; Macomber *J. Am. Chem. Soc.* **1975**, 97, 1531.

[106]Gassman; Zeller; Lamb *Chem. Commun.* **1968**, 69.

[107]Nevertheless, there is evidence from ^{13}C nmr spectra that some π participation is present, even in the cation derived from **31**: Olah; Berrier; Arvanaghi; Prakash *J. Am. Chem. Soc.* **1981**, *103*, 1122.

[108]Gassman; Fentiman *J. Am. Chem. Soc.* **1969**, *91*, 1545, **1970**, *92*, 2549.

[109]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; Mark; Holcomb; Magyar *Acc. Chem. Res.* **1979**, *12*, 317-324.

[110]Gassman; Hall *J. Am. Chem. Soc.* **1984**, *106*, 4267.

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 **34** ($R^1 = R^2 = CF_3$) was about the same as (actually about 17 times slower than) the rate for the saturated substrate **27** ($X = OMos$). Thus, the two CF_3 groups completely remove the ability of the $C\!\!=\!\!C$ bond to act as a neighboring group.

2. *Cyclopropyl*[111] *as a neighboring group.*[112]   On p. 152 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 also be a neighboring group. Thus *endo-anti*-tricyclo-[3.2.1.0²·⁴]octan-8-yl *p*-nitrobenzoate (**35**) solvolyzed about 10^{14} times

Ar = *p*-NO₂C₆H₄

    35   **36**   **37**
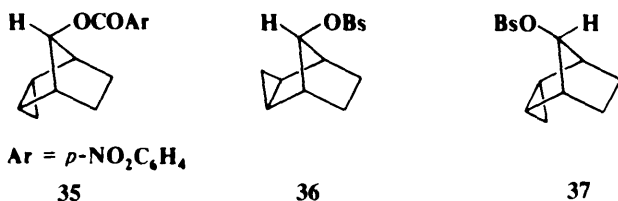
faster that the *p*-nitrobenzoate of **27-OH**.[113] Obviously, a suitably placed cyclopropyl ring can be even more effective[114] as a neighboring group than a double bond.[115] The need for suitable placement is emphasized by the fact that **37** solvolyzed only about five times faster than **27-OBs**,[116] while **36** solvolyzed three times *slower* than **27-OBs**.[117] In the case of **35** 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.[118] 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.[118] 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. 169, 324). Rate enhancements, though considerably smaller, have also been reported for suitably placed cyclobutyl rings.[119]

3. *Aromatic rings as neighboring groups.*[120]   There is a great deal of evidence that aromatic rings in the β position can function as neighboring groups. Stereochemical evidence

[111]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. 323.

[112]For a review, see Haywood-Farmer *Chem. Rev.* **1974**, *74*, 315-350.

[113]Tanida; Tsuji; Irie *J. Am. Chem. Soc.* **1967**, *89*, 1953; Battiste; Deyrup; Pincock; Haywood-Farmer *J. Am. Chem. Soc.* **1967**, *89*, 1954.

[114]For a competitive study of cyclopropyl vs. double-bond participation, see Lambert; Jovanovich; Hamersma; Koeng; Oliver *J. Am. Chem. Soc.* **1973**, *95*, 1570.

[115]For other evidence for anchimeric assistance by cyclopropyl, see Sargent; Lowry; Reich *J. Am. Chem. Soc.* **1967**, *89*, 5985; Battiste; Haywood-Farmer; Malkus; Seidl; Winstein *J. Am. Chem. Soc.* **1970**, *92*, 2144; Coates; Yano *Tetrahedron Lett.* **1972**, 2289; Masamune; Vukov; Bennett; Purdham *J. Am. Chem. Soc.* **1972**, *94*, 8239; Gassman; Creary *J. Am. Chem. Soc.* **1973**, *95*, 2729; Costanza; Geneste; Lamaty; Roque *Bull. Soc. Chim. Fr.* **1975**, 2358; Takakis; Rhodes *Tetrahedron Lett.* **1983**, *24*, 4959.

[116]Battiste; Deyrup; Pincock; Haywood-Farmer, Ref. 113; Haywood,-Farmer; Pincock *J. Am. Chem. Soc.* **1969**, *91*, 3020.

[117]Haywood-Farmer; Pincock; Wells *Tetrahedron* **1966**, *22*, 2007; Haywood-Farmer; Pincock, Ref. 116. For some other cases where there was little or no rate enhancement by cyclopropyl, see Wiberg; Wenzinger *J. Org. Chem.* **1965**, *30*, 2278; Sargent; Taylor; Demisch *Tetrahedron Lett.* **1968**, 2275; Rhodes; Takino *J. Am. Chem. Soc.* **1970**, *92*, 4469; Hanack; Krause *Liebigs Ann. Chem.* **1972**, *760*, 17.

[118]Gassman; Seter; Williams *J. Am. Chem. Soc.* **1971**, *93*, 1673. For a discussion, see Haywood-Farmer; Pincock, Ref. 116. See also Chenier; Jenson; Wulff *J. Org. Chem.* **1982**, *47*, 770.

[119]For example, see Sakai; Diaz; Winstein *J. Am. Chem. Soc.* **1970**, *92*, 4452; Battiste; Nebzydoski *J. Am. Chem. Soc.* **1970**, *92*, 4450; Schipper; Driessen; de Haan; Buck *J. Am. Chem. Soc.* **1974**, *96*, 4706; Ohkata; Doecke; Klein; Paquette *Tetrahedron Lett.* **1980**, *21*, 3253.

[120]For a review, see Lancelot; Cram; Schleyer, in Olah; Schleyer, Ref. 92, vol. 3, 1972, pp. 1347-1483.

was obtained by solvolysis of L-*threo*-3-phenyl-2-butyl tosylate (**38**) in acetic acid.[121] Of the acetate product 96% was the threo isomer and only about 4% was erythro. Moreover, both
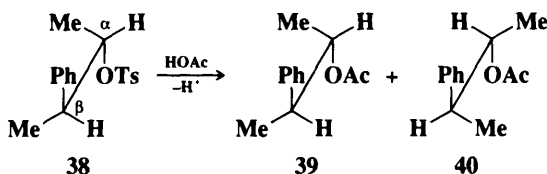
the ($+$) and ($-$) threo isomers (**39** and **40**) were produced in approximately equal amounts (a racemic mixture). When solvolysis was conducted in formic acid, even less erythro isomer was obtained. This result is similar to that found on reaction of 3-bromo-2-butanol with HBr (p. 309) and leads 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.[122] 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* (**41**), and is in turn pushed out by the solvent
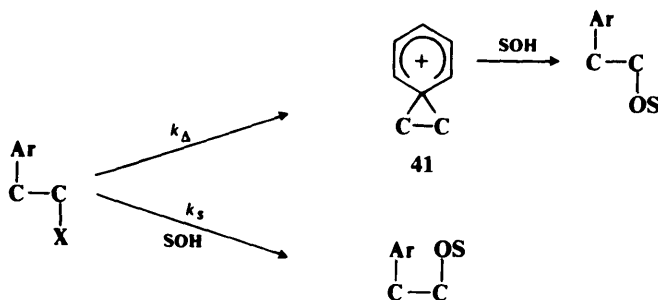
SOH, so the net result is substitution with retention of configuration (or rearrangement, if **41** is opened from the other side). The other pathway (k_s) is simple S$_N$2 attack by the solvent at the leaving-group carbon. The net result here is substitution with inversion and no possibility of rearrangement. Whether the leaving group is located at a primary or a secondary carbon, there is no crossover between these pathways; they are completely independent.[123] (Both the k_Δ and k_s pathways are unimportant when the leaving group is at a tertiary carbon. In these cases the mechanism is S$_N$1 and open carbocations ArCH$_2$CR$_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. 312), the k_Δ/k_s ratio is highest for solvents that are poor nucleophiles and so compete very poorly with the aryl group. For several common solvents the k_Δ/k_s ratio increases in the order EtOH < CH$_3$COOH <

[121]Cram *J. Am. Chem. Soc.* **1949**, *71*, 3863, **1952**, *74*, 2129.

[122]Winstein; Heck *J. Am. Chem. Soc.* **1956**, *78*, 4801; Brookhart; Anet; Cram; Winstein *J. Am. Chem. Soc.* **1966**, *88*, 5659; Lee; Unger; Vassie *Can. J. Chem.* **1972**, *50*, 1371.

[123]Harris; Schadt; Schleyer; Lancelot *J. Am. Chem. Soc.* **1969**, *91*, 7508; Brown; Kim; Lancelot; Schleyer *J. Am. Chem. Soc.* **1970**, *92*, 5244; Brown; Kim *J. Am. Chem. Soc.* **1971**, *93*, 5765.

HCOOH < CF$_3$COOH.[124] 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$_3$COOH 35%, HCOOH 85%.[124] 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;[125] deuterium labeling showed 100% retention.[126] This case provides a clear example of neighboring-group rate enhancement by phenyl: the rate of solvolysis of PhCH$_2$CH$_2$OTs at 75°C in CF$_3$COOH is 3040 times the rate for CH$_3$CH$_2$OTs.[125]

With respect to the aromatic ring, the k_Δ pathway is electrophilic aromatic substitution (Chapter 11). We predict that groups on the ring which activate that reaction (p. 507) 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 **38** solvolyzed in acetic acid 190 times slower than **38**, and there was much less retention of configuration; the acetate produced was only 7% threo and 93% erythro.[127] At 90°C, acetolysis of *p*-ZC$_6$H$_4$CH$_2$CH$_2$OTs gave the rate ratios shown in Table 10.1.[128] 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,[129] 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.[130] 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. 315).

Several phenonium ions have been prepared as stable ions in solution where they can be studied by nmr, among them **42**,[131] **43**,[132] and the unsubstituted **41**.[133] These were

TABLE 10.1 Approximate k_Δ/k_s ratios for acetolysis of *p*-ZC$_6$H$_4$CH$_2$CH$_2$OTs at 90°C[128]

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$_6$H$_4$CH$_2$CHMeOTs[130]

Z	Solvent	Percent by k_Δ
H	CH$_3$COOH	35–38
H	HCOOH	72–79
MeO	CH$_3$COOH	91–93
MeO	HCOOH	99

[124]Diaz; Lazdins; Winstein *J. Am. Chem. Soc.* **1968**, *90*, 6546; Diaz; Winstein *J. Am. Chem. Soc.* **1969**, *91*, 4300. See also Schadt; Lancelot; Schleyer *J. Am. Chem. Soc.* **1978**, *100*, 228.

[125]Nordlander; Deadman *J. Am. Chem. Soc.* **1968**, *90*, 1590; Nordlander; Kelly *J. Am. Chem. Soc.* **1969**, *91*, 996.

[126]Jablonski; Snyder *J. Am. Chem. Soc.* **1969**, *91*, 4445.

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

[128]Coke; McFarlane; Mourning; Jones *J. Am. Chem. Soc.* **1969**, *91*, 1154; Jones; Coke *J. Am. Chem. Soc.* **1969**, *91*, 4284. See also Harris; Schadt; Schleyer; Lancelot, Ref. 123.

[129]The k_Δ pathway is important for *p*-nitrophenyl in CF$_3$COOH: Ando; Shimizu; Kim; Tsuno; Yukawa *Tetrahedron Lett.* **1973**, 117.

[130]Lancelot; Schleyer *J. Am. Chem. Soc.* **1969**, *91*, 4291, 4296; Lancelot; Harper; Schleyer *J. Am. Chem. Soc.* **1969**, *91*, 4294; Schleyer; Lancelot *J. Am. Chem. Soc.* **1969**, *91*, 4297.

[131]Olah; Comisarow; Namanworth; Ramsey *J. Am. Chem. Soc.* **1967**, *89*, 5259; Ramsey; Cook; Manner *J. Org. Chem.* **1972**, *37*, 3310.

[132]Olah; Comisarow; Kim *J. Am. Chem. Soc.* **1969**, *91*, 1458. See, however, Ramsey; Cook; Manner, Ref. 131.

[133]Olah; Porter *J. Am. Chem. Soc.* **1971**, *93*, 6877; Olah; Spear; Forsyth *J. Am. Chem. Soc.* **1976**, *98*, 6284.

42   **43**
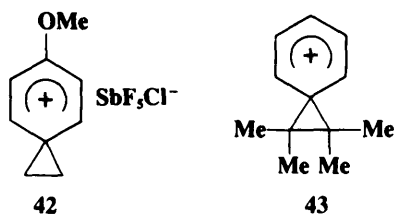
prepared[134] by the method shown for **41:** treatment of the corresponding β-arylethyl chloride with SbF₅–SO₂ at low temperatures. These conditions are even more extreme than the

41

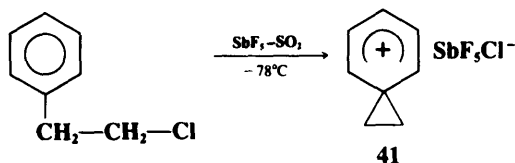solvolysis in CF₃COOH mentioned earlier. The absence of any nucleophile at all eliminates not only the k_s pathways but also nucleophilic attack on **41.** Although **41** is not in equilibrium with the open-chain ion PhCH₂CH₂⁺ (which is primary and hence unstable), **43** is in equi-librium with the open-chain tertiary ions PhĊMe₂CMe₂ and PhĊMeCMe₃, though only **43** is present in appreciable concentration. Proton and ¹³C nmr show that **41, 42,** and **43** are classical carbocations where the only resonance is in the six-membered ring. The three-

44
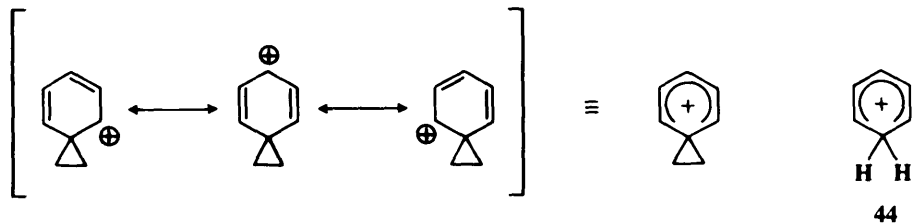
membered ring is a normal cyclopropane ring that is influenced only to a relatively small extent by the positive charge on the adjacent ring. Nmr spectra show that the six-membered rings have no aromatic character but are similar in structure to the arenium ions, e.g., **44,** that are intermediates in electrophilic aromatic substitution (Chapter 11). A number of phenonium ions, including **41,** have also been reported to be present in the gas phase, where their existence has been inferred from reaction products and from ¹³C labeling.[135]

It is thus clear that β-aryl groups can function as neighboring groups.[136] Much less work

[134]For some others, see Olah; Singh; Liang *J. Org. Chem.* **1984,** *49,* 2922; Olah; Singh *J. Am. Chem.Soc.* **1984,** *106,* 3265.

[135]Fornarini; Sparapani; Speranza *J. Am. Chem. Soc.* **1988,** *110,* 34, 42; Fornarini; Muraglia *J. Am. Chem. Soc.* **1989,** *111,* 873; Mishima; Tsuno; Fujio *Chem. Lett.* **1990,** 2277.

[136]For additional evidence, see Tanida *Acc. Chem. Res.* **1968,** *1,* 239-245; Kingsbury; Best *Tetrahedron Lett.* **1967,** 1499; Braddon; Wiley; Dirlam; Winstein *J. Am. Chem. Soc.* **1968,** *90,* 1901; Tanida; Ishitobi; Irie *J. Am. Chem. Soc.* **1968,** *90,* 2688; Brown; Tritle *J. Am. Chem. Soc.* **1968,** *90,* 2689; Bentley; Dewar *J. Am. Chem. Soc.* **1970,** *92,* 3996; Raber; Harris; Schleyer *J. Am. Chem. Soc.* **1971,** *93,* 4829; Shiner; Seib *J. Am. Chem. Soc.* **1976,** *98,* 862; Faïn; Dubois *Tetrahedron Lett.* **1978,** 791; Yukawa; Ando; Token; Kawada; Matsuda; Kim; Yamataka *Bull. Chem. Soc. Jpn.* **1981,** *54,* 3536; Ferber; Gream *Aust. J. Chem.* **1981,** *34,* 2217; Fujio; Goto; Seki; Mishima; Tsuno; Sawada; Takai *Bull. Chem. Soc. Jpn.* **1987,** *60,* 1097. For a discussion of evidence obtained from isotope effects, see Scheppele *Chem. Rev.* **1972,** *72,* 511-532, pp. 522-525.

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.[137]

4. *The carbon-carbon single bond as a neighboring group.*[138]

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 has been paid to the 2-norbornyl system.[139] Winstein and Trifan found that solvolysis in acetic acid of optically active *exo*-2-norbornyl brosylate (**45**) gave a racemic mixture of the two exo acetates; no endo isomers were formed:[140]

45   46   47   48
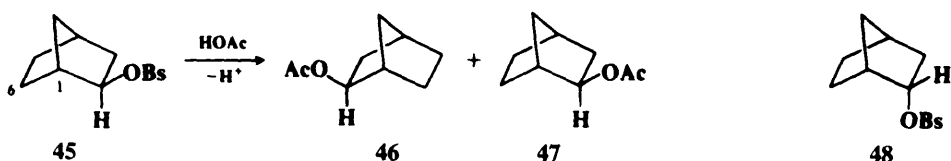
Futhermore, **45** solvolyzed about 350 times faster than its endo isomer **48**. Similar high exo/endo rate ratios have been found in many other [2.2.1] systems. These two results—(1) that solvolysis of an optically active exo isomer gave only racemic exo isomers and (2) the high exo/endo rate ratio—were 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 (**49**)

45   49   46

47
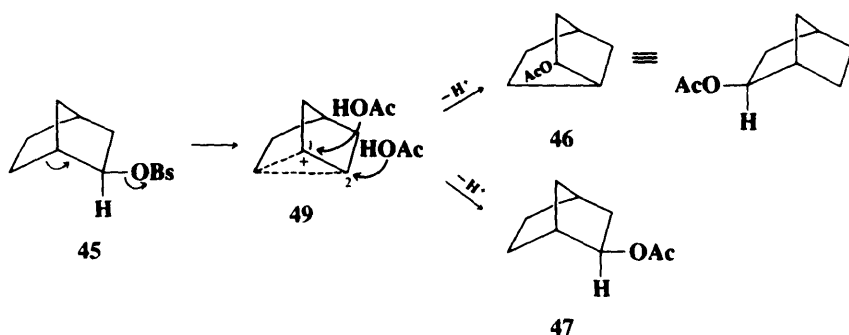
is involved. They reasoned that solvolysis of the endo isomer **48** is not assisted by the 1,6 bond because it is not in a favorable position for backside attack, and that consequently solvolysis of **48** takes place at a "normal" rate. Therefore the much faster rate for the solvolysis of **45** must be caused by anchimeric assistance. The stereochemistry of the product is also explained by the intermediacy of **49**, since in **49** 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 **48** also leads exclusively to the exo acetates (**46**

[137]Heck; Winstein *J. Am. Chem. Soc.* **1957**, *79*, 3105; Muneyuki; Tanida *J. Am. Chem. Soc.* **1968**, *90*, 656; Ouellette; Papa; Attea; Levin *J. Am. Chem. Soc.* **1970**, *92*, 4893; Jackman; Haddon *J. Am. Chem. Soc.* **1974**, *96*, 5130; Gates; Frank; von Felten *J. Am. Chem. Soc.* **1974**, *96*, 5138; Ando; Yamawaki; Saito *Bull. Chem. Soc. Jpn.* **1978**, *51*, 219.

[138]For a review pertaining to studies of this topic at low temperatures, see Olah *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 173-212, pp. 192-198 [*Angew. Chem. 85*, 183-225].

[139]For reviews, see Olah; Prakash; Williams *Hypercarbon Chemistry*; Wiley: New York, 1987, pp. 157-170; Grob *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 87-96 [*Angew. Chem. 94*, 87-96]; Sargent, in Olah; Schleyer, Ref. 92, vol. 3, 1972, pp. 1099-1200; Sargent *Q. Rev., Chem. Soc.* **1966**, *20*, 301-371; Gream *Rev. Pure Appl. Chem.* **1966**, *16*, 25-60; Ref. 92. For a closely related review, see Kirmse *Acc. Chem. Res.* **1986**, *19*, 36-41. See also Ref. 143.

[140]Winstein; Trifan *J. Am. Chem. Soc.* **1952**, *74*, 1147, 1154; Winstein; Clippinger; Howe; Vogelfanger *J. Am. Chem. Soc.* **1965**, *87*, 376.

and **47**), so that in this case Winstein and Trifan postulated that a classical ion (**50**) is first formed and then converted to the more stable **49**. Evidence for this interpretation is that the product from solvolysis of **48** is not racemic but contains somewhat more **47** than **46** (corresponding to 3 to 13% inversion, depending on the solvent),[140] suggesting that when **50** is formed, some of it goes to give **47** before it can collapse to **49**.

The concepts of σ participation and the nonclassical ion **49** have been challenged by H. C. Brown,[96] who has suggested that the two results can also be explained by postulating that **45** solvolyzes without participation of the 1,6 bond to give the classical ion **50** which is in rapid equilibrium with **51**. This rapid interconversion has been likened to the action of

45   **50**   **51**
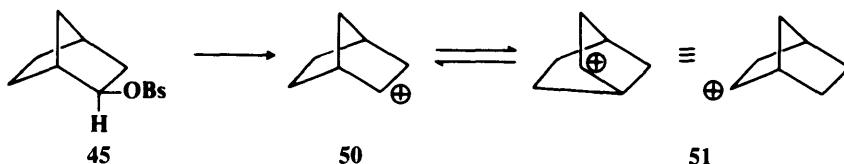
a windshield wiper.[141] Obviously, in going from **50** to **51** and back again, **49** must be present, but in Brown's view it is a transition state and not an intermediate. Brown's explanation for the stereochemical result is that exclusive exo attack is a property to be expected from any 2-norbornyl 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. As for the obtention of a racemic mixture, this will obviously happen if **50** and **51** are present in equal amounts, since they are equivalent and exo attack on **50** and **51** gives, respectively, **47** and **46**. Brown explains 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.[142]

A vast amount of work has been done[143] on solvolysis of the 2-norbornyl system in an effort to determine whether the 1,6 bond participates and whether **49** is an intermediate. Most,[144] although not all,[145] chemists now accept the intermediacy of **49**.

Besides the work done on solvolysis of 2-norbornyl compounds, the 2-norbornyl cation

[141]Another view is somewhere in between: There are two interconverting ions, but each is asymmetrically bridged: Bielmann; Fuso; Grob *Helv. Chim. Acta* **1988**, *71*, 312; Flury; Grob; Wang; Lennartz; Roth *Helv. Chim. Acta* **1988**, *71*, 1017.

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

[143]For thorough discussions, see Lenoir; Apeloig; Arad; Schleyer *J. Org. Chem.* **1988**, *53*, 661; Grob *Acc. Chem. Res.* **1983**, *16*, 426-431; Brown *Acc. Chem. Res.* **1983**, *16*, 432-440; Walling *Acc. Chem. Res.* **1983**, *16*, 448-454; Refs. 92, 96, and 139. For commentary on the controversy, see Arnett; Hofelich; Schriver *React. Intermed. (Wiley)* **1985**, *3*, 189-226, pp. 193-202.

[144]For some recent evidence in favor of a nonclassical **49**, see Arnett; Petro; Schleyer *J. Am. Chem. Soc.* **1979**, *101*, 522; Albano; Wold *J. Chem. Soc., Perkin Trans. 2* **1980**, 1447; Wilcox; Tuszynski *Tetrahedron Lett.* **1982**, *23*, 3119; Kirmse; Siegfried *J. Am. Chem. Soc.* **1983**, *105*, 950; Creary; Geiger *J. Am. Chem. Soc.* **1983**, *105*, 7123; Chang; le Noble *J. Am. Chem. Soc.* **1984**, *106*, 810; Kirmse; Brandt *Chem. Ber.* **1984**, *117*, 2510; Wilcox; Brungardt *Tetrahedron Lett.* **1984**, *25*, 3403; Lajunen *Acc. Chem. Res.* **1985**, *18*, 254-258; Sharma; Sen Sharma; Hiraoka; Kebarle *J. Am. Chem. Soc.* **1985**, *107*, 3747; Servis; Domenick; Forsyth; Pan *J. Am. Chem. Soc.* **1987**, *109*, 7263; Lenoir et al., Ref. 143.

[145]For some recent evidence against a nonclassical **49**, see Dewar; Haddon; Komornicki; Rzepa *J. Am. Chem. Soc.* **1977**, *99*, 377; Lambert; Mark *J. Am. Chem. Soc.* **1978**, *100*, 2501; Christol; Coste; Pietrasanta; Plénat; Renard *J. Chem. Soc., (S)* **1978**, 62; Brown; Ravindranathan; Rao; Chloupek; Rei *J. Org. Chem.* **1978**, *43*, 3667; Brown; Rao *J. Org. Chem.* **1979**, *44*, 133, 3536, **1980**, 45, 2113; Liu; Yen; Hwang *J. Chem. Res.(S)* **1980**, 152; Werstiuk; Dhanoa; Timmins *Can. J. Chem.* **1983**, 61, 2403; Brown; Chloupek; Takeuchi *J. Org. Chem.* **1985**, *50*, 826; Brown; Ikegami; Vander Jagt *J. Org. Chem.* **1985**, *50*, 1165; Nickon; Swartz; Sainsbury; Toth *J. Org. Chem.* **1986**, *51*, 3736. See also Brown *Top. Curr. Chem.* **1979**, *80*, 1-18.

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.[146] Studies by proton and ^{13}C nmr, as well as by laser Raman spectra and x-ray electron spectroscopy, led to the conclusion[147] that under these conditions the ion is nonclassical.[148] A similar result has been reported for the 2-norbornyl cation in the solid state where at 77 K and even 5 K, ^{13}C nmr spectra gave no evidence of the freezing out of a single classical ion.[149]

Olah and co-workers represented the nonclassical structure as a corner-protonated nortricyclane (52); the symmetry is better seen when the ion is drawn as in 53. Almost all the

Nortricyclane   52   53   54
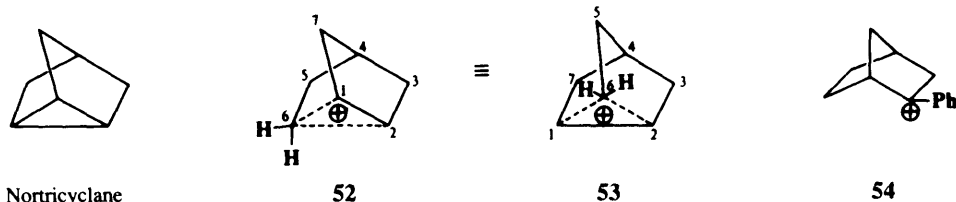
positive charge resides on C-1 and C-2 and very little on the bridging carbon C-6. Other evidence for the nonclassical nature of the 2-norbornyl cation in stable solutions comes from heat of reaction measurements that show that the 2-norbornyl cation is more stable (by about 6-10 kcal/mol or 25-40 kJ/mol) than would be expected without the bridging.[150] Studies of ir spectra of the 2-norbornyl cation in the gas phase also show the nonclassical structure.[151] Ab inito calculations show that the nonclassical structure corresponds to an energy minimum.[152]

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,[153] and the 2-phenylnorbornyl cation (54) is essentially classical,[154] as are the 2-methoxy-[155] and 2-chloronorbornyl cations.[156] We may recall (p. 170) that methoxy and halo groups also

[146]The presence of hydride shifts (p. 1069) under solvolysis conditions has complicated the interpretation of the data.
[147]Olah; White; DeMember; Commeyras; Lui *J. Am. Chem. Soc.* **1970**, *92*, 4627; Olah *J. Am. Chem. Soc.***1972**, *94*, 808; *Acc. Chem. Res.* **1976**, *9*, 41-52; Olah; Liang; Mateescu; Riemenschneider *J. Am. Chem. Soc.* **1973**, *95*, 8698; Saunders; Kates *J. Am. Chem. Soc.* **1980**, *102*, 6867, **1983**, *105*, 3571; Olah; Prakash; Arvanaghi; Anet *J. Am. Chem. Soc.* **1982**, *104*, 7105; Olah; Prakash; Saunders *Acc. Chem. Res.* **1983**, *16*, 440-448. See also Schleyer; Lenoir; Mison; Liang; Prakash; Olah *J. Am. Chem. Soc.* **1980**, *102*, 683; Johnson; Clark *J. Am. Chem. Soc.* **1988**, *110*, 4112.
[148]This conclusion has been challenged: Fong *J. Am. Chem. Soc.* **1974**, *96*, 7638; Kramer *Adv. Phys. Org. Chem.* **1975**, *11*, 177-224; Brown; Periasamy; Kelly; Giansiracusa *J. Org. Chem.* **1982**, *47*, 2089; Kramer; Scouten *Adv. Carbocation Chem.* **1989**, *1*, 93-120. See, however, Olah; Prakash; Farnum; Clausen *J. Org. Chem.* **1983**, *48*, 2146.
[149]Yannoni; Macho; Myhre *J. Am. Chem. Soc.* **1982**, *104*, 907, 7380, *Bull. Soc. Chim. Belg.* **1982**, *91*, 422; Myhre; Webb; Yannoni *J. Am. Chem. Soc.* **1990**, *112*, 8991.
[150]For some examples, see Hogeveen; Gaasbeek *Recl. Trav. Chim. Pays-Bas* **1969**, *88*, 719; Hogeveen *Recl. Trav. Chim. Pays-Bas* **1970**, *89*, 74; Solomon; Field *J. Am. Chem. Soc.* **1976**, *98*, 1567; Staley; Wieting; Beauchamp *J. Am. Chem. Soc.* **1977**, *99*, 5964; Arnett; Petro *J. Am. Chem. Soc.* **1978**, *100*, 2563; Arnett; Pienta; Petro *J. Am. Chem. Soc.* **1980**, *102*, 398; Saluja; Kebarle *J. Am. Chem. Soc.* **1979**, *101*, 1084; Schleyer; Chandrasekhar *J. Org. Chem.* **1981**, *46*, 225; Lossing; Holmes *J. Am. Chem. Soc.* **1984**, *106*, 6917.
[151]Koch; Liu; DeFrees; Sunko; Vančik *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 183 [*Angew. Chem. 102*, 198].
[152]See, for example Koch; Liu; DeFrees *J. Am. Chem. Soc.* **1989**, *111*, 1527.
[153]Olah; DeMember; Lui; White *J. Am. Chem. Soc.* **1969**, *91*, 3958. See also Laube *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 560 [*Angew. Chem. 99*, 578]; Forsyth; Panyachotipun *J. Chem. Soc., Chem. Commun.* **1988**, 1564.
[154]Olah; Liang *J. Am. Chem. Soc.* **1974**, *96*, 195; Olah; White; DeMember; Commeyras; Lui, Ref. 147; Farnum; Mehta *J. Am. Chem. Soc.* **1969**, *91*, 3256; Ref. 153. See also Schleyer; Kleinfelter; Richey *J. Am. Chem. Soc.* **1963**, *85*, 479; Farnum; Wolf *J. Am. Chem. Soc.***1974**, *96*, 5166.
[155]Nickon; Lin *J. Am. Chem. Soc.* **1969**, *91*, 6861. See also Montgomery; Grendze; Huffman *J. Am. Chem. Soc.* **1987**, *109*, 4749.
[156]Fry; Farnham *J. Org. Chem.* **1969**, *34*, 2314.

stabilize a positive charge. ^{13}C nmr data show that electron-withdrawing groups on the benzene ring of **54** cause the ion to become less classical, while electron-donating groups enhance the classical nature of the ion.[157]

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.[158] It has long been known that cyclopropylmethyl substrates solvolyze with abnormally high rates and that the products often include not only unrearranged cyclopropylmethyl but also cyclobutyl and homoallylic compounds. An example is[159]

$$\sim 48\% \qquad \sim 47\% \qquad \sim 5\%$$
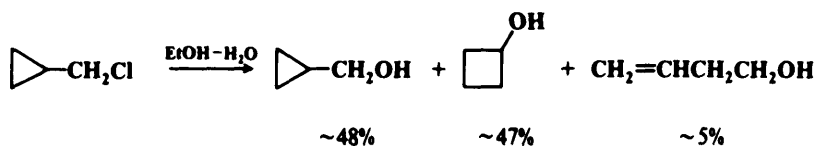
Cyclobutyl substrates also solvolyze abnormally rapidly and give similar products. Furthermore, when the reactions are carried out with labeled substrates, considerable, though not complete, scrambling is observed. For these reasons it has been suggested that a common intermediate (some kind of nonclassical intermediate, e.g., **23**, p. 313) is present in these cases. This common intermediate could then be obtained by three routes:

$$CH_2{=}CH{-}CH_2{-}CH_2{-}X$$
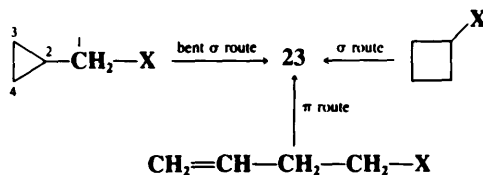
In recent years much work has been devoted to the study of these systems, and it is apparent that matters are not so simple. Though there is much that is still not completely understood, some conclusions can be drawn.

i. In solvolysis of simple primary cyclopropylmethyl systems the rate is enhanced because of participation by the σ bonds of the ring.[160] The ion that forms initially is an unrearranged cyclopropylmethyl cation[161] 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. 169) 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 **55**. Among the evidence that **55** is a

55

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

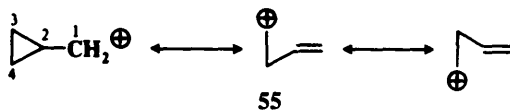[157]Olah; Prakash; Liang *J. Am. Chem. Soc.* **1977**, *99*, 5683; Farnum; Botto; Chambers; Lam *J. Am. Chem. Soc.* **1978**, *100*, 3847. See also Olah; Berrier; Prakash *J. Org. Chem.* **1982**, *47*, 3903.
[158]For reviews, see in Olah; Schleyer, Ref. 92, vol. 3, 1972, the articles by Richey, pp. 1201-1294, and by Wiberg; Hess; Ashe, pp. 1295-1345; Hanack; Schneider *Fortschr. Chem. Forsch.* **1967**, *8*, 554-607, *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 666-677 [*Angew. Chem. 79*, 709-720]; Sarel; Yovell; Sarel-Imber *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 577-588 [*Angew. Chem. 90*, 592-603].
[159]Roberts; Mazur *J. Am. Chem. Soc.* **1951**, *73*, 2509.
[160]See, for example, Roberts; Snyder *J. Org. Chem.* **1979**, *44*, 2860, and references cited therein.
[161]Wiberg; Ashe *J. Am. Chem. Soc.* **1968**, *90*, 63.

a factor of 10 for *each* methyl group.[162] If only one of the σ bonds (say, the 2,3 bond) 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.[163]

ii. The most stable geometry of simple cyclopropylmethyl cations is the bisected one shown on p. 169. There is much evidence that in systems where this geometry cannot be obtained, solvolysis is greatly slowed.[164]

iii. Once a cyclopropylmethyl cation is formed, it can rearrange to two other cyclopropylmethyl cations:
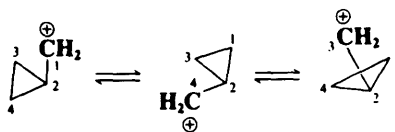
This rearrangement, which accounts for the scrambling, is completely stereospecific.[165] The rearrangements probably take place through a nonplanar cyclobutyl cation intermediate or transition state. The formation of cyclobutyl and homoallylic products from a cyclopropylmethyl cation is also completely stereospecific. These products may arise by direct attack of the nucleophile on **55** or on the cyclobutyl cation intermediate.[165] 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 **55**, which accounts for the fact that solvolysis of cyclobutyl and of cyclopropylmethyl substrates often gives similar product
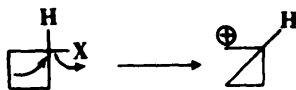
mixtures. There is no evidence that requires the cyclobutyl cations to be intermediates in most secondary cyclobutyl systems, though tertiary cyclobutyl cations can be solvolysis intermediates.

v. The unsubstituted cyclopropylmethyl cation has been generated in super-acid solutions at low temperatures, where ^{13}C nmr spectra have led to the conclusion that it consists of a mixture of the bicyclobutonium ion **23** and the bisected cyclopropylmethyl cation **55**, in equilibrium with **23**.[166] Molecular orbital calculations show that these two species are energy minima, and that both have nearly the same energy.[167]

[162]Schleyer; Van Dine *J. Am. Chem. Soc.* **1966**, *88*, 2321.
[163]For a summary of additional evidence for the symmetrical nature of cyclopropylmethyl cations, see Wiberg; Hess; Ashe, Ref. 158, pp. 1300-1303.
[164]For example, see Ree; Martin *J. Am. Chem. Soc.* **1970**, *92*, 1660; Rhodes; DiFate *J. Am. Chem. Soc.* **1972**, *94*, 7582. See, however, Brown; Peters *J. Am. Chem. Soc.* **1975**, *97*, 1927.
[165]Wiberg; Szeimies *J. Am. Chem. Soc.* **1968**, *90*, 4195, **1970**, *92*, 571; Majerski; Schleyer *J. Am. Chem. Soc.* **1971**, *93*, 665.
[166]Staral; Yavari; Roberts; Prakash; Donovan; Olah *J. Am. Chem. Soc.* **1978**, *100*, 8016. See also Olah; Jeuell; Kelly; Porter *J. Am. Chem. Soc.* **1972**, *94*, 146; Olah; Spear; Hiberty; Hehre *J. Am. Chem. Soc.* **1976**, *98*, 7470; Saunders; Siehl *J. Am. Chem. Soc.* **1980**, *102*, 6868; Brittain; Squillacote; Roberts *J. Am. Chem. Soc.* **1984**, *106*, 7280; Siehl; Koch *J. Chem. Soc., Chem. Commun.* **1985**, 496; Prakash; Arvanaghi; Olah *J. Am. Chem. Soc.* **1985**, *107*, 6017; Myhre; Webb; Yannoni *J. Am. Chem. Soc.* **1990**, *112*, 8992.
[167]Koch; Liu; DeFrees *J. Am. Chem. Soc.* **1988**, *110*, 7325; Saunders; Laidig; Wiberg; Schleyer *J. Am. Chem. Soc.* **1988**, *110*, 7652.

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 **56** must lie on the reaction path, but the two questions

$$
\begin{array}{cccc}
\text{CH}_3 & \text{CH}_3 & \overset{\oplus}{\text{CH}_3} & \text{CH}_3 \\
| & |\diagdown| & \diagup\diagdown & | \\
\text{CH}_3-\text{C}-\text{CH}_2-\text{OTs} & -\text{C}-\text{C}-\text{OTs} \longrightarrow -\text{C}-\text{C}- & \longrightarrow -\overset{\oplus}{\text{C}}-\text{C}- \\
| & |\ \ | & |\ \ | & |\ \ | \\
\text{CH}_3 & & &
\end{array}
$$

Neopentyl tosylate   **56**
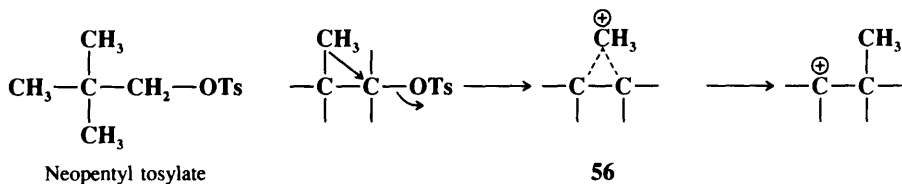
that have been asked are: (1) Is the departure of the leaving group concerted with the formation of the CH₃—C bond (that is, does the methyl participate)? (2) Is **56** an intermediate or only a transition state? With respect to the first question, there is evidence, chiefly from isotope effect studies, that indicates that the methyl group in the neopentyl system does indeed participate,[168] though it may not greatly enhance the rate. As to the second question, evidence that **56** is an intermediate is that small amounts of cyclopropanes (10 to 15%) can be isolated in these reactions.[169] **56** is a protonated cyclopropane and would give cyclopropane on loss of a proton.[170] In an effort to isolate a species that has structure **56**, the 2,3,3-trimethyl-2-butyl cation was prepared in super-acid solutions at low temperatures.[171] However, proton and ¹³C nmr, as well as Raman spectra, showed this to be a pair of rapidly equilibrating open ions.

$$
\begin{array}{ccc}
\text{CH}_3 & \text{CH}_3 & \overset{\oplus}{\text{CH}_3} \\
\overset{\oplus}{} | & | \overset{\oplus}{} & \diagup\diagdown \\
\text{CH}_3-\text{C}-\text{C}-\text{CH}_3 \rightleftharpoons \text{CH}_3-\text{C}-\text{C}-\text{CH}_3 & \text{CH}_3-\text{C}-\text{C}-\text{CH}_3 \\
| \ \ | & | \ \ | & |\ \ | \\
\text{CH}_3\text{CH}_3 & \text{CH}_3\text{CH}_3 & \text{CH}_3\text{CH}_3
\end{array}
$$

57
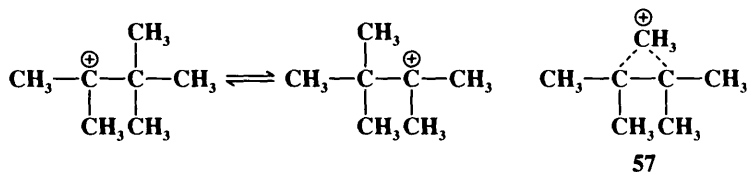
Of course, **57** must lie on the reaction path connecting the two open ions, but it is evidently a transition state and not an intermediate. However, evidence from x-ray photoelectron spectroscopy (ESCA) has shown that the 2-butyl cation is substantially methyl bridged.[172]

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 departure of the leaving group? (2) Is **58** an intermediate or only a transition state? There is some evidence that a β hydrogen can

[168]For example, see Dauben; Chitwood *J. Am. Chem. Soc.* **1968**, *90*, 6876; Ando; Morisaki *Tetrahedron Lett.* **1979**, 121; Shiner; Seib *Tetrahedron Lett.* **1979**, 123; Shiner; Tai *J. Am. Chem. Soc.* **1981**, *103*, 436; Yamataka; Ando *J. Am. Chem. Soc.* **1982**, *104*, 1808; Yamataka; Ando; Nagase; Hanamura; Morokuma *J. Org. Chem.* **1984**, *49*, 631. For an opposing view, see Zamashchikov; Rudakov; Bezbozhnaya; Matveev *J. Org. Chem. USSR* **1984**, *20*, 11.
[169]Skell; Starer *J. Am. Chem. Soc.* **1960**, 82, 2971; Silver *J. Am. Chem. Soc.* **1960**, 82, 2971; Friedman; Bayless *J. Am. Chem. Soc.* **1969**, *91*, 1790; Friedman; Jurewicz *J. Am. Chem. Soc.* **1969**, *91*, 1800, 1803; Dupuy; Hudson; Karam *Tetrahedron Lett.* **1971**, 3193; Silver; Meek *Tetrahedron Lett.* **1971**, 3579; Dupuy; Hudson *J. Chem. Soc., Perkin Trans. 2* **1972**, 1715.
[170]For further discussions of protonated cyclopropanes, see pp. 757, 1056.
[171]Olah; White *J. Am. Chem. Soc.* **1969**, *91*, 5801; Olah; Comisarow; Kim *J. Am. Chem. Soc.* **1969**, *91*, 1458; Olah; DeMember; Commeyras; Bribes *J. Am. Chem. Soc.* **1971**, *93*, 459.
[172]Johnson; Clark, Ref. 147. See also Carneiro; Schleyer; Koch; Raghavachari *J. Am. Chem. Soc.* **1990**, *112*, 4064.

participate.[173] Evidence that **58** can be an intermediate in solvolysis reactions comes from a study of the solvolysis in trifluoroacetic acid of deuterated *sec*-butyl tosylate **59**. In this

$$\overset{\oplus}{\underset{\displaystyle -\!\!\underset{|}{C}\!-\!\underset{|}{C}\!-}{H}}$$

58
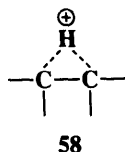
solvent of very low nucleophilic power, the products were an equimolar mixture of **60** and **61**,[174] but *no* **62** or **63** was found. If this reaction did not involve neighboring hydrogen at

$$\underset{\textbf{59}}{\overset{\displaystyle OTs}{CH_3CH_2\overset{|}{C}DCD_3}} \xrightarrow{CF_3COOH} \underset{\textbf{60}}{\overset{\displaystyle OOCCF_3}{CH_3CH_2\overset{|}{C}DCD_3}} + \underset{\textbf{61}}{\overset{\displaystyle OOCCF_3}{CH_3\overset{|}{C}HCDHCD_3}}$$

all (pure SN2 or SN1), the product would be only **60**. On the other hand, if hydrogen does migrate, but only open cations are involved, then there should be an equilibrium among

$$\underset{\textbf{62}}{\overset{\displaystyle OOCCF_3}{CH_3CHD\overset{|}{C}HCD_3}} \qquad \underset{\textbf{63}}{\overset{\displaystyle OOCCF_3}{CH_3\overset{|}{C}DCH_2CD_3}} \qquad \underset{\textbf{64}}{\overset{\displaystyle \overset{\oplus}{H}}{CH_3-\overset{\frown}{CH}-CD-CD_3}}$$
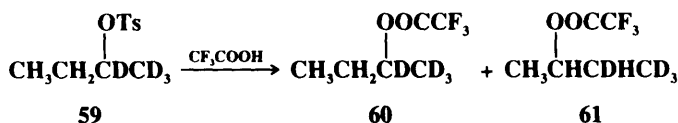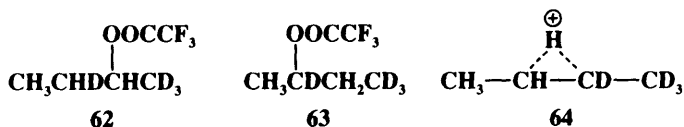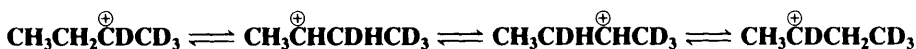
these four cations:

$$CH_3CH_2\overset{\oplus}{C}DCD_3 \rightleftharpoons CH_3\overset{\oplus}{C}HCDHCD_3 \rightleftharpoons CH_3CDH\overset{\oplus}{C}HCD_3 \rightleftharpoons CH_3\overset{\oplus}{C}DCH_2CD_3$$

leading not only to **60** and **61**, but also to **62** and **63**. The results are most easily compatible with the intermediacy of the bridged ion **64** which can then be attacked by the solvent equally at the 2 and 3 positions. Attempts to prepare **58** as a stable ion in super-acid solutions at low temperatures have not been successful.[172]

The SNi 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 SNi mechanism (*substitution nucleophilic internal*) part of the leaving group must be able to attack the substrate, detaching

[173]See, for example, Shiner; Jewett *J. Am. Chem. Soc.* **1965**, *87*, 1382; Pánková; Sicher; Tichý; Whiting *J. Chem. Soc. B* **1968**, 365; Tichý; Hapala; Sicher *Tetrahedron Lett.* **1969**, 3739; Myhre; Evans *J. Am. Chem. Soc.* **1969**, *91*, 5641; Inomoto; Robertson; Sarkis *Can. J. Chem.* **1969**, *47*, 4599; Shiner; Stoffer *J. Am. Chem. Soc.* **1970**, *92*, 3191; Krapcho; Johanson *J. Org. Chem.* **1971**, *36*, 146; Chuit; Felkin; Le Ny; Lion; Prunier *Tetrahedron* **1972**, *28*, 4787; Stéhelin; Lhomme; Ourisson *J. Am. Chem. Soc.* **1971**, *93*, 1650; Stéhelin; Kanellias; Ourisson *J. Org. Chem.* **1973**, *38*, 847, 851; Hiršl-Starčević; Majerski; Sunko *J. Org. Chem.* **1980**, *45*, 3388; Buzek; Schleyer; Sieber; Koch; Carneiro; Vančik; Sunko *J. Chem. Soc., Chem. Commun.* **1991**, 671; Imhoff; Ragain; Moore; Shiner *J. Org. Chem.* **1991**, *56*, 3542.

[174]Dannenberg; Goldberg; Barton; Dill; Weinwurzel; Longas *J. Am. Chem. Soc.* **1981**, *103*, 7764. See also Dannenberg; Barton; Bunch; Goldberg; Kowalski *J. Org. Chem.* **1983**, *48*, 4524; Allen; Ambidge; Tidwell *J. Org. Chem.* **1983**, *48*, 4527.

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 SN1 mechanism—dissociation into an intimate ion pair.[175] But in the second step part of the leaving group attacks, necessarily from the front since it is unable to get to the rear. This results in retention of configuration:

Step 1 $R—OSOCl \longrightarrow R^+$

Step 2
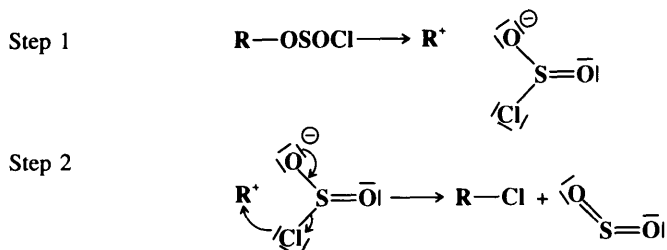
The example shown is the most important case of this mechanism yet discovered, since the reaction of alcohols with thionyl chloride to give alkyl halides usually proceeds in this way, with the first step in this case being $ROH + SOCl_2 \rightarrow ROSOCl$ (these alkyl chlorosulfites can be isolated).

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 $ROSON\overset{\oplus}{C_5}H_5$ 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.[176]

The SNi mechanism is relatively rare. Another example is the decomposition of ROCOCl (alkyl chloroformates) into RCl and CO_2.[177]

Nucleophilic Substitution at an Allylic Carbon. Allylic Rearrangements

Allylic substrates undergo nucleophilic substitution reactions especially rapidly (see p. 341), but we discuss them in a separate section because they are usually accompanied by a certain kind of rearrangement known as an *allylic rearrangement*.[178] When allylic substrates are treated with nucleophiles under SN1 conditions, two products are usually obtained: the normal one and a rearranged one.

$$R—CH=CH—CH_2X \xrightarrow{Y^-} R—CH=CH—CH_2Y + R—\underset{\underset{Y}{|}}{CH}—CH=CH_2$$
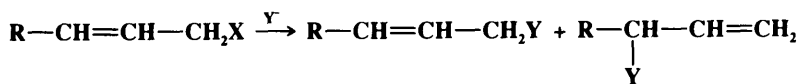
[175]Lee; Finlayson *Can. J. Chem.* **1961**, *39*, 260; Lee; Clayton; Lee; Finlayson *Tetrahedron* **1962**, *18*, 1395.

[176]Lewis; Boozer *J. Am. Chem. Soc.* **1952**, *74*, 308.

[177]Lewis; Herndon; Duffey *J. Am. Chem. Soc.* **1961**, *83*, 1959; Lewis; Witte *J. Chem. Soc. B* **1968**, 1198. For other examples, see Hart; Elia *J. Am. Chem. Soc.* **1961**, *83*, 985; Stevens; Dittmer; Kovacs *J. Am. Chem. Soc.* **1963**, *85*, 3394; Kice; Hanson *J. Org. Chem.* **1973**, *38*, 1410; Cohen; Solash *Tetrahedron Lett.* **1973**, 2513; Verrinder; Hourigan; Prokipcak *Can. J. Chem.* **1978**, *56*, 2582.

[178]For a review, see DeWolfe, in Bamford; Tipper *Comprehensive Chemical Kinetics*, vol. 9; Elsevier: New York, 1973, pp. 417-437. For comprehensive older reviews, see DeWolfe; Young *Chem. Rev.* **1956**, *56*, 753-901; in Patai *The Chemistry of Alkenes*; Wiley: New York, 1964, the sections by Mackenzie, pp. 436-453 and DeWolfe; Young, pp. 681-738.

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

$$R—CH=CH—CH_2^{\oplus} \longleftrightarrow R—\overset{\oplus}{C}H—CH=CH_2$$
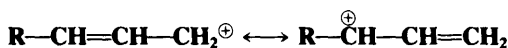
so that C-1 and C-3 each carry a partial positive charge and both are attacked by Y. Of course, an allylic rearrangement is undetectable in the case of symmetrical allylic cations, as in the case where R = H, unless isotopic labeling is used. This mechanism has been called the SN1' mechanism. The IUPAC 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.

As with other SN1 reactions, there is clear evidence that SN1' reactions can involve ion pairs. If the intermediate attacked by the nucleophile is a completely free carbocation, then, say,

$$CH_3CH=CHCH_2Cl \quad \text{and} \quad CH_3CHClCH=CH_2$$
$$\quad\quad 65 \quad\quad\quad\quad\quad\quad\quad 66$$

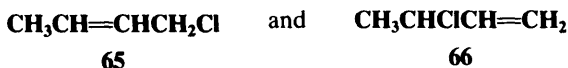should give the same mixture of alcohols when reacting with hydroxide ion, since the carbocation from each should be the same. When treated with 0.8 N aqueous NaOH at 25°C, 65 gave 60% $CH_3CH=CHCH_2OH$ and 40% $CH_3CHOHCH=CH_2$, while 66 gave the products in yields of 38 and 62%, respectively.[179] 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, 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 $ClCH_2CH=CMe_2$,[180] 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, 65 and 66, 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.[181]

Nucleophilic substitution at an allylic carbon can also take place by an SN2 mechanism, in which case no allylic rearrangement usually takes place. However, allylic rearrangements can also take place under SN2 conditions, by the following mechanism, in which the nucleophile attacks at the γ carbon rather than the usual position:[182]

SN2' mechanism
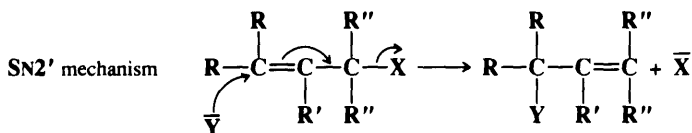
[179]DeWolfe; Young, *Chem. Rev.*, Ref. 178, give several dozen such examples.
[180]Young; Winstein; Goering *J. Am. Chem. Soc.* **1951**, *73*, 1958.
[181]For additional evidence for the involvement of ion pairs in SN1' reactions, see Goering; Linsay *J. Am. Chem. Soc.* **1969**, *91*, 7435; d'Incan; Viout *Bull. Soc. Chim. Fr.* **1971**, 3312; Astin; Whiting *J. Chem. Soc., Perkin Trans. 2* **1976**, 1157; Kantner; Humski; Goering *J. Am. Chem. Soc.* **1982**, *104*, 1693; Thibblin *J. Chem. Soc., Perkin Trans. 2* **1986**, 313; Ref. 56.
[182]For a review of the SN2' mechanism, see Magid *Tetrahedron* **1980**, *36*, 1901-1930, pp. 1901-1910.

The IUPAC designation is $3/1/A_ND_N$. This mechanism is a second-order allylic rearrangement; it usually comes about where SN2 conditions hold but where α substitution sterically retards the normal SN2 mechanism. There are thus few well-established cases of the SN2' mechanism on substrates of the type C=C—CH$_2$X, while compounds of the form C=C—CR$_2$X give the SN2' rearrangement almost exclusively when they give bimolecular reactions at all. Increasing the size of the nucleophile can also increase the extent of the SN2' reaction at the expense of the SN2.[183] In certain cases the leaving group can also have an affect on whether the rearrangment occurs. Thus PhCH=CHCH$_2$X, treated with LiAlH$_4$, gave 100% SN2 reaction (no rearrangement) when X = Br or Cl, but 100% SN2' when X = PPh$_3$$^+$ Br$^-$.[184]

The SN2' 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,[185] and that a true SN2' mechanism is a myth. There is evidence both for[186] and against[187] this proposal.

The stereochemistry of SN2' reactions has been investigated. It has been found that both syn[188] (the nucleophile enters on the side from which the leaving group departs) and anti[189]

syn   anti

reactions can take place, depending on the nature of X and Y,[190] though the syn pathway predominates in most cases.

When a molecule has in an allylic position a nucleofuge capable of giving the SNi reaction, it is possible for the nucleophile to attack at the γ position instead of the α position. This is called the SNi' mechanism and has been demonstrated on 2-buten-1-ol and 3-buten-2-ol,
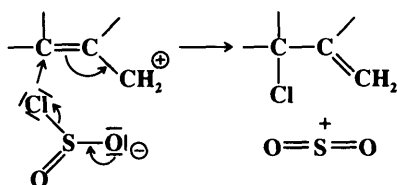
[183]Bordwell; Clemens; Cheng J. Am. Chem. Soc.1987, 109, 1773.

[184]Hirabe; Nojima; Kusabayashi J. Org. Chem. 1984, 49, 4084.

[185]Bordwell; Schexnayder J. Org. Chem. 1968, 33, 3240; Bordwell; Mecca J. Am. Chem. Soc. 1972, 94, 5829; Bordwell Acc. Chem. Res. 1970, 3, 281-290, pp. 282-285. See also de la Mare; Vernon J. Chem. Soc. B 1971, 1699; Dewar J. Am. Chem. Soc. 1984, 106, 209.

[186]See Uebel; Milaszewski; Arlt J. Org. Chem. 1977, 42, 585.

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

[188]See, for example, Stork; White J. Am. Chem. Soc. 1956, 78, 4609; Jefford; Sweeney; Delay Helv. Chim. Acta 1972, 55, 2214; Kirmse; Scheidt; Vater J. Am. Chem. Soc. 1978, 100, 3945; Gallina; Ciattini J. Am. Chem. Soc. 1979, 101, 1035; Magid; Fruchey J. Am. Chem. Soc. 1979, 101, 2107; Bäckvall; Vågberg; Genêt J. Chem. Soc., Chem. Commun. 1987, 159.

[189]See, for example, Borden; Corey Tetrahedron Lett. 1969, 313; Takahashi; Satoh Bull. Chem. Soc. Jpn. 1975, 48, 69; Staroscik; Rickborn J. Am. Chem. Soc. 1971, 93, 3046; See also Liotta Tetrahedron Lett. 1975, 523; Stork; Schoofs J. Am. Chem. Soc. 1979, 101, 5081.

[190]Stork; Kreft J. Am. Chem. Soc. 1977, 99, 3850, 3851; Oritani; Overton J. Chem. Soc., Chem. Commun. 1978, 454; Bach; Wolber J. Am. Chem. Soc. 1985, 107, 1352. See also Chapleo; Finch; Roberts; Woolley; Newton; Selby J. Chem. Soc., Perkin Trans. 1 1980, 1847; Stohrer Angew. Chem. Int. Ed. Engl. 1983, 22, 613 [Angew. Chem. 95, 642].

both of which gave 100% allylic rearrangement when treated with thionyl chloride in ether.[191] 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:

$$R—CH=CH—CH_2Cl \longrightarrow R—CH=CH—CH_2^+ \; Cl^- \longrightarrow R—\underset{\underset{Cl}{|}}{CH}—CH=CH_2$$

Most S_Ni' reactions are of this type.

Allylic rearrangements have also been demonstrated in propargyl systems, e.g.,[192]

$$PhC\equiv CCH_2OTs + MeMgBr \xrightarrow{\;CuBr\;} Ph—\underset{\underset{Me}{|}}{C}=C=CH_2 \quad \text{(Reaction 0-87)}$$

The product in this case is an allene,[193] 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.

$$R—C\equiv C—\underset{\underset{X}{|}}{CR_2} \xrightarrow{\;OH^-\;} R—\underset{\underset{OH}{|}}{C}=C=CR_2 \longrightarrow R—\underset{\underset{O}{\|}}{C}—C=CR_2$$

When X = OH, this conversion of acetylenic alcohols to unsaturated aldehydes or ketones is called the *Meyer–Schuster rearrangement*.[194] The propargyl rearrangement can also go the other way; that is, 1-haloalkenes, treated with organocopper compounds, give alkynes.[195]
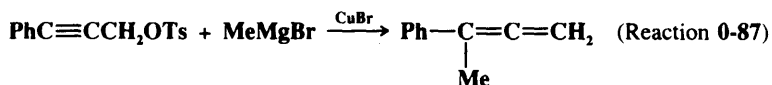
Nucleophilic Substitution at an Aliphatic Trigonal Carbon. The Tetrahedral Mechanism

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. Nucleophilic substitution at vinylic carbons is considered in the next section; at aromatic carbons in Chapter 13.

Substitution at a carbonyl group (or the corresponding nitrogen and sulfur analogs) most often proceeds by a second-order mechanism, which in this book is called the *tetrahedral*[196]

[191]Young, *J. Chem. Educ.* **1962**, *39*, 456. For other examples, see Pegolotti; Young *J. Am. Chem. Soc.* **1961**, *83*, 3251; Mark *Tetrahedron Lett.* **1962**, 281; Czernecki; Georgoulis; Labertrande; Prévost *Bull. Soc. Chim. Fr.* **1969**, 3568; Lewis; Witte, Ref. 177; Corey; Boaz *Tetrahedron Lett.* **1984**, *25*, 3055.

[192]Vermeer; Meijer; Brandsma *Recl. Trav. Chim.Pays-Bas* **1975**, *94*, 112.

[193]For reviews of such rearrangements, see Schuster; Coppola *Allenes in Organic Synthesis*; Wiley: New York, 1984, pp. 12-19, 26-30; Taylor *Chem. Rev.* **1967**, *67*, 317-359, pp. 324-328.

[194]For a review, see Swaminathan; Narayanan *Chem. Rev.* **1971**, *71*, 429-438. For discussions of the mechanism, see Edens; Boerner; Chase; Nass; Schiavelli *J. Org. Chem.* **1977**, *42*, 3403; Andres; Cardenas, Silla; Tapia *J. Am. Chem. Soc.* **1988**, *110*, 666.

[195]Corey; Boaz *Tetrahedron Lett.* **1984**, *25*, 3059, 3063.

[196]This mechanism has also been called the "addition–elimination mechanism," but in this book we limit this term to the type of mechanism shown on p. 335.

mechanism.[197] The IUPAC designation is $A_N + D_N$. SN1 mechanisms, involving carbocations, are sometimes found with these substrates, especially with essentially ionic substrates such as $RCO^+ BF_4^-$; there is evidence that in certain cases simple SN2 mechanisms can take place, especially with a very good leaving group such as Cl^-;[198] and an SET mechanism has also been reported.[199] However, the tetrahedral mechanism is by far the most prevalent. Although this mechanism displays second-order kinetics, it is not the same as the SN2 mechanism previously discussed. In the tetrahedral mechanism, first Y attacks to give an intermediate containing both X and Y, and then X leaves. This sequence, impossible at a saturated carbon, is possible at an unsaturated one because the central carbon can release a pair of electrons to the oxygen and so preserve its octet:

Step 1

67

Step 2

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

Preliminary

Step 1

Step 2

Final

[197]For reviews of this mechanism, see Talbot, in Bamford; Tipper, Ref. 178, vol. 10, 1972, pp. 209-223; Jencks *Catalysis in Chemistry and Enzymology;* McGraw-Hill: New York, 1969, pp. 463-554; Satchell; Satchell, in Patai *The Chemistry of Carboxylic Acids and Esters;* Wiley: New York, 1969, pp. 375-452; Johnson *Adv. Phys. Org. Chem.* **1967,** *5,* 237-330.
[198]For a review, see Williams *Acc. Chem. Res.* **1989,** *22,* 387-392. For examples, see Kevill; Foss *J. Am. Chem. Soc.* **1969,** *91,* 5054; Haberfield; Trattner *Chem. Commun.* **1971,** 1481; Shpan'ko; Goncharov; Litvinenko *J. Org. Chem. USSR* **1979,** *15,* 1472, 1478; De Tar *J. Am. Chem. Soc.* **1982,** *104,* 7205; Bentley; Carter; Harris *J. Chem. Soc., Perkin Trans. 2* **1985,** 983; Shpan'ko; Goncharov *J. Org. Chem. USSR* **1987,** *23,* 2287; Guthrie; Pike *Can. J. Chem.* **1987,** *65,* 1951; Kevill; Kim *Bull. Soc. Chim. Fr.* **1988,** 383, *J. Chem. Soc., Perkin Trans. 2* **1988,** 1353; Bentley; Koo *J. Chem. Soc., Perkin Trans. 2* **1989,** 1385. See however, Buncel; Um; Hoz *J. Am. Chem. Soc.* **1989,** *111,* 971.
[199]Bacaloglu; Blaskó; Bunton; Ortega *J. Am. Chem. Soc.* **1990,** *112,* 9336.

The hydrogen ion is a catalyst. The reaction rate is increased because it is easier for the nucleophile to attack the carbon when the electron density of the latter has been decreased.[200]

Evidence for the existence of the tetrahedral mechanism is as follows:[201]

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

2. There is other kinetic evidence in accord with a tetrahedral intermediate. For example, the rate "constant" for the reaction between acetamide and hydroxylamine is not constant but decreases with increasing hydroxylamine concentration.[202] This is not a smooth decrease; there is a break in the curve. A straight line is followed at low hydroxylamine concentration and another straight line at high concentration. This means that the identity of the rate-determining step is changing. Obviously, this cannot happen if there is only one step: there must be two steps and hence an intermediate. Similar kinetic behavior has been found in other cases as well,[203] in particular, plots of rate against pH are often bell-shaped.

3. Basic hydrolysis has been carried out on carboxylic esters labeled with ^{18}O in the carbonyl group.[204] If this reaction proceeded by the normal S_N2 mechanism, all the ^{18}O would remain in the carbonyl group, even if, in an equilibrium process, some of the carboxylic acid formed went back to the starting material:

$$OH^- + R-\underset{\underset{^{18}O}{\|}}{C}-OR' \rightleftharpoons R-\underset{\underset{^{18}O}{\|}}{C}-OH + OR'^- \rightleftharpoons R-\underset{\underset{^{18}O}{\|}}{C}-O^- + R'OH$$

On the other hand, if the tetrahedral mechanism operates

$$R-\underset{\underset{^{18}O}{\|}}{C}-OR' + OH^- \rightleftharpoons R-\underset{\underset{^{18}|O|^\ominus}{|}}{\overset{OH}{C}}-OR' \overset{H_2O}{\rightleftharpoons} R-\underset{\underset{^{18}OH}{|}}{\overset{OH}{C}}-OR'$$

$$\textbf{68} \qquad\qquad \textbf{69}$$

then the intermediate **68**, by gaining a proton, becomes converted to the symmetrical intermediate **69**. In this intermediate the OH groups are equivalent, and (except for the small $^{18}O/^{16}O$ isotope effect) either one can lose a proton with equal facility:
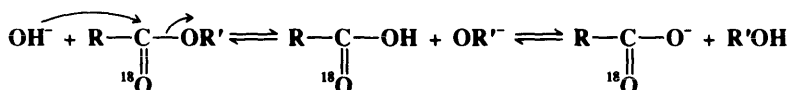
$$R-\underset{\underset{^{18}OH}{|}}{\overset{OH}{C}}-OR' \begin{cases} R-\underset{\underset{^{18}OH}{|}}{\overset{|O|^\ominus}{C}}-OR' \rightleftharpoons R-\underset{\|}{\overset{O}{C}}-OR' + {}^{18}OH^- \\ \textbf{70} \\ R-\underset{\underset{^{18}|O|^\ominus}{|}}{\overset{OH}{C}}-OR' \rightleftharpoons R-\underset{\underset{^{18}O}{\|}}{C}-OR' + OH^- \end{cases}$$

$$\textbf{69} \qquad\qquad\qquad\qquad \textbf{68}$$

[200]For discussions of general acid and base catalysis of reactions at a carbonyl group, see Jencks *Acc. Chem. Res.* **1976**, *9*, 425-432, *Chem. Rev.* **1972**, *72*, 705-718.

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

[202]Jencks; Gilchrist *J. Am. Chem. Soc.* **1964**, *86*, 5616.

[203]Hand; Jencks *J. Am. Chem. Soc.* **1962**, *84*, 3505; Bruice; Fedor *J. Am. Chem. Soc.* **1964**, *86*, 4886; Johnson *J. Am. Chem. Soc.* **1964**, *86*, 3819; Fedor; Bruice *J. Am. Chem. Soc.* **1964**, *86*, 5697, **1965**, *87*, 4138; Kevill; Johnson *J. Am. Chem. Soc.* **1965**, *87*, 928; Leinhard; Jencks *J. Am. Chem. Soc.* **1965**, *87*, 3855; Schowen; Jayaraman; Kershner *J. Am. Chem. Soc.* **1966**, *88*, 3373.

[204]Bender *J. Am. Chem. Soc.* **1951**, *73*, 1626; Bender; Thomas *J. Am. Chem. Soc.* **1961**, *83*, 4183, 4189.

The intermediates **68** and **70** can now lose OR' to give the acid (not shown in the equations given), or they can lose OH to regenerate the carboxylic ester. If **68** goes back to ester, the ester will still be labeled, but if **70** reverts to ester, the ^{18}O will be lost. A test of the two possible mechanisms is to stop the reaction before completion and to analyze the recovered ester for ^{18}O. This is just what was done by Bender, who found that in alkaline hydrolysis of methyl, ethyl, and isopropyl benzoates, the esters had lost ^{18}O. A similar experiment carried out for acid-catalyzed hydrolysis of ethyl benzoate showed that here too the ester lost ^{18}O. However, alkaline hydrolysis of substituted benzyl benzoates showed *no* ^{18}O loss.[205] This result does not necessarily mean that no tetrahedral intermediate is involved in this case. If **68** and **70** do not revert to ester, but go entirely to acid, no ^{18}O loss will be found even with a tetrahedral intermediate. In the case of benzyl benzoates this may very well be happening, because formation of the acid relieves steric strain. Another possibility is that **68** loses OR' before it can become protonated to **69**.[206] Even the experiments that *do* show ^{18}O loss do not *prove* the existence of the tetrahedral intermediate, since it is possible that ^{18}O is lost by some independent process not leading to ester hydrolysis. To deal with this possibility, Bender and Heck[207] measured the rate of ^{18}O loss in the hydrolysis of ethyl trifluorothioloacetate-^{18}O:

$$F_3C-\underset{\underset{^{18}O}{\overset{\|}{}}}{C}-SEt + H_2O \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \text{intermediate} \overset{k_3}{\longrightarrow} F_3CCOOH + EtSH$$

This reaction had previously been shown[208] to involve an intermediate by the kinetic methods mentioned on p. 332. Bender and Heck showed that the rate of ^{18}O loss and the value of the partitioning ratio k_2/k_3 as determined by the oxygen exchange technique were exactly in accord with these values as previously determined by kinetic methods. Thus the original ^{18}O-exchange measurements showed that there is a tetrahedral species present, though not necessarily on the reaction path, while the kinetic experiments showed that there is some intermediate present, though not necessarily tetrahedral. Bender and Heck's results demonstrate that there is a tetrahedral intermediate and that it lies on the reaction pathway.

4. In some cases, tetrahedral intermediates have been isolated[209] or detected spectrally.[210]

Several studies have been made of the directionality of approach by the nucleophile.[211] Menger has proposed for reactions in general, and specifically for those that proceed by the tetrahedral mechanism, that there is no single definable preferred transition state, but rather a "cone" of trajectories. All approaches within this cone lead to reaction at comparable rates; it is only when the approach comes outside of the cone that the rate falls.

Directionality has also been studied for the second step. Once the tetrahedral intermediate (**67**) is formed, it loses Y (giving the product) or X (reverting to the starting compound). Deslongchamps has proposed that one of the factors affecting this choice is the conformation of the intermediate; more specifically, the positions of the lone pairs. In this view, a leaving

[205]Bender; Matsui; Thomas; Tobey *J. Am. Chem. Soc.* **1961**, *83*, 4193. See also Shain; Kirsch *J. Am. Chem. Soc.* **1968**, *90*, 5848.

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

[207]Bender; Heck *J. Am. Chem. Soc.* **1967**, *89*, 1211.

[208]Fedor; Bruice *J. Am. Chem. Soc.* **1965**, *87*, 4138.

[209]Rogers; Bruice *J. Am. Chem. Soc.* **1974**, *96*, 2481; Khouri; Kaloustian *J. Am. Chem. Soc.* **1986**, *108*, 6683.

[210]For reviews, see Capon; Dosunmu; Sanchez *Adv. Phys. Org. Chem.* **1985**, *21*, 37-98; McClelland; Santry *Acc. Chem. Res.* **1983**, *16*, 394-399; Capon; Ghosh; Grieve *Acc. Chem. Res.* **1981**, *14*, 306-312. See also Lobo; Marques; Prabhakar; Rzepa *J. Chem. Soc., Chem. Commun.* **1985**, 1113; van der Wel; Nibbering *Recl. Trav. Chim. Pays-Bas* **1988**, *107*, 479, 491.

[211]For discussions, see Menger *Tetrahedron* **1983**, *39*, 1013-1040; Liotta; Burgess; Eberhardt *J. Am. Chem. Soc.* **1984**, *106*, 4849.

group X or Y can depart only if the other two atoms on the carbon both have an orbital antiperiplanar to the C—X or C—Y bond. For example, consider an intermediate

$$\begin{array}{c} \text{OR} \\ | \\ \text{R}'\!\!-\!\!\overset{|}{\underset{|}{\text{C}}}\!\!-\!\!\text{X} \\ | \\ \text{O}_- \end{array}$$

formed by attack of OR$^-$ on a substrate R'COX. Cleavage of the C—X bond with loss of X can take place from conformation **A,** because the two lone-pair orbitals marked * are

A   **B**

antiperiplanar to the C—X bond, but not from **B** because only the O$^-$ has such an orbital. If the intermediate is in conformation **B,** the OR may leave (if X has a lone-pair orbital in the proper position) rather than X. This factor is called *stereoelectronic control.*[212] Of course, there is free rotation in acyclic intermediates, and many conformations are possible, but some are preferred, and cleavage reactions may take place faster than rotation, so stereoelectronic control can be a factor in some situations. Much evidence has been presented for this concept.[213] More generally, the term *stereoelectronic effects* refers to any case in which orbital position requirements affect the course of a reaction. The backside attack in the SN2 mechanism is an example of a stereoelectronic effect.

Some nucleophilic substitutions at a carbonyl carbon are *catalyzed* by nucleophiles.[214] There occur, in effect, two tetrahedral mechanisms:

$$\begin{array}{ccccccc} \text{R}\!\!-\!\!\overset{\|}{\underset{\|}{\text{C}}}\!\!-\!\!\text{X} & + & \text{Z} & \xrightarrow{} & \text{R}\!\!-\!\!\overset{\|}{\underset{\|}{\text{C}}}\!\!-\!\!\text{Z} & + \text{Y} \longrightarrow & \text{R}\!\!-\!\!\overset{\|}{\underset{\|}{\text{C}}}\!\!-\!\!\text{Y} \\ \text{O} & & \text{Catalyst} & & \text{O} & & \text{O} \end{array}$$

(For an example, see **0-9.**) When this happens internally, we have an example of a neighboring-group mechanism at a carbonyl carbon.[215] For example, the hydrolysis of phthalamic

[212]It has also been called the "antiperiplanar lone pair hypothesis (ALPH)." For a reinterpretation of this factor in terms of the principle of least nuclear motion (see **5-10**), see Hosie; Marshall; Sinnott *J. Chem. Soc., Perkin Trans. 2* **1984,** 1121; Sinnott *Adv. Phys. Org. Chem.* **1988,** *24,* 113-204.

[213]For monographs, see Kirby *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer: New York, 1983; Deslongchamps *Stereoelectronic Effects in Organic Chemistry*; Pergamon: New York, 1983. For lengthy treatments, see Sinnott, Ref. 212; Gorenstein *Chem. Rev.* **1987,** *87,* 1047-1077; Deslongchamps *Heterocycle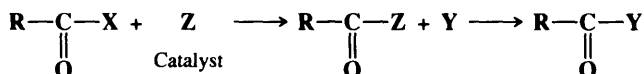s* **1977,** *7,* 1271-1317, *Tetrahedron* **1975,** *31,* 2463-2490. For additional evidence, see Deslongchamps; Barlet; Taillefer *Can. J. Chem.* **1980,** *58,* 2167; Perrin; Arrhenius *J. Am. Chem. Soc.* **1982,** *104,* 2839; Briggs; Evans; Glenn; Kirby *J. Chem. Soc., Perkin Trans. 2* **1983,** 1637; Deslongchamps; Guay; Chênevert *Can. J. Chem. 63,* **1985,** 2493; Ndibwami; Deslongchamps *Can. J. Chem.* **1986,** *64,* 1788; Hegarty; Mullane *J. Chem. Soc., Perkin Trans. 2* **1986,** 995. For evidence against the theory, see Perrin; Nuñez *J. Am. Chem. Soc.* **1986,** *108,* 5997, **1987,** *109,* 522.

[214]For reviews of nucleophilic catalysis, see Bender *Mechanisms of Homogeneous Catalysis from Protons to Proteins*; Wiley: New York, 1971, pp. 147-179; Jencks, Ref. 197, pp. 67-77; Johnson, Ref. 197, pp. 271-318. For a review where Z = a tertiary amine (the most common case), see Cherkasova; Bogatkov; Golovina *Russ. Chem. Rev.* **1977,** *46,* 246-263.

[215]For reviews, see Kirby; Fersht *Prog. Bioorg. Chem.* **1971,** *1,* 1-82; Capon *Essays Chem.* **1972,** *3,* 127-156.

acid (**71**) takes place as follows:

71   **NH₃**

Evidence comes from comparative rate studies.[216] Thus **71** was hydrolyzed about 10^5 times faster than benzamide ($PhCONH_2$) at about the same concentration of hydrogen ions. That this enhancement of rate was not caused by the resonance or field effects of COOH (an electron-withdrawing group) was shown by the fact both *o*-nitrobenzamide and terephthalamic acid (the para isomer of **71**) were hydrolyzed more slowly than benzamide. Many other examples of neighboring-group participation at a carbonyl carbon have been reported.[217] It is likely that nucleophilic catalysis is involved in enzyme catalysis of ester hydrolysis.

The attack of a nucleophile on a carbonyl group can result in substitution or addition (Chapter 16), though the first step of each mechanism is the same. The main factor that determines the product is the identity of the group X in RCOX. When X is alkyl or hydrogen, addition usually takes place. When X is halogen, OH, OCOR, NH_2, etc., the usual reaction is substitution.

For a list of some of the more important reactions that operate by the tetrahedral mechanism, see Table 10.8.

Nucleophilic Substitution at a Vinylic Carbon

Nucleophilic substitution at a vinylic carbon[218] is difficult (see p. 341), but many examples are known. The most common mechanisms are the tetrahedral mechanism 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 (**72**) and ArS^-, catalyzed by EtO^-.[219] The product was

[216]Bender; Chow; Chloupek *J. Am. Chem. Soc.* **1958**, *80*, 5380.

[217]For examples, see Bruice; Pandit *J. Am. Chem. Soc.* **1960**, *82*, 5858; Zimmering; Westhead; Morawetz *Biochim. Biophys. Acta* **1957**, *25*, 376; Kirby; McDonald; Smith *J. Chem. Soc., Perkin Trans. 2* **1974**, 1495; Martin; Tan *J. Chem. Soc., Perkin Trans. 2* **1974**, 129; Kluger; Lam *J. Am. Chem. Soc.* **1978**, *100*, 2191; Page; Render; Bernáth *J. Chem. Soc., Perkin Trans. 2* **1986**, 867.

[218]For reviews, see Rappoport *Recl. Trav. Chim. Pays-Bas* **1985**, *104*, 309-349, *React. Intermed. (Plenum)* **1983**, *3*, 427-615, *Adv. Phys. Org. Chem.* **1969**, 7, 1-114; Shainyan *Russ. Chem. Rev.* **1986**, *55*, 511-530; Modena *Acc. Chem. Res.* **1971**, *4*, 73-80.

[219]Truce; Boudakian *J. Am. Chem. Soc.* **1956**, *78*, 2748.

not the 1,1-dithiophenoxy compound **73** but the "rearranged" compound **74.** Isolation of **75** and **76** showed that an addition–elimination mechanism had taken place. In the first step ArSH adds to the double bond (nucleophilic addition, p. 741) to give the saturated **75.** The second step is an E2 elimination reaction (p. 983) to give the alkene **76.** A second elimination and addition give **74.**

The tetrahedral mechanism, often also called addition–elimination (Ad_N-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:

$$-\overset{|}{\underset{\curvearrowleft}{C}}{=}\overset{|}{C}-X + Y^- \longrightarrow \underset{\ominus}{-\overset{|}{\underset{\curvearrowright}{C}}}\overset{|}{-}\overset{|}{C}-\overset{\curvearrowright}{X} \longrightarrow -\overset{|}{C}{=}\overset{|}{C}$$
$$\underset{Y}{} \qquad\qquad \underset{Y}{}$$

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:[220]

Isolated

In the case of $Ph(MeO)C{=}C(NO_2)Ph + RS^-$, the intermediate lived long enough to be detected by uv spectroscopy.[221]

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" (as in the conversion of **72** to **74**), but of course the mechanism could still take place even if no rearrangement is found. Evidence[222] that a tetrahedral or an addition–elimination mechanism takes place in certain cases (as opposed, for example, 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*).[223] 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. 352). The rate is fa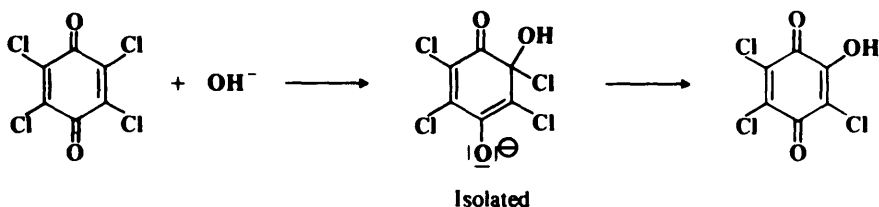ster with fluorides in the cases cited, because the superior electron-withdrawing character of the fluorine makes the carbon of the C—F bond more positive and hence more susceptible to nucleophilic attack.

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

[220]Hancock; Morrell; Rhom *Tetrahedron Lett.* **1962**, 987.
[221]Bernasconi; Fassberg; Killion; Rappoport *J. Am. Chem. Soc.* **1989**, *112*, 3169, *J. Org. Chem.* **1990**, *55*, 4568.
[222]Additional evidence comes from the pattern of catalysis by amines, similar to that discussed for aromatic substrates on p. 643. See Rappoport; Peled *J. Am. Chem. Soc.* **1979**, *101*, 2682, and references cited therein.
[223]Beltrame; Favini; Cattania; Guella *Gazz. Chim. Ital.* **1968**, *98*, 380. See also Rappoport; Rav-Acha *Tetrahedron Lett.* **1984**, *25*, 117; Solov'yanov; Shtern; Beletskaya; Reutov *J. Org. Chem. USSR* **1983**, *19*, 1945; Avramovitch; Weyerstahl; Rappoport *J. Am. Chem. Soc.* **1987**, *109*, 6687.

group such as HCO, RCO,[224] EtOOC, ArSO$_2$, NC, F, etc., since these β groups stabilize the carbanion:

$$ZCH{=}CHX \xrightarrow{Y^-} Z{-}\overset{\ominus}{\underset{\underset{X}{|}}{\underset{|}{C}}}{-}\overset{\overset{Y}{|}}{\underset{|}{C}}H \longrightarrow ZCH{=}CHY$$

Many such examples are known. In most cases where the stereochemistry has been investigated, retention of configuration is observed,[225] but stereoconvergence (the same product mixture from an E or Z substrate) has also been observed,[226] especially where the carbanionic carbon bears two electron-withdrawing groups. It is not immediately apparent why the tetrahedral mechanism 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.[227]

Vinylic substrates are in general very reluctant to undergo S$_N$1 reactions, but they can be made to do so in two ways:[228] (1) By the use of an α group that stabilizes the vinylic cation. For example, α-aryl vinylic halides ArCBr=CR$_2'$ have often been shown to give S$_N$1 reactions.[229] S$_N$1 reactions have also been demonstrated with other stabilizing groups: cyclopropyl,[230] vinylic,[231] alkynyl,[232] and an adjacent double bond (R$_2$C=C=CR'X).[233] (2) Even without α stabilization, by the use of a very good leaving group, e.g., OSO$_2$CF$_3$ (triflate).[234] The stereochemical outcome of S$_N$1 reactions at a vinylic substrate is often randomization,[235] 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.[236] However, a linear vinylic cation need not give random products.[237] The empty p orbital lies in the plane of the double bond, so entry of the nucleophile can be and often

$$\underset{R^2}{\overset{R^1}{{}}}\!\!C{=}\overset{\oplus}{C}{-}R^3$$

[224]For a review, see Rybinskaya; Nesmeyanov; Kochetkov *Russ. Chem. Rev.* **1969**, *38*, 433-456.

[225]Rappoport *Adv. Phys. Org. Chem.*, Ref. 218, pp. 31-62; Shainyan, Ref. 218, pp. 516-520. See also Rappoport; Gazit *J. Am. Chem. Soc.* **1987**, *109*, 6698.

[226]See Rappoport; Gazit *J. Org. Chem.* **1985**, *50*, 3184, *J. Am. Chem. Soc.* **1986**, *51*, 4112; Park; Ha *Bull. Chem. Soc. Jpn.* **1990**, *63*, 3006.

[227]Apeloig; Rappoport *J. Am. Chem. Soc.* **1979**, *101*, 5095.

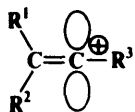[228]For reviews of the S$_N$1 mechanism at a vinylic substrate, see Stang; Rappoport; Hanack; Subramanian *Vinyl Cations*, Chapter 5; Academic Press: New York, 1979; Stang *Acc. Chem. Res.* **1978**, *11*, 107-114, *Prog. Phys. Org. Chem.* **1973**, *10*, 205-325; Rappoport *Acc. Chem. Res.* **1976**, *9*, 265-273; Subramanian; Hanack *J. Chem. Educ.* **1975**, *52*, 80-86; Hanack *Acc. Chem. Res.* **1970**, *3*, 209-216; Modena; Tonellato *Adv. Phys. Org. Chem.* **1971**, *9*, 185-280, pp. 231-253; Grob *Chimia* **1971**, *25*, 87-91; Rappoport; Bässler; Hanack *J. Am. Chem. Soc.* **1970**, *92*, 4985-4987.

[229]For a review, see Stang; Rappoport; Hanack; Subramanian, Ref. 228, Chapter 6.

[230]Sherrod; Bergman *J. Am. Chem. Soc.* **1969**, *91*, 2115, **1971**, *93*, 1925; Kelsey; Bergman *J. Am. Chem. Soc.* **1970**, *92*, 238, **1971**, *93*, 1941; Hanack; Bässler *J. Am. Chem. Soc.* **1969**, *91*, 2117; Hanack; Bässler; Eymann; Heyd; Kopp *J. Am. Chem. Soc.* **1974**, *96*, 6686.

[231]Grob; Spaar *Tetrahedron Lett.* **1969**, 1439, *Helv. Chim. Acta* **1970**, *53*, 2119.

[232]Hassdenteufel; Hanack *Tetrahedron Lett.* **1980**, 503. See also Kobayashi; Nishi; Koyama; Taniguchi *J. Chem. Soc., Chem. Commun.* **1980**, 103.

[233]Schiavelli; Gilbert; Boynton; Boswell *J. Am. Chem. Soc.* **1972**, *94*, 5061.

[234]See, for example, Stang; Summerville *J. Am. Chem. Soc.* **1969**, *91*, 4600; Clarke; Bergman *J. Am. Chem. Soc.* **1972**, *94*, 3627, **1974**, *96*, 7934; Summerville; Schleyer *J. Am. Chem. Soc.* **1972**, *94*, 3629, **1974**, *96*, 1110; Eckes; Subramanian; Hanack *Tetrahedron Lett.* **1973**, 1967; Hanack; Märkl; Martinez *Chem. Ber.* **1982**, *115*, 772.

[235]Rappoport; Apeloig *J. Am. Chem. Soc.* **1969**, *91*, 6734; Kelsey; Bergman, Ref. 230.

[236]Pfeifer; Bahn; Schleyer; Bocher; Harding; Hummel; Hanack; Stang *J. Am. Chem. Soc.* **1971**, *93*, 1513.

[237]For examples of inversion, see Clarke; Bergman, Ref. 234; Summerville; Schleyer, Ref. 234.

is influenced by the relative size of R^1 and R^2.[238] It must be emphasized that even where vinylic substrates do give S_N1 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.

$$R—C{\equiv}C—T \xrightarrow{\beta\ decay} R—C{\equiv}C—{}^3He \xrightarrow[fast]{very} R—C{\equiv}C^+ + {}^3He$$

When the tritium (half-life 12.26 y) 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, $RC{\equiv}CC_6H_5$ was isolated.[239] The tritium-decay technique has also been used to generate vinylic and aryl cations.[240]

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. 646). An example of a reaction involving this mechanism is the reaction of 1,2-dichloroethane with ArS^- and OEt^- to produce **74**. 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[241] 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 **77** and **74**. (3) **77**, treated with ArS^-, gave no reaction but, when EtO^- was added, **74** 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.[242] 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.

[238]Maroni; Melloni; Modena *J. Chem. Soc., Chem. Commun.* **1972**, 857.

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

[240]For a review, see Cacace *Adv. Phys. Org. Chem.* **1970**, *8*, 79-149. See also Angelini; Fornarini; Speranza *J. Am. Chem. Soc.* **1982**, *104*, 4773; Fornarini; Speranza *Tetrahedron Lett.* **1984**, *25*, 869, *J. Am. Chem. Soc.* **1985**, *107*, 5358.

[241]Truce; Boudakian; Heine; McManimie *J. Am. Chem. Soc.* **1956**, *78*, 2743; Flynn; Badiger; Truce *J. Org. Chem.* **1963**, *28*, 2298. See also Shainyan; Mirskova *J. Org. Chem. USSR* **1984**, *20*, 885, 1989, **1985**, *21*, 283.

[242]Montgomery; Scardiglia; Roberts *J. Am. Chem. Soc.* **1965**, *87*, 1917; Montgomery; Clouse; Crelier; Applegate *J. Am. Chem. Soc.* **1967**, *89*, 3453; Caubere; Brunet *Tetrahedron* **1971**, *27*, 3515; Bottini; Corson; Fitzgerald; Frost *Tetrahedron* **1972**, *28*, 4883.

The elimination–addition sequence has also been demonstrated for certain reactions of saturated substrates, e.g., $ArSO_2CH_2CH_2SO_2Ar$.[243] Treatment of this with ethoxide proceeds as follows:

$$ArSO_2CH_2CH_2SO_2Ar \xrightarrow[\text{E2 elimination}]{EtO^-} ArSO_2CH=CH_2 \xrightarrow[\text{addition}]{EtO^-} ArSO_2CH_2CH_2OEt$$

Mannich bases (see **6-16**) of the type $RCOCH_2CH_2NR_2$ similarly undergo nucleophilic substitution by the elimination–addition mechanism.[244] The nucleophile replaces the NR_2 group.

The simple SN2 mechanism has never been convincingly demonstrated for vinylic substrates.[245]

REACTIVITY

A large amount of work has been done on this subject. Though 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 caried out in the gas phase.[246]

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 SN2 mechanism, branching at either the α or the β carbon decreases the rate. Tertiary systems seldom[247] react by the SN2 mechanism and neopentyl systems react so slowly as to make such reactions, in general, synthetically useless.[248] Table 10.3 shows average relative rates for some alkyl substrates.[249] The reason for these low rates is almost certainly steric.[250] The transition state **1** is more crowded when larger groups are close to the central carbon.

TABLE 10.3 Average relative SN2 rates for some alkyl substrates[249]

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		

[243]Kader; Stirling *J. Chem. Soc.* **1962,** 3686. For another example, see Popov; Piskunova; Matvienko *J. Org. Chem. USSR* **1986,** *22,* 1299.

[244]For an example, see Andrisano; Angeloni; De Maria; Tramontini *J. Chem. Soc. C* **1967,** 2307.

[245]For discussions, see Miller *Tetrahedron* **1977,** *33,* 1211; Texier; Henri-Rousseau; Bourgois *Bull. Soc. Chim. Fr.* **1979,** II-11,86; Rappoport *Acc. Chem. Res.* **1981,** *14,* 7-15; Rappoport; Avramovitch *J. Org. Chem.* **1982,** *47,* 1397.

[246]See, for example DePuy; Gronert; Mullin; Bierbaum *J. Am. Chem. Soc.* **1990,** *112,* 8650.

[247]For a reported example, see Edwards; Grieco *Can. J. Chem.* **1974,** *52,* 3561.

[248]SN2 reactions on neopentyl tosylates have been conveniently carried out in the solvents HMPA and Me₂SO: Lewis; Gustafson; Erman *Tetrahedron Lett.* **1967,** 401; Paquette; Philips *Tetrahedron Lett.* **1967,** 4645; Stephenson; Solladié; Mosher *J. Am. Chem. Soc.* **1972,** *94,* 4184; Anderson; Stephenson; Mosher *J. Am. Chem. Soc.* **1974,** *96,* 3171.

[249]This table is from Streitwieser, Ref. 1, p. 13. Also see Table 9.2.

[250]For evidence, see Caldwell; Magnera; Kebarle *J. Am. Chem. Soc.* **1984,** *106,* 959.

The tetrahedral mechanism for substitution at a carbonyl carbon is also slowed or blocked completely by α or β branching for similar reasons. For example, esters of the formula

$$Y \cdots \overset{\displaystyle \diagdown \quad \diagup}{\underset{\displaystyle |}{C}} \cdots X$$

1

R_3CCOOR' cannot generally be hydrolyzed by the tetrahedral mechanism (see **0-10**), nor can acids R_3CCOOH be easily esterified.[251] 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.

For the SN1 mechanism, α branching increases the rate, as shown in Table 10.4.[252] 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. 215) to make the assumption that the transition states resemble the cations and that anything (such as α branching) that lowers the free energy of the ions also lowers it for the transition states. For simple alkyl groups, the SN1 mechanism is important under all conditions only for tertiary substrates.[253] As previously indicated (p. 306), secondary substrates generally react by the SN2 mechanism,[254] except that the SN1 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 t-butyl bromide, where the mechanism is certainly SN1), 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 SN1 mechanism because backside attack is hindered for steric reasons.[255] Because there is no SN2 component, this system provides an opportunity for comparing the pure SN1 reactivity of secondary and tertiary substrates. It has been found that substitution of a methyl group for the α hydrogen of 2-adamantyl substrates (thus changing a secondary to a tertiary system) increases solvolysis rates by a factor of about 10^8.[256] Simple primary substrates react by the SN2 mechanism (or with participation by neighboring alkyl or hydrogen) but not by the SN1 mechanism, even when solvolyzed in

TABLE 10.4   Relative rates of solvolysis of RBr in two solvents[252]

RBr substrate	In 60% ethanol at 55°C	In water at 50°C
MeBr	2.08	1.05
EtBr	1.00	1.00
iso-**PrBr**	1.78	11.6
t-**BuBr**	2.41×10^4	1.2×10^6

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

[252]These values are from Streitwieser, Ref. 1, p. 43, where values are also given for other conditions. Methyl bromide reacts faster than ethyl bromide (and in the case of 60% ethanol, isopropyl bromide) because most of it (probably all) reacts by the SN2 mechanism.

[253]For a report of an SN1 mechanism at a primary carbon, see Zamashchikov; Bezbozhnaya; Chanysheva *J. Org. Chem. USSR* **1986**, *22*, 1029.

[254]See Raber; Harris *J. Chem. Educ.* **1972**, *49*, 60; Lambert; Putz; Mixan *J. Am. Chem. Soc.* **1972**, *94*, 5132; Nordlander; McCrary *J. Am. Chem. Soc.* **1972**, *94*, 5133; Ref. 38; Dietze; Jencks, Ref. 62; Dietze; Hariri; Khattak, Ref. 62.

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

[256]Fry; Engler; Schleyer *J. Am. Chem. Soc.* **1972**, *94*, 4628. See also Gassman; Pascone *J. Am. Chem. Soc.* **1973**, *95*, 7801.

solvents of very low nucleophilicity (e.g., trifluoroacetic acid or trifluoroethanol[257]), and even when very good leaving groups (e.g., OSO_2F) are present[258] (see, however, p. 359).

For some tertiary substrates, the rate of SN1 reactions is greatly increased by the relief of B strain in the formation of the carbocation (see p. 276). Except where B strain is involved, β branching has little effect on the SN1 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 SN1 mechanism, but not more slowly than the corresponding ethyl or propyl compounds.

To sum up, primary and secondary substrates generally react by the SN2 mechanism and tertiary by the SN1 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.[259]

2. Unsaturation at the α carbon. Vinylic, acetylenic,[260] and aryl substrates are very unreactive toward nucleophilic substitutions. For these systems both the SN1 and SN2 mechanisms are greatly slowed or stopped altogether. One reason that has been suggested for this is that sp^2 (and even more, sp) carbons have a higher electronegativity than sp^3 carbons and thus a greater attraction for the electrons of the bond. As we have seen (p. 269), an sp—H bond has a higher acidity than an sp^3—H bond, with that of an sp^2—H bond in 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. 20) 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. 337) that SN1 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. 335, 338).

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 SN2 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. SN1 rates are increased when there is a double bond in the β position, so that allylic and benzylic substrates react rapidly (Table 10.5).[261] The

[257]Dafforn; Streitwieser *Tetrahedron Lett.* **1970**, 3159.

[258]Cafferata; Desvard; Sicre *J. Chem. Soc., Perkin Trans. 2* **1981**, 940.

[259]Kornblum et al. *J. Org. Chem.* **1987**, *52*, 196.

[260]For a discussion of SN reactions at acetylenic substrates, see Miller; Dickstein *Acc. Chem. Res.* **1976**, *9*, 358-363.

[261]Streitwieser, Ref. 1, p. 75. Actually, the figures for Ph₂CHOTs and Ph₃COTs are estimated from the general reactivity of these substrates.

TABLE 10.5 Relative rates for
the S_N1 reaction between ROTs
and ethanol at 25°C[261]

Group	Relative rate
Et	0.26
iso-Pr	0.69
$CH_2=CHCH_2$	8.6
$PhCH_2$	100
Ph_2CH	$\sim 10^5$
Ph_3C	$\sim 10^{10}$

reason is that allylic (p. 168) and benzylic (p. 169) 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. It should be remembered 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.[262] Among these are alkyl, aryl, and halo groups.

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 $(PhCH_2)_2SEt^+$.[263] The cyclic **78** 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.[264] 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,[265] 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. 170). The field effects of these groups would be expected to decrease S_N1 rates (see Section 6, p. 344), so the resonance effect is far more important.

When Z in ZCH_2X is RCO,[266] HCO, ROCO, NH_2CO, NC, or F_3C,[267] S_N1 rates are decreased compared to CH_3X, owing to the electron-withdrawing field effects of these

[262]For a discussion of the relative reactivities of different allylic substrates, see DeWolfe; Young, in Patai, Ref. 178, pp. 683-688, 695-697.

[263]King; Tsang; Abdel-Malik; Payne J. Am. Chem. Soc. **1985**, 107, 3224.

[264]Hatch; Chiola J. Am. Chem. Soc. **1951**, 73, 360; Jacobs; Brill J. Am. Chem. Soc. **1953**, 75, 1314.

[265]For a review of the reactions of α-haloamines, sulfides, and ethers, see Gross; Höft Angew. Chem. Int. Ed. Engl. **1967**, 6, 335-355 [Angew. Chem. 79, 358-378].

[266]For a review of α-halo ketones, including reactivity, see Verhé; De Kimpe, in Patai; Rappoport, Ref. 88, pt. 1, pp. 813-931. This review has been reprinted, and new material added, in De Kimpe; Verhé The Chemistry of α-Haloketones, α-Haloaldehydes, and α-Haloimines; Wiley: New York, 1988, pp. 225-368.

[267]Allen; Jansen; Koshy; Mangru; Tidwell J. Am. Chem. Soc. **1982**, 104, 207; Liu; Kuo; Shu J. Am. Chem. Soc. **1982**, 104, 211; Gassman; Harrington J. Org. Chem. **1984**, 49, 2258; Allen; Girdhar; Jansen; Mayo; Tidwell J. Org. Chem. **1986**, 51, 1324; Allen; Kanagasabapathy; Tidwell J. Am. Chem. Soc. **1986**, 108, 3470; Richard J. Am. Chem. Soc. **1989**, 111, 1455.

groups. Furthermore, carbocations[268] with an α CO or CN group are greatly destabilized because of the partial positive charge on the adjacent carbon (**79**). SN1 reactions have been carried out on such compounds,[269] but the rates are very low. For example, from a comparison of the solvolysis rates of **80** and **81**, a rate-retarding effect of $10^{7.3}$ was estimated for the

$$R\overset{\oplus}{\underset{\underset{R}{|}}{C}}\overset{\delta+}{\underset{\underset{O\delta-}{||}}{C}}R$$

79   **80**   **81**

C=O group.[270] However, when a different kind of comparison is made: $RCOCR_2'X$ vs. $HCR_2'X$ (where X = a leaving group), the RCO had only a small or negligible rate-retarding effect, indicating that resonance stabilization[271]

$$R-\overset{\overset{R}{|}}{\underset{\underset{|\underline{O}}{\oplus}}{C}}-\overset{||}{C}-R \longleftrightarrow R-\overset{\overset{R}{|}}{C}=\overset{|}{\underset{\underline{O}_{\oplus}}{C}}-R$$

C   **D**

may be offsetting the inductive destabilization for this group.[272] For a CN group also, the rate-retarding effect is reduced by this kind of resonance.[273] A carbocation with an α COR group has been isolated.[274]

When SN2 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.[275] For example, α-chloroacetophenone ($PhCOCH_2Cl$) reacts with KI in acetone at 75° about 32,000 times faster than 1-chlorobutane,[276] but α-bromoacetophenone reacts with the nucleophile triethylamine 0.14 times as fast as iodomethane.[275] The reasons 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.[277]

[268]For reviews of such carbocations, see Bégué; Charpentier-Morize *Acc. Chem. Res.* **1980**, *13*, 207-212; Charpentier-Morize *Bull. Soc. Chim. Fr.* **1974**, 343-351.
[269]For reviews, see Creary *Acc. Chem. Res.* **1985**, *18*, 3-8; Creary; Hopkinson; Lee-Ruff *Adv. Carbocation Chem.* **1989**, *1*, 45-92; Charpentier-Morize; Bonnet-Delpon *Adv. Carbocation Chem.* **1989**, *1*, 219-253.
[270]Creary *J. Org. Chem.* **1979**, *44*, 3938.
[271]**D**, which has the positive charge on the more electronegative atom, is less stable than **C**, according to rule c on p. 36, but it nevertheless seems to be contributing in this case.
[272]Creary; Geiger *J. Am. Chem. Soc.* **1982**, *104*, 4151; Creary *J. Am. Chem. Soc.* **1984**, *106*, 5568. See however Takeuchi; Yoshida; Ohga; Tsugeno; Kitagawa *J. Org. Chem.* **1990**, *55*, 6063.
[273]Gassman; Saito; Talley *J. Am. Chem. Soc.* **1980**, *102*, 7613.
[274]Takeuchi; Kitagawa; Okamoto *J. Chem. Soc., Chem. Commun.* **1983**, 7. See also Dao; Maleki; Hopkinson; Lee-Ruff *J. Am. Chem. Soc.* **1986**, *108*, 5237.
[275]Halvorsen; Songstad *J. Chem. Soc., Chem. Commun.* **1978**, 327.
[276]Bordwell; Brannen *J. Am. Chem. Soc.* **1964**, *86*, 4645. For some other examples, see Conant; Kirner; Hussey *J. Am. Chem. Soc.* **1925**, *47*, 488; Sisti; Lowell *Can. J. Chem.* **1964**, *42*, 1896.
[277]For discussions of possible reasons, see McLennan; Pross *J. Chem. Soc., Perkin Trans. 2* **1984**, 981; Yousaf; Lewis *J. Am. Chem. Soc.* **1987**, *109*, 6137; Lee; Shim; Chung; Lee *J. Chem. Soc., Perkin Trans. 2* **1988**, 975; Yoh; Lee *Tetrahedron Lett.* **1988**, *29*, 4431.

When Z is SOR or SO_2R (e.g., α-halo sulfoxides and sulfones), nucleophilic substitution is retarded.[278] The SN1 mechanism is slowed by the electron-withdrawing effect of the SOR or SO_2R group,[279] and the SN2 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 or phenyl, SN1 rates are lower than for unsubstituted systems, because the resonance effects mentioned in Section 4 are absent, but the field effects are still there, though smaller. These groups in the β position do not have much effect on SN2 rates unless they behave as neighboring groups and enhance the rate through anchimeric assistance,[280] or unless their size causes the rates to decrease for steric reasons.[281]

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 SN1 reactions electron-withdrawing Z decrease the rate and electron-donating Z increase it,[282] because the latter decrease the energy of the transition state (and of the carbocation) by spreading the positive charge, e.g.,

while electron-withdrawing groups concentrate the charge. The Hammett σρ relationship (p. 278) 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 SN2 reactions no such simple correlations are found.[283] 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 SN2 mechanism.[282]

For Z = alkyl, the Baker–Nathan order (p. 68) is usually observed both for SN1 and SN2 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 (**82**).[284] In this system steric effects are completely

$$Z-\!\!\!\left\langle\;\;\right\rangle\!\!\!-CH_2OTs$$

82

[278]Bordwell; Jarvis *J. Org. Chem.* **1968**, *33*,1182; Loeppky; Chang *Tetrahedron Lett.* **1968,** 5414; Cinquini; Colonna; Landini; Maia *J. Chem. Soc., Perkin Trans. 2* **1976,** 996.

[279]See, for example Creary; Mehrsheikh-Mohammadi; Eggers *J. Am. Chem. Soc.* **1987,** *109*, 2435.

[280]For example, substrates of the type $RSCH_2CH_2X$ are so prone to the neighboring-group mechanism that ordinary SN2 reactions have only recently been observed: Sedaghat-Herati; McManus; Harris *J. Org. Chem.* **1988,** *53*, 2539.

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

[282]Jorge; Kiyan; Miyata; Miller *J. Chem. Soc., Perkin Trans. 2* **1981,** 100; Vitullo; Grabowski; Sridharan *J. Chem. Soc., Chem. Commun.* **1981,** 737.

[283]See Sugden; Willis *J. Chem. Soc.* **1951,** 1360; Baker; Nathan *J. Chem. Soc.* **1935,** 1840; Hayami; Tanaka; Kurabayashi; Kotani; Kaji *Bull. Chem. Soc. Jpn.* **1971,** *44*, 3091; Westaway; Waszczylo *Can. J. Chem.* **1982,** *60*, 2500; Lee; Sohn; Oh; Lee *Tetrahedron* **1986,** *42*, 4713.

[284]Holtz; Stock *J. Am. Chem. Soc.* **1965,** *87*, 2404.

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.[285] For example, cyclopropyl tosylate solvolyzes about 10^6 times more slowly than cyclobutyl tosylate in acetic acid at 60°C.[286] When such attack does take place, the result is generally not normal substitution (though exceptions are known,[287] especially when an α stabilizing group such as aryl or alkoxy is present) but ring opening:[286]

$$\overset{3}{\underset{2}{\triangleright}}\!\!\!-\!\!X \longrightarrow CH_2\!\!=\!\!CH\!-\!CH_2^{\oplus} \xrightarrow{Y} CH_2\!\!=\!\!CH\!-\!CH_2Y$$

There is much evidence that the ring opening is usually concerted with the departure of the leaving group[288] (as in the similar case of cyclobutyl substrates, p. 324), from which we can conclude that if the 2,3 bond of the cyclopropane ring did not assist, the rates would 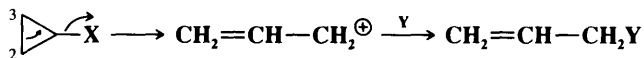be lower still. It has been estimated[289] that without this assistance the rates of these already slow reactions would be further reduced by a factor of perhaps 10^{12}. For a discussion of the stereochemistry of the ring opening, see p. 1119. For larger rings, we have seen (p. 276) that, because of 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.*[10] The S_N2 mechanism is impossible at bridgeheads (p. 296). S_N1 reactions can take place if the rings are large enough (p. 301).[290] Solvolytic reactivity at bridgehead positions spans a wide range; e.g., from $k = 4 \times 10^{-17}$ s^{-1} for **83** (very slow)

83   **84**

to 3×10^6 s^{-1} for the [3.3.3] compound **84** (very fast);[291] a range of 22 orders of magnitude. Molecular mechanics calculations show that S_N1 bridgehead reactivity is determined by strain changes between the substrate and the carbocation intermediate.[292]

[285]For reviews, see Friedrich, in Rappoport *The Chemistry of the Cyclopropyl Group*, pt. 1; Wiley: New York, 1987, pp. 633-700; Aksenov; Terent'eva; Savinykh *Russ. Chem. Rev.* **1980**, *49*, 549-557.

[286]Roberts; Chambers *J. Am. Chem. Soc.* **1951**, *73*, 5034.

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

[288]For example, see Schleyer; Van Dine; Schöllkopf; Paust *J. Am. Chem. Soc.* **1966**, *88*, 2868; DePuy; Schnack; Hausser *J. Am. Chem. Soc.* **1966**, *88*, 3343; Jefford; Medary *Tetrahedron* **1967**, *23*, 4123; Jefford; Wojnarowski *Tetrahedron* **1969**, *25*, 2089; Hausser; Uchic *J. Org. Chem.* **1972**, *37*, 4087.

[289]Sliwinski; Su; Schleyer *J. Am. Chem. Soc.* **1972**, *94*, 133; Brown; Rao; Ravindranathan *J. Am. Chem. Soc.* **1978**, *100*, 7946.

[290]For a review of organic synthesis using bridgehead carbocations, see Kraus; Hon; Thomas; Laramay; Liras; Hanson *Chem. Rev.* **1989**, *89*, 1591-1598.

[291]Bentley; Roberts *J. Org. Chem.* **1985**, *50*, 5852.

[292]Gleicher; Schleyer *J. Am. Chem. Soc.* **1967**, *89*, 582; Bingham; Schleyer *J. Am. Chem. Soc.* **1971**, *93*, 3189; Müller; Blanc; Mareda *Chimia* **1987**, *41*, 399; Müller; Mareda *Helv. Chim. Acta* **1987**, *70*, 1017; Ref. 291.

TABLE 10.6 List of groups in approximately descending order of reactivity toward S_N1 and S_N2 reactions
Z is RCO, HCO, ROCO, NH_2CO, NC, or a similar group

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
$ArCH_2X$	$-\overset{\mid}{C}=\overset{\mid}{C}CH_2X$
$-\overset{\mid}{C}=\overset{\mid}{C}CH_2X$	$RCH_2X \approx RCHDX \approx RCHDCH_2X$
R_2CHX	R_2CHX
$RCH_2X \approx R_3CCH_2X$	R_3CX
$RCHDX$	ZCH_2CH_2X
$RCHDCH_2X$	R_3CCH_2X
$-\overset{\mid}{C}=\overset{\mid}{C}X$	$-\overset{\mid}{C}=\overset{\mid}{C}X$
ZCH_2X	
ZCH_2CH_2X	ArX
ArX	Bridgehead-X
[2.2.1] Bridgehead-X	

TABLE 10.7 The more important synthetic reactions of Chapter 10 that take place by the S_N2 mechanism (R = primary, often secondary, alkyl). Catalysts are not shown[a]

0-1	$RX + OH^- \rightarrow ROH$
0-12	$RX + OR'^- \rightarrow ROR'$
0-13	$-\overset{\mid}{\underset{Cl}{C}}-\overset{\mid}{\underset{OH}{C}}- \longrightarrow -\overset{\mid}{C}\underset{O}{\diagdown\diagup}\overset{\mid}{C}-$
0-14	$R-OSO_2OR'' + OR'^- \rightarrow ROR'$
0-16	$2ROH \rightarrow ROR$
0-18	$-\overset{\mid}{C}\underset{O}{\diagdown\diagup}\overset{\mid}{C}- \longrightarrow -\overset{\mid}{\underset{OH}{C}}-\overset{\mid}{\underset{OR}{C}}-$
0-19	$R_3O^+ + R'OH \rightarrow ROR'$
0-24	$RX + R'COO^- \rightarrow R'COOR$
0-31	$RX + OOH^- \rightarrow ROOH$

0-35	$RX + SH^- \rightarrow RSH$
0-36	$RX + R'S^- \rightarrow RSR'$
0-38	$RX + S_2^{2-} \rightarrow RSSR$
0-41	$RX + SO_3^{2-} \rightarrow RSO_2O^-$
0-42	$RX + SCN^- \rightarrow RSCN$

0-43	$RX + R'_2NH \rightarrow RR'_2N$
0-43	$RX + R'_3N \rightarrow RR'_3N^+\ X^-$
0-44	$RX + (CH_2)_6N_4 \rightarrow N_2(CH_2)_6NR^+\ X^- \xrightarrow{H^+} RNH_2$
0-49	$-\overset{\mid}{C}\underset{O}{\diagdown\diagup}\overset{\mid}{C}- + RNH_2 \longrightarrow -\overset{\mid}{\underset{OH}{C}}-\overset{\mid}{\underset{NHR}{C}}-$
0-58	$RX + R'CONH^- \rightarrow RNHCOR'$

TABLE 10.7   (Continued)

0-60	$RX + NO_2^- \rightarrow RNO_2 + RONO$
0-61	$RX + N_3^- \rightarrow RN_3$
0-62	$RX + NCO^- \rightarrow RNCO$
0-62	$RX + NCS^- \rightarrow RNCS$

0-65	$RX + X'^- \rightarrow RX'$
0-66	$R-OSO_2OR' + X^- \rightarrow RX$
0-67	$ROH + PCl_5 \rightarrow RCl$
0-68	$ROR' + 2HI \rightarrow RI + R'I$

0-69

$$-\overset{|}{\underset{}{C}}\!\!\!\overset{}{\underset{O}{\diagdown\diagup}}\!\!\!\overset{|}{\underset{}{C}}- + HX \longrightarrow -\overset{|}{\underset{OH}{C}}-\overset{|}{\underset{X}{C}}-$$

0-70	$R-O-COR' + LiI \rightarrow RI + R'COO^-$

0-76	$RX + LiAlH_4 \rightarrow RH$
0-77	$R-OSO_2R' + LiAlH_4 \rightarrow RH$

0-80

$$-\overset{|}{\underset{}{C}}\!\!\!\overset{}{\underset{O}{\diagdown\diagup}}\!\!\!\overset{|}{\underset{}{C}}- + LiAlH_4 \longrightarrow -\overset{|}{\underset{OH}{C}}-\overset{|}{\underset{H}{C}}-$$

0-87	$RX + R'_2CuLi \rightarrow RR'$

0-93

$$-\overset{|}{\underset{}{C}}\!\!\!\overset{}{\underset{O}{\diagdown\diagup}}\!\!\!\overset{|}{\underset{}{C}}- + RMgX \longrightarrow -\overset{|}{\underset{OH}{C}}-\overset{|}{\underset{R}{C}}-$$

0-94	$RX + H\overset{\ominus}{\underset{}{C}}(CO_2R')_2 \rightarrow RCH(CO_2R')_2$
0-95	$RX + R''\overset{\ominus}{\underset{}{C}}H-COR' \rightarrow RCR''-COR'$
0-96	$RX + R'\overset{\ominus}{\underset{}{C}}HCOO^- \rightarrow RR'CHCOO^-$

0-97

$$RX + \overset{\ominus}{\underset{H}{\diagup}}\!\!\!\overset{S-}{\underset{S-}{\diagup\diagdown}}\!\!\! \longrightarrow \overset{R}{\underset{H}{\diagup}}\!\!\!\overset{S-}{\underset{S-}{\diagup\diagdown}}$$

0-100	$RX + R'C\equiv C^\ominus \rightarrow RC\equiv CR'$
0-101	$RX + CN^- \rightarrow RCN$

ᵃThis is 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.

9. *Deuterium substitution.* α and β secondary isotope effects affect the rate in various ways (p. 228). The measurement of α 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.[293] 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); Table 10.8 shows the main reactions that proceed by the tetrahedral mechanism.

[293]Ref. 39. For a review of secondary isotope effects in S_N2 reactions, see Westaway *Isot. Org. Chem.* **1987,** 7, 275-392.

TABLE 10.8 The more important synthetic reactions of Chapter 10 that take place by the tetrahedral mechanism. Catalysts are not shown

0-8	$RCOX + H_2O \rightarrow RCOOH$
0-9	$RCOOCOR' + H_2O \rightarrow RCOOH + R'COOH$
0-10	$RCO_2R' + H_2O \rightarrow RCOOH + R'OH$
0-11	$RCONR_2' + H_2O \rightarrow RCOOH + R_2'NH$ $\quad$ (R' = H, alkyl, aryl)
0-20	$RCOX + R'OH \rightarrow RCO_2R'$
0-21	$RCOOCOR + R'OH \rightarrow RCO_2R'$
0-22	$RCOOH + R'OH \rightarrow RCO_2R'$
0-23	$RCO_2R' + R''OH \rightarrow RCO_2R'' + R'OH$
0-27	$RCOX + R'COO^- \rightarrow RCOOCOR'$
0-31	$RCOX + H_2O_2 \rightarrow RCO_3H$

0-37	$RCOX + R'SH \rightarrow RCOSR'$
0-52	$RCOX + NHR_2' \rightarrow RCONR_2'$ $\quad$ (R' = H, alkyl, aryl)
0-53	$RCOOCOR + NHR_2' \rightarrow RCONR_2'$ $\quad$ (R' = H, alkyl, aryl)
0-54	$RCOOH + NHR_2' \xrightarrow[\text{agent}]{\text{coupling}} RCONR_2'$ $\quad$ (R' = H, alkyl, aryl)
0-55	$RCO_2R' + NHR_2'' \quad$ (R'' = H, alkyl, aryl)
0-74	$RCOOH + SOCl_2 \rightarrow RCOCl$
0-83	$RCOX + LiAlH(O\text{-}t\text{-}Bu)_3 \rightarrow RCHO$
0-85	$RCONR_2' + LiAlH_4 \rightarrow RCHO$
0-104	$RCOX + R_2CuLi \rightarrow RCOR'$
0-108	$2RCH_2CO_2R' \rightarrow RCH_2COCHRCO_2R'$

The Effect of the Attacking Nucleophile[294]

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 SN1 reactions are independent of the identity of the nucleophile, since it does not appear in the rate-determining step.[295] 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 SN2 mechanism, the rate is multiplied more than 5000 by the change to the more powerful nucleophile OH^-, but for t-butyl bromide, which reacts by an SN1 mechanism, the rate is unaffected.[296] A change in nucleophile can, however, change the *product* of an SN1 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 SN2 reactions in solution there are four main principles that govern the effect of the nucleophile on the rate, though the nucleophilicity order is not invariant but depends on substrate, solvent, leaving group, etc.

    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, etc.

[294]For a monograph, see Harris; McManus *Nucleophilicity*; American Chemical Society: Washington, 1987. For reviews, see Klumpp *Reactivity in Organic Chemistry*; Wiley: New York, 1982, pp. 145-167, 181-186; Hudson, in Klopman *Chemical Reactivity and Reaction Paths*; Wiley: New York, 1974, pp. 167-252.

[295]It is, however, possible to measure the rates of reaction of nucleophiles with fairly stable carbocations: see Ritchie *Acc. Chem. Res.* **1972**, *5*, 348-354; Ritchie; Minasz; Kamego; Sawada *J. Am. Chem. Soc.* **1977**, *99*, 3747; McClelland; Banait; Steenken *J. Am. Chem. Soc.* **1986**, *108*, 7023.

[296]Bateman; Cooper; Hughes; Ingold *J. Chem. Soc.* **1940**, 925.

2. In comparing nucleophiles whose attacking atom is in the same row of the periodic table, nucleophilicity is approximately in order of basicity, though 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.[297]

3. Going down the periodic table, nucleophilicity increases, though basicity decreases. Thus the usual order of halide nucleophilicity is $I^- > Br^- > Cl^- > F^-$ (though as we shall 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 vs. 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[298] and that, in DMF, an aprotic solvent, the order of nucleophilicity was $Cl^- > Br^- > I^-$.[299] 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.[300] In a further experiment halide ions were allowed to react with the molten salt (n-C_5H_{11})$_4N^+$ X^- at 180°C in the absence of a solvent.[301] 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 $OH^- > F^- \sim MeO^- > MeS^- \gg Cl^- > CN^- > Br^-$,[302] providing further evidence that solvation 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.[303] To explain these cases we may use the principle of hard and soft acids and bases (p. 261).[304] 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. 263, 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.

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

[298]Parker *J. Chem. Soc.* **1961**, 1328 has a list of about 20 such reactions.

[299]Weaver; Hutchison *J. Am. Chem. Soc.* **1964**, *86*, 261; See also Rodewald; Mahendran; Bear; Fuchs *J. Am. Chem. Soc.* **1968**, *90*, 6698; Fuchs; Mahendran *J. Org. Chem.* **1971**, *36*, 730; Müller; Siegfried *Helv. Chim. Acta* **1971**, *54*, 2675; Liotta; Grisdale; Hopkins *Tetrahedron Lett.* **1975**, 4205; Bordwell; Hughes *J. Org. Chem.* **1981**, *46*, 3570. For a contrary result in liquid SO₂, see Lichtin; Puar; Wasserman *J. Am. Chem. Soc.* **1967**, *89*, 6677.

[300]Winstein; Savedoff; Smith; Stevens; Gall *Tetrahedron Lett.* **1960**, no. 9, 24.

[301]Gordon; Varughese *Chem. Commun.* **1971**, 1160. See also Ford; Hauri; Smith *J. Am. Chem. Soc.* **1974**, *96*, 4316.

[302]Olmstead; Brauman *J. Am. Chem. Soc.* **1977**, *99*, 4219. See also Tanaka; Mackay; Payzant; Bohme *Can. J. Chem.* **1976**, *54*, 1643.

[303]Parker *J. Chem. Soc.* **1961**, 4398.

[304]Pearson *Surv. Prog. Chem.* **1969**, *5*, 1-52, pp. 21-38.

4. The freer the nucleophile, the greater the rate.[305] We have already seen one instance of this.[300] Another is that the rate of attack by $(EtOOC)_2CBu^-$ Na^+ in benzene was increased by the addition of substances (for example, 1,2-dimethoxyethane, adipamide) that specifically solvated the Na^+ and thus left the anion freer.[306] In a nonpolar solvent such as benzene, salts such as $(EtOOC)_2CBu^-$ Na^+ usually exist as ion-pair aggregations of large molecular weights.[307] 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}.[308] Presumably, the potassium ion leaves the negative ion most free to attack most rapidly. Further evidence is that in the gas phase,[309] where nucleophilic ions are completely free, without solvent or counterion, reactions take place orders of magnitude faster than the same reactions in solution.[302] 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.[310] The rates were, with the number of water molecules 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.[311] 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.[312]

In Chapter 3 we saw that cryptands specifically solvate the alkali metal portion of salts like KF, KOAc, etc. 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. 364).

However, the four rules given above do not always hold. One reason is that steric influences often play a part. For example, the t-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 SN2 mechanisms (in protic solvents) was given by Edwards and Pearson:[313] $RS^- > ArS^- > I^- > CN^- > OH^- > N_3^- > Br^- > ArO^- > Cl^- >$ pyridine $> AcO^- > H_2O$. A quantitative relationship[314] (the *Swain-Scott equation*) has been worked out similar to the linear free-energy equations considered in Chapter 9:[315]

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

[305]For a review of the effect of nucleophile association on nucleophilicity, see Guibe; Bram *Bull. Soc. Chim. Fr.* **1975**, 933-948.

[306]Zaugg; Horrom; Borgwardt *J. Am. Chem. Soc.* **1960**, *82*, 2895; Zaugg; Leonard *J. Org. Chem.* **1972**, *37*, 2253. See also Solov'yanov; Dem'yanov; Beletskaya; Reutov *J. Org. Chem. USSR* **1976**, *12*, 714, 2215; Solov'yanov; Ahmed; Beletskaya; Reutov *J. Org. Chem. USSR* **1987**, *23*, 1243; Jackman; Lange *J. Am. Chem. Soc.* **1981**, *103*, 4494.

[307]See, for example Williard; Carpenter *J. Am. Chem. Soc.* **1986**, *108*, 462.

[308]Zook; Gumby *J. Am. Chem. Soc.* **1960**, *82*, 1386. See also Cacciapaglia; Mandolini *J. Org. Chem.* **1988**, *53*, 2579.

[309]For some other measurements of rates of SN2 reactions in the gas phase, see Barlow; Van Doren; Bierbaum *J. Am. Chem. Soc.* **1988**, *110*, 7240; Merkel; Havlas; Zahradnalak *J. Am. Chem. Soc.* **1988**, *110*, 8355.

[310]Bohme; Mackay *J. Am. Chem. Soc.* **1981**, *103*, 978; Bohme; Raksit *J. Am. Chem. Soc.* **1984**, *106*, 3447. See also Hierl; Ahrens; Henchman; Viggiano; Paulson; Clary *J. Am. Chem. Soc.* **1986**, *108*, 3142.

[311]Bohme; Raksit *Can. J. Chem.* **1985**, *63*, 3007.

[312]Landini; Maia; Rampoldi *J. Org. Chem.* **1989**, *54*, 328.

[313]Edwards; Pearson *J. Am. Chem. Soc.* **1962**, *84*, 16.

[314]Swain; Scott *J. Am. Chem. Soc.* **1953**, *75*, 141.

[315]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 *Pure Appl. Chem.* **1978**, *50*, 1281-1290; Duboc, in Chapman; Shorter *Correlation Analysis in Chemistry: Recent Advances*; Plenum: New York, 1978, pp. 313-355; Ibne-Rasa *J. Chem. Educ.* **1967**, *44*, 89-94. See also Hoz; Speizman *J. Org. Chem.* **1983**, *48*, 2904; Kawazoe; Ninomiya; Kohda; Kimoto *Tetrahedron Lett.* **1986**, *27*, 2897; Kevill; Fujimoto *J. Chem. Res. (S)* **1988**, 408.

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. s is defined as 1.0 for methyl bromide. Table 10.9 contains values of n for some common nucleophiles.[316] The order is similar to that of Edwards and Pearson. The Swain–Scott equation can be derived from Marcus theory.[317]

It is now evident that an absolute order of either nucleophilicity[318] 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.[319] Although this effect is smaller than the effects in paragraphs 1 and 4 above, it still prevents an absolute scale of either nucleophilicity or leaving-group ability. 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.[320]

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 determmined:[321] $Me_2C{=}NO^- > EtO^- > MeO^- > OH^- > OAr^- > N_3^- > F^- > H_2O > Br^- \sim I^-$. Soft bases are ineffective at a carbonyl carbon.[322] 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, though in the unsolvated case, the more basic alkoxide is the better nucleophile.[323] In this study, the product ion $R''O^-$ was also solvated by one molecule of ROH or $R'OH$.

If, adjacent to the attacking atom on the nucleophile, there is an atom containing one or more unshared pairs, the nucleophilicity is enhanced. Examples of such nucleophiles are HO_2^-, $Me_2C{=}NO^-$, NH_2NH_2, etc. This is called the *alpha effect*,[324] and the reasons for it

TABLE 10.9 Nucleophilicities of some common reagents[316]

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

[316]From Wells *Chem. Rev.* **1963**, *63*, 171-219, p. 212. See also Koskikallio *Acta Chem. Scand.* **1969**, *23*, 1477, 1490.

[317]Albery; Kreevoy *Adv. Phys. Org. Chem.* **1978**, *16*, 87-157, pp. 113-115.

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

[319]Olmstead; Brauman, Ref. 302.

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

[321]Hudson; Green *J. Chem. Soc.* **1962**, 1055; Bender; Glasson *J. Am. Chem. Soc.* **1959**, *81*, 1590; Jencks; Gilchrist *J. Am. Chem. Soc.* **1968**, *90*, 2622.

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

[323]Baer; Stoutland; Brauman *J. Am. Chem. Soc.* **1989**, *111*, 4097.

[324]For reviews, see Grekov; Veselov *Russ. Chem. Rev.* **1978**, *47*, 631-648; Fina; Edwards *Int. J. Chem. Kinet.* **1973**, *5*, 1-26.

are not completely understood. Several possible explanations have been offered.[325] One is that the ground state of the nucleophile is destabilized by repulsion between the adjacent pairs of electrons;[326] another is that the transition state is stabilized by the extra pair of electrons;[327] a third is that the adjacent electron pair reduces solvation of the nucleophile.[328] 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,[329] though HO_2^- shows a strong alpha effect in solution. The alpha effect is substantial for substitution at a carbonyl or other unsaturated carbon, at some inorganic atoms,[330] and for reactions of a nucleophile with a carbocation,[331] but is generally smaller or absent entirely for substitution at a saturated carbon.[332]

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 $RORH^+$.[333] Reactions in which the leaving group does not come off until it has been protonated have been called SN1cA or SN2cA, depending on whether after protonation the reaction is an SN1 or SN2 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 SN1 and SN2, 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.[334] At higher temperatures they cleave to give carbocations.

It is obvious that the best nucleophiles (e.g., NH_2^-, OH^-) cannot take part in SN1cA or SN2cA processes, because they would be converted to their conjugate acids under the acidic conditions necessary to protonate the leaving groups.[335] Because SN1 reactions do not require powerful nucleophiles but do require good leaving groups, most of them take place under

[325]For discussions, see Wolfe; Mitchell; Schlegel; Minot; Eisenstein *Tetrahedron Lett.* **1982**, *23*, 615; Hoz; Buncel *Isr. J. Chem.* **1985**, *26*, 313.

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

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

[328]For other explanations, see Hudson; Hansell; Wolfe; Mitchell *J. Chem. Soc., Chem. Commun.* **1985**, 1406; Shustov *Doklad. Chem.* **1985**, *280*, 80. For a discussion, see Herschlag; Jencks *J. Am. Chem. Soc.* **1990**, *112*, 1951.

[329]DePuy; Della; Filley; Grabowski; Bierbaum *J. Am. Chem. Soc.* **1983**, *105*, 2481; Buncel; Um *J. Chem. Soc., Chem. Commun.* **1986**, 595; Terrier; Degorre; Kiffer; Laloi *Bull. Soc. Chim. Fr.* **1988**, 415. For some evidence against this explanation, see Moss; Swarup; Ganguli *J. Chem. Soc., Chem. Commun.* **1987**, 860.

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

[331]Dixon; Bruice *J. Am. Chem. Soc.* **1971**, *93*, 3248, 6592.

[332]Gregory; Bruice *J. Am. Chem. Soc.* **1967**, *89*, 4400; Oae; Kadoma; Yano *Bull. Chem. Soc. Jpn.* **1969**, *42*, 1110; McIsaac; Subbaraman; Subbaraman; Mulhausen; Behrman *J. Org. Chem.* **1972**, *37*, 1037. See, however, Beale *J. Org. Chem.* **1972**, *37*, 3871; Buncel; Wilson; Chuaqui *J. Am. Chem. Soc.* **1982**, *104*, 4896; *Int. J. Chem. Kinet.* **1982**, *14*, 823.

[333]For a review of ORH^+ as a leaving group, see Staude; Patat, in Patai *The Chemistry of the Ether Linkage*; Wiley: New York, 1967, pp. 22-46.

[334]Olah; O'Brien *J. Am. Chem. Soc.* **1967**, *89*, 1725; Olah; Sommer; Namanworth *J. Am. Chem. Soc.* **1967**, *89*, 3576; Olah; Olah, in Olah; Schleyer, Ref. 92, vol. 2, 1970, pp. 743-747.

[335]Even in the gas phase, NH_3 takes a proton from $CH_3OH_2^+$ rather than acting as a nucleophile: Okada; Abe; Taniguchi; Yamabe *J. Chem. Soc., Chem. Commun.* **1989**, 610.
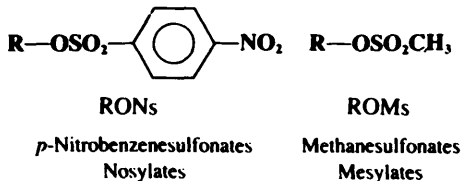
acidic conditions. In contrast, S_N2 reactions, which do require powerful nucleophiles (which are generally strong bases), most often take place under basic or neutral conditions.

Another circumstance that increases leaving-group power is ring strain. Ordinary ethers do not cleave at all and protonated ethers only under strenuous conditions, but epoxides[336] are cleaved quite easily and protonated epoxides even more easily. Aziridines[337] and epi-

sulfides, three-membered rings containing, respectively, nitrogen and sulfur, are also easily cleaved (see p. 368).[338]

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. Other leaving groups are still better, and compounds containing these groups make powerful alkylating agents. Among them are oxonium ions (ROR_2^+),[339] alkyl perchlorates $(ROClO_3)$,[340] ammonioalkanesulfonate esters (*betylates*) $(ROSO_2(CH_2)_nNMe_3^+)$,[341] alkyl fluorosulfonates $(ROSO_2F)$,[342] and the fluorinated com-

[336]For a review of the reactions of epoxides, see Smith *Synthesis* **1984**, 629-656. For a review of their synthesis and reactions, see Bartók; Láng, in Patai *The Chemistry of Functional Groups, Supplement E*; Wiley: New York, 1980, pp. 609-681.

[337]For a review of aziridine cleavages in the synthesis of natural products, see Kametani; Honda *Adv. Heterocycl. Chem.* **1986**, *39*, 181-236.

[338]There is evidence that relief of ring strain is not the only factor responsible for the high rates of ring-opening of 3-membered rings: Di Vona; Illuminati; Lillocci *J. Chem. Soc., Perkin Trans. 2* **1985**, 1943; Bury; Earl; Stirling *J. Chem. Soc., Chem. Commun.* **1985**, 393.

[339]For a monograph, see Perst, Ref. 84. For reviews, see Perst, in Olah; Schleyer, Ref. 92, vol. 5, 1976, pp. 1961-2047; Granik; Pyatin; Glushkov *Russ. Chem. Rev.* **1971**, *40*, 747-759. For a discussion of their use, see Curphey *Org. Synth.* **VI**, 1021.

[340]Baum; Beard *J. Am. Chem. Soc.* **1974**, *96*, 3233. See also Kevill; Lin *Tetrahedron Lett.* **1978**, 949.

[341]King; Loosmore; Aslam; Lock; McGarrity *J. Am. Chem. Soc.* **1982**, *104*, 7108; King; Lee *Can. J. Chem.* **1981**, *59*, 356, 362; King; Skonieczny; Poole *Can. J. Chem.* **1983**, *61*, 235.

[342]Ahmed; Alder; James; Sinnott; Whiting *Chem. Commun.* **1968**, 1533; Ahmed; Alder *Chem. Commun.* **1969**, 1389; Alder *Chem. Ind. (London)* **1973**, 983. For a discussion of the hazards involved in the use of these and other alkylating agents, see Alder; Sinnott; Whiting; Evans *Chem. Br.* **1978**, 324.

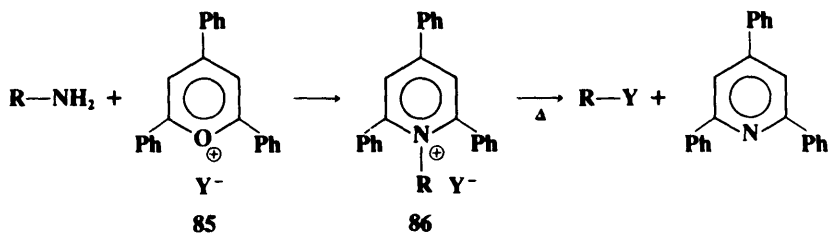pounds *triflates*[343] and *nonaflates*.[343] *Tresylates* are about 400 times less reactive than triflates, but still about 100 times more reactive than tosylates.[344] Halonium ions ($RClR^+$, $RBrR^+$,

$R—OSO_2CF_3$	$R—OSO_2C_4F_9$	$R—OSO_2CH_2CF_3$
ROTf	Nonafluorobutanesulfonates	2,2,2-Trifluoroethanesulfonates
Trifluoromethanesulfonates	Nonaflates	Tresylates
Triflates		

RIR^+), which can be prepared in super-acid solutions (p. 312) and isolated as solid SbF_6^- salts, are also extremely reactive in nucleophilic substitution.[345] 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.

NH_2, NHR, and NR_2 are extremely poor leaving groups,[346] 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.[347] Another way of converting NH_2 into a good leaving group has been extensively developed by Katritzky and co-workers.[348] In this method the amine is converted to a pyridinium compound (**86**) by treatment with a pyrylium salt (frequently a 2,4,6-triphenylpyrylium salt, **85**).[349] When the salt is heated, the counterion acts as a nucleophile. In some cases a

nonnucleophilic ion such as BF_4^- is used as the counterion for the conversion **85** → **86**, and then Y^- is added to **86**. 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 **6-16**).[350] The elimination-addition mechanism applies in this case.

[343]For reviews of triflates, nonaflates, and other fluorinated ester leaving groups, see Stang; Hanack; Subramanian *Synthesis* **1982**, 85-126; Howells; Mc Cown *Chem. Rev.* **1977**, 77, 69-92, pp. 85-87.

[344]Crossland; Wells; Shiner *J. Am. Chem. Soc.* **1971**, 93, 4217.

[345]Peterson; Clifford; Slama, Ref. 89; Olah; DeMember; Schlosberg; Halpern *J. Am. Chem. Soc.* **1972**, 94, 156; Peterson; Waller *J. Am. Chem. Soc.* **1972**, 94, 5024; Olah; Svoboda *Synthesis* **1973**, 203; Olah; Mo *J. Am. Chem. Soc.* **1974**, 96, 3560.

[346]For a review of the deamination of amines, see Baumgarten; Curtis, in Patai *The Chemistry of Functional Groups, Supplement F*, pt. 2; Wiley: New York, 1982, pp. 929-997.

[347]For references, see Müller; Thi *Helv. Chim. Acta* **1980**, 63, 2168; Curtis; Knutson; Baumgarten *Tetrahedron Lett.* **1981**, 22, 199.

[348]For reviews, see Katritzky; Marson *Angew. Chem. Int. Ed. Engl.* **1984**, 23, 420-429 [*Angew. Chem.* 96, 403-413]; Katritzky *Tetrahedron* **1980**, 36, 679-699. For reviews of the use of such leaving groups to study mechanistic questions, see Katritzky; Sakizadeh; Musumarra *Heterocycles* **1985**, 23, 1765-1813; Katritzky; Musumarra *Chem. Soc. Rev.* **1984**, 13, 47-68.

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

[350]For a review of Mannich bases, see Tramontini *Synthesis* **1973**, 703-775.
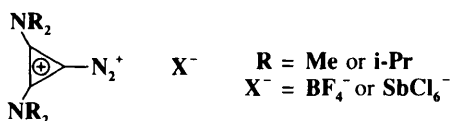
   Probably the best leaving group is N_2 from the species RN_2^+, which can be generated in several ways,[351] of which the two most important are the treatment of primary amines with nitrous acid (see p. 635 for this reaction)

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

and the protonation of diazo compounds[352]

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

No matter how produced, RN_2^+ are usually too unstable to be isolable,[353] reacting presumably by the SN1 or SN2 mechanism.[354] Actually, the exact mechanisms are in doubt because the rate laws, stereochemistry, and products have proved difficult to interpret.[355] If there are free carbocations they should give the same ratio of substitution to elimination to rearrangements, etc. as carbocations generated in other SN1 reactions, but they often do not. "Hot" carbocations (unsolvated and/or chemically activated) that can hold their configuration have been postulated,[356] as have ion pairs, in which OH^- (or OAc^-, etc., depending on how the diazonium ion is generated) is the counterion.[357] One class of aliphatic diazonium salts of which several members have been isolated as stable salts are the cyclopropeniumyldiazonium salts:[358]

   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.[359]

[351]For reviews, see Kirmse *Angew. Chem. Int. Ed. Engl.* **1976,** *15,* 251-261 [*Angew. Chem.* **88,** 273-283]; Collins *Acc. Chem. Res.* **1971,** *4,* 315-322; Moss *Chem. Eng. News* **1971,** *49,* 28-36 (No. 48, Nov. 22).

[352]For a treatise, see Regitz; Maas *Diazo Compounds*; Academic Press: New York, 1986. For reviews of the reactions of aliphatic diazo compounds with acids, see Hegarty, in Patai *The Chemistry of Diazonium and Diazo Groups,* pt. 2; Wiley: New York, 1978, pp. 511-591, pp. 571-575; More O'Ferrall *Adv. Phys. Org. Chem.* **1967,** *5,* 331-399. For review of the structures of these compounds, see Studzinskii; Korobitsyna *Russ. Chem. Rev.* **1970,** *39,* 834-843.

[353]*Aromatic* diazonium salts can, of course, be isolated (see Chapter 13), but only a few aliphatic diazonium salts have been prepared (see also Ref. 358). For reviews see Laali; Olah *Rev. Chem. Intermed.* **1985,** *6,* 237-253; Bott, in Patai; Rappoport *The Chemistry of Functional Groups, Supplement C,* pt. 1; Wiley: New York, 1983, pp. 671-697; Bott *Angew. Chem. Int. Ed. Engl.* **1979,** *18,* 259-265 [*Angew. Chem.* **91,** 279-285]. The simplest aliphatic diazonium ion $CH_3N_2^+$ has been prepared at $-120°$ in super-acid solution, where it lived long enough for an nmr spectrum to be taken: Berner; McGarrity *J. Am. Chem. Soc.* **1979,** *101,* 3135.

[354]For an example of a diazonium ion reacting by an SN2 mechanism, see Mohrig; Keegstra; Maverick; Roberts; Wells *J. Chem. Soc., Chem. Commun.* **1974,** 780.

[355]For reviews of the mechanism, see Manuilov; Barkhash *Russ. Chem. Rev.* **1990,** *59,* 179-192; Saunders; Cockerill *Mechanisms of Elimination Reactions*; Wiley: New York, 1973, pp. 280-317; in Olah; Schleyer, Ref. 92, vol. 2, **1970,** the articles by Keating; Skell, pp. 573-653; and by Friedman, pp. 655-713; White; Woodcock, in Patai *The Chemistry of the Amino Group*; Wiley: New York, 1968, pp. 440-483; Ref. 351.

[356]Semenow; Shih; Young *J. Am. Chem. Soc.* **1958,** *80,* 5472. For a review of "hot" or "free" carbocations, see Keating; Skell, Ref. 355.

[357]Collins, Ref. 351; Collins; Benjamin *J. Org. Chem.* **1972,** *37,* 4358; White; Field *J. Am. Chem. Soc.* **1975,** *97,* 2148; Cohen; Daniewski; Solash *J. Org. Chem.* **1980,** *45,* 2847; Maskill; Thompson; Wilson *J. Chem. Soc., Perkin Trans. 2* **1984,** 1693; Connor; Maskill *Bull. Soc. Chim. Fr.* **1988,** 342.

[358]Weiss; Wagner; Priesner; Macheleid *J. Am. Chem. Soc.* **1985,** *107,* 4491.

[359]Whitmore; Langlois *J. Am. Chem. Soc.* **1932,** *54,* 3441; Streitwieser; Schaeffer *J. Am. Chem. Soc.* **1957,** *79,* 2888.

In the SN1cA and SN2cA mechanisms (p. 352) there is a preliminary step, the addition of a proton, before the normal SN1 or SN2 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.

Step 1
$$-\overset{|}{\underset{H}{C}}-Br + base \overset{fast}{\rightleftharpoons} -\overset{|}{\underset{\ominus}{C}}-Br$$

Step 2
$$-\overset{|}{\underset{\ominus}{C}}-Br \overset{slow}{\longrightarrow} -\overset{|}{\underset{..}{C}} + Br^-$$

Step 3
$$-\overset{|}{\underset{..}{C}} \longrightarrow any\ carbene\ reaction$$

Once formed by this process, the carbene may undergo any of the normal carbene reactions (see p. 199). When the net result is substitution, this mechanism has been called the SN1cB (for conjugate base) mechanism.[360] Though the slow step is an SN1 step, the reaction is second order; first order in substrate and first order in base.

Table 10.10 lists some leaving groups in approximate order of ability to leave. The order of leaving-group ability is about the same for SN1 and SN2 reactions.

2. *At a carbonyl carbon.*   In both the SN1 and SN2 mechanisms the leaving group departs during the rate-determining step and so directly affects the rate. In the tetrahedral mechanism at a carbonyl carbon, the bond between the substrate and leaving group is still intact during the slow step. Nevertheless, the nature of the leaving group still affects the reactivity in two ways: (1) By altering the electron density at the carbonyl carbon, the rate of the reaction is affected. The greater the electron-withdrawing character of X, the greater the partial positive charge on C and the more rapid the attack by a nucleophile. (2) The nature of the leaving group affects the *position of equilibrium.* In the intermediate **67** (p. 331) there is competition between X and Y as to which group leaves. If X is a poorer leaving group than Y, then Y will preferentially leave and **67** will revert to the starting compounds. Thus there is a partitioning factor between **67** going on to product (loss of X) or back to starting compound (loss of Y). The sum of these two factors causes the sequence of reactivity to be RCOCl > RCOOCOR' > RCOOAr > RCOOR' > RCONH₂ > RCONR'₂ > RCOO⁻.[361] Note that this order is approximately the order of decreasing stability of the leaving-group anion. If the leaving group is bulky, it may exert a steric effect and retard the rate for this reason.

[360]Pearson; Edgington *J. Am. Chem. Soc.* **1962,** *84,* 4607.
[361]RCOOH would belong in this sequence just after RCOOAr, but it fails to undergo many reactions for a special reason. Many nucleophiles, instead of attacking the C=O group, are basic enough to take a proton from the acid, converting it to the unreactive RCOO⁻.

TABLE 10.10 Leaving groups listed in approximate order of decreasing ability to leave. Groups that are common leaving groups at saturated and carbonyl carbons are indicated

	Common leaving groups	
Substrate RX	At saturated carbon	At carbonyl carbon
RN_2^+	×	
$ROR_2'^+$		
$ROSO_2C_4F_9$		
$ROSO_2CF_3$	×	
$ROSO_2F$		
ROTs, etc.^{a}	×	
RI	×	
RBr	×	
ROH_2^+	× (conjugate acid of alcohol)	
RCl	×	× (acyl halides)
$RORH^+$	× (conjugate acid of ether)	
$RONO_2$, etc.^{a}		
$RSR_2'^{+363}$		
$RNR_3'^+$	×	
RF		
ROCOR'^{364}	×	× (anhydrides)
RNH_3^+		
ROAr^{365}		× (aryl esters)
ROH		× (carboxylic acids)
ROR		× (alkyl esters)
RH		
RNH_2		× (amides)
RAr		
RR		

^{a}ROTs, etc., includes esters of sulfuric and sulfonic acids in general, for example, $ROSO_2OH$, $ROSO_2OR$, $ROSO_2R$, etc. $RONO_2$, etc., includes inorganic ester leaving groups, such as $ROPO(OH)_2$, $ROB(OH)_2$, etc.

The Effect of the Reaction Medium[362]

The effect of solvent polarity on the rate of Sn1 reactions depends on whether the substrate is neutral or positively charged. 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 10.11[366]) and the energy of an ionic transition state is reduced by polar solvents. However, when the substrate is positively charged, the charge is more spread out in the transition state than in the starting ion, and

[362]For a monograph, see Reichardt *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed.; VCH: New York, 1988. For reviews, see Klumpp, Ref. 294, pp. 186-203; Bentley; Schleyer *Adv. Phys. Org. Chem.* **1977**, *14*, 1-67.

[363]For a review of the reactions of sulfonium salts, see Knipe, in Stirling *The Chemistry of the Sulphonium Group*, pt. 1; Wiley: New York, 1981, pp. 313-385. See also Badet; Julia; Lefebvre *Bull. Soc. Chim. Fr.* **1984**, II-431.

[364]For a review of Sn2 reactions of carboxylic esters, where the leaving group is OCOR', see McMurry *Org. React.* **1976**, *24*, 187-224.

[365]Nitro substitution increases the leaving-group ability of ArO groups, and alkyl picrates [2,4,6-ROC$_6$H$_2$(NO$_2$)$_3$] react at rates comparable to tosylates: Sinnott; Whiting *J. Chem. Soc. B* **1971**, 965. See also Page; Pritt; Whiting *J. Chem. Soc., Perkin Trans. 2* **1972**, 906.

[366]This analysis is due to Ingold *Structure and Mechanism in Organic Chemistry*, 2d ed.; Cornell University Press: Ithaca, NY, 1969, pp. 457-463.

TABLE 10.11 Transition states for S$_N$1 reactions of charged and uncharged substrates, and for S$_N$2 reactions of the four charge types[366]

Reactants and transition states	Charge in the transition state relative to starting materials	How an increase in solvent polarity affects the rate
Type I RX + Y$^-$ $\longrightarrow$ Y$^{\delta-}$-----R----X$^{\delta-}$	Dispersed	Small decrease
Type II RX + Y $\longrightarrow$ Y$^{\delta+}$-----R----X$^{\delta-}$	Increased	Large increase
Type III RX$^+$ + Y$^-$ $\longrightarrow$ Y$^{\delta-}$-----R----X$^{\delta+}$	Decreased	Large decrease
Type IV RX$^+$ + Y $\longrightarrow$ Y$^{\delta+}$-----R----X$^{\delta+}$	Dispersed	Small decrease
RX $\longrightarrow$ R$^{\delta+}$-----X$^{\delta-}$	Increased	Large increase
RX$^-$ $\longrightarrow$ R$^{\delta+}$-----X$^{\delta-}$	Dispersed	Small decrease

(S$_N$2 brackets Types I–IV; S$_N$1 brackets the RX and RX$^-$ rows.)

a greater solvent polarity slows the reaction. Even for solvents with about the same polarity, there is a difference between protic and aprotic solvents.[367] S$_N$1 reactions of un-ionized substrates are more rapid in protic solvents, which can form hydrogen bonds with the leaving group. Examples of protic solvents are water, alcohols, and carboxylic acids, while some polar aprotic solvents are dimethylformamide (DMF), dimethyl sulfoxide,[368] acetonitrile, acetone, sulfur dioxide, and hexamethylphosphoramide [(Me$_2$N)$_3$PO], HMPA.[369]

For S$_N$2 reactions, the effect of the solvent depends on which of the four charge types the reaction belongs to (p. 293). In types I and IV, an initial charge is dispersed in the transition state, so the reaction is hindered by polar solvents. In type III initial charges are *decreased* in the transition state, so that the reaction is even more hindered by polar solvents. Only type II, where the reactants are uncharged but the transition state has built up a charge, is aided by polar solvents. These effects are summarized in Table 10.11.[366] Westaway has proposed a "solvation rule" for S$_N$2 reactions, which states that changing the solvent will not change the structure of the transition state for type I reactions, but will change it for type II reactions.[370] For S$_N$2 reactions also, the difference between protic and aprotic solvents must be considered.[371] For reactions of types I and III the transition state is more solvated in polar aprotic solvents than in protic ones,[372] while (as we saw on p. 349) the original charged nucleophile is less solvated in aprotic solvents[373] (the second factor is generally much greater than the first[374]). So the change from, say, methanol to dimethyl sulfoxide should greatly increase the rate. As an example, the relative rates at 25°C for the reaction between methyl iodide and Cl$^-$ were[298] in MeOH, 1; in HCONH$_2$ (still protic though a weaker acid), 12.5; in HCONHMe, 45.3; and HCONMe$_2$, 1.2 $\times$ 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

[367]See, for example Ponomareva; Dvorko; Kulik; Evtushenko *Doklad. Chem.* **1983**, *272*, 291.
[368]For reviews of reactions in dimethyl sulfoxide, see Buncel; Wilson *Adv. Phys. Org. Chem.* **1977**, *14*, 133-202; Martin; Weise; Niclas *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 318-334 [*Angew. Chem. 79*, 340-357].
[369]For reviews of HMPA, see Normant *Russ. Chem. Rev.* **1970**, *39*, 457-484, *Bull. Soc. Chim. Fr.* **1968**, 791-826, *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 1046-1067 [*Angew. Chem. 79*, 1029-1050].
[370]Westaway *Can. J. Chem.* **1978**, *56*, 2691; Westaway; Lai *Can. J. Chem.* **1989**, *67*, 345.
[371]For reviews of the effects of protic and aprotic solvents, see Parker *Chem. Rev.* **1969**, *69*, 1-32, *Adv. Phys. Org. Chem.* **1967**, *5*, 173-235, *Adv. Org. Chem.* **1965**, *5*, 1-46; Madaule-Aubry *Bull. Soc. Chim. Fr.* **1966**, 1456.
[372]However, even in aprotic solvents, the transition state is less solvated than the charged nucleophile: Magnera; Caldwell; Sunner; Ikuta; Kebarle *J. Am. Chem. Soc.* **1984**, *106*, 6140.
[373]See, for example, Fuchs; Cole *J. Am. Chem. Soc.* **1973**, *95*, 3194.
[374]See, however, Haberfield; Clayman; Cooper *J. Am. Chem. Soc.* **1969**, *91*, 787.

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. 371 have lists of several dozen reactions of charge types I and III in which 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 SN1 rates go up and SN2 rates go down in solvents of increasing polarity, it is quite possible for the same reaction to go by the SN1 mechanism in one solvent and the SN2 in another. Table 10.12 is a list of solvents in order of ionizing power;[375] a solvent high on the list is a good solvent for SN1 reactions. Trifluoroacetic acid, which was not studied by Smith, Fainberg, and Winstein, has greater ionizing power than any solvent listed in Table 10.12.[376] Because it also has very low nucleophilicity, it is an excellent solvent for SN1 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 $(F_3C)_2CHOH$.[377]

We have seen how the polarity of the solvent influences the rates of SN1 and SN2 reactions. The ionic strength of the medium has similar effects. In general, the addition of an external salt affects the rates of SN1 and SN2 reactions in the same way as an increase in solvent polarity, though this is not quantitative; different salts have different effects.[378] However, there are exceptions: though the rates of SN1 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. 300). There is also the special salt effect of $LiClO_4$, mentioned on p. 303. In addition to these effects, SN1 rates are also greatly accelerated when there are ions present that specifically help in pulling off the leaving group.[379] Especially important are Ag^+, Hg^{2+}, and Hg_2^{2+}, but H^+ helps to pull off F (hydrogen bonding).[380] Even primary halides have been reported to undergo SN1 reactions when assisted by metal ions.[381] This does not mean, however, that reactions in the presence of metallic ions invariably proceed

TABLE 10.12   Relative rates of ionization of *p*-methoxyneophyl toulenesulfonate in various solvents[375]

Solvent	Relative rate	Solvent	Relative rate
HCOOH	153	**Ac₂O**	0.020
H₂O	39	Pyridine	0.013
80% **EtOH-H₂O**	1.85	Acetone	0.0051
AcOH	1.00	**EtOAc**	6.7×10^{-4}
MeOH	0.947	Tetrahydrofuran	5.0×10^{-4}
EtOH	0.370	**Et₂O**	3×10^{-5}
Me₂SO	0.108	CHCl₃ ⎫	
Octanoic acid	0.043	Benzene ⎬	Lower still
MeCN	0.036	Alkanes ⎭	
HCONMe₂	0.029		

[375]Smith; Fainberg; Winstein *J. Am. Chem. Soc.* **1961**, *83*, 618.
[376]Refs. 87, 125; Streitwieser; Dafforn *Tetrahedron Lett.* **1969**, 1263.
[377]Schadt; Schleyer; Bentley *Tetrahedron Lett.* **1974**, 2335.
[378]See, for example, Duynstee; Grunwald; Kaplan *J. Am. Chem. Soc.* **1960**, *82*, 5654; Bunton; Robinson *J. Am. Chem. Soc.* **1968**, *90*, 5965.
[379]For a review, see Kevill, in Patai; Rappoport, Ref. 88, pt. 2, pp. 933-984.
[380]For a review of assistance by metallic ions, see Rudakov; Kozhevnikov; Zamashchikov *Russ. Chem. Rev.* **1974**, *43*, 305-316. For an example of assistance in removal of F by H^+, see Coverdale; Kohnstam *J. Chem. Soc.* **1960**, 3906.
[381]Zamashchikov; Rudakov; Litvinenko; Uzhik *Doklad. Chem.* **1981**, *258*, 186; Zamashchikov; Rudakov; Bezbozhnaya; Matveev *J. Org. Chem. USSR* **1984**, *20*, 424. See, however, Kevill; Fujimoto *J. Chem. Soc., Chem. Commun.* **1983**, 1149.

by the SN1 mechanism. It has been shown that alkyl halides can react with $AgNO_2$ and $AgNO_3$ by the SN1 or SN2 mechanism, depending on the reaction conditions.[382]

The effect of solvent has been treated quantitatively (for SN1 mechanisms, in which the solvent pulls off the leaving group) by a linear free-energy relationship[383]

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

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. 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.[384] 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.[385] Table 10.13 contains a list of some Y values.[386]

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 to leave (nucleophilic assistance; k_s, p. 317). Actually, there is evidence that many solvents do lend some nucleophilic assistance,[387] even with tertiary substrates.[387a] 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. 340). Such a scale, called Y_{OTs}, was developed, with m defined as 1.00 for 2-adamantyl tosylate.[388] Some values of Y_{OTs} are given in Table 10.13. 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[389]) 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[390] have been set up for OTf,[391] Cl,[392] Br,[392] I,[393] and other nucleofuges,[394] all based on the corresponding adamantyl compounds.

[382]Kornblum; Jones; Hardies *J. Am. Chem. Soc.* **1966**, *88*, 1704; Kornblum; Hardies *J. Am. Chem. Soc.* **1966**, *88*, 1707.

[383]Grunwald; Winstein *J. Am. Chem. Soc.* **1948**, *70*, 846.

[384]For reviews of polarity scales of solvent mixtures, see Reichardt, Ref. 362, pp. 339-405; Langhals *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 724-733 [*Angew. Chem.* *94*, 739-749].

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

[386]Y values are from Fainberg; Winstein *J. Am. Chem. Soc.* **1956**, *78*, 2770, except for the value for CF_3CH_2OH which is from Shiner; Dowd; Fisher; Hartshorn; Kessick; Milakofsky; Rapp *J. Am. Chem. Soc.* **1969**, *91*, 4838. Y_{OTs} values are from Bentley; Llewellyn, Ref. 390, pp. 143-144. Z values are from Ref. 396. $E_T(30)$ values are from Reichardt; Dimroth *Fortschr. Chem. Forsch.* **1969**, *11*, 1-73; Reichardt *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 98-110 [*Angew. Chem.* *91*, 119-131]; Reichardt; Harbusch-Görnert *Liebigs Ann. Chem.* **1983**, 721-743; Laurence; Nicolet; Reichardt *Bull. Soc. Chim. Fr.* **1987**, 125; Laurence; Nicolet; Lucon; Reichardt *Bull. Soc. Chim. Fr.* **1987**, 1001; Reichardt; Eschner; Schäfer *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, Ref. 362.

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

[387a]For discussions, with references, see Kevill; Anderson *J. Am. Chem. Soc.* **1986**, *108*, 1579; McManus; Neamati-Mazreah; Karaman; Harris *J. Org. Chem.* **1986**, *51*, 4876; Abraham; Doherty; Kamlet; Harris; Taft *J. Chem. Soc., Perkin Trans. 2* **1987**, 913.

[388]Schadt; Bentley; Schleyer *J. Am. Chem. Soc.* **1976**, *98*, 7667.

[389]Bentley; Carter *J. Org. Chem.* **1983**, *48*, 579.

[390]For a review of these scales, see Bentley; Llewellyn *Prog. Phys. Org. Chem.* **1990**, *17*, 121-158.

[391]Kevill; Anderson *J. Org. Chem.* **1985**, *50*, 3330. See also Creary; McDonald *J. Org. Chem.* **1985**, *50*, 474.

[392]Bentley; Carter *J. Am. Chem. Soc.* **1982**, *104*, 5741. See also Liu; Sheu *J. Org. Chem.* **1991**, *56*, 3021.

[393]Bentley; Carter; Roberts *J. Org. Chem.* **1984**, *49*, 5183.

[394]See Kevill; Bahari; Anderson *J. Am. Chem. Soc.* **1984**, *106*, 2895; Bentley; Roberts *J. Org. Chem.* **1985**, *50*, 4821; Takeuchi; Ikai; Shibata; Tsugeno *J. Org. Chem.* **1988**, *53*, 2852; Kevill; Bahnke *Tetrahedron* **1988**, *44*, 7541; Hawkinson; Kevill *J. Org. Chem.* **1988**, *53*, 3857, **1989**, *54*, 154; Kevill; Hawkinson *J. Org. Chem.* **1990**, *55*, 5394.

TABLE 10.13 Y, Y_{OTs}, Z, and E_T (30) values for some solvents[386]

Solvent	Y	Y_{OTs}	Z	$E_T(30)$
CF₃COOH		4.57		
H₂O	3.5	4.1	94.6	63.1
(CF₃)₂CHOH		3.82		65.3
HCOOH	2.1	3.04		
H₂O—EtOH (1:1)	1.7	1.29	90	55.6
CF₃CH₂OH	1.0	1.77		59.8
HCONH₂	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
iso-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
Me₂SO			71.1	45.1
HCONMe₂		−4.14	68.5	43.8
Acetone			65.7	42.2
HMPA				40.9
CH₂Cl₂				40.7
Pyridine			64.0	40.5
CHCl₃			63.2	39.1
PhCl				37.5
THF				37.4
Dioxane				36.0
Et₂O				34.5
C₆H₆			54	34.3
PhMe				33.9
CCl₄				32.4
n-Octane				31.1
n-Hexane				31.0
Cyclohexane				30.9

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.[395] Kosower found that the position of the charge-transfer peak (see p. 79) in the uv spectrum of the complex (**87**) between iodide ion and 1-methyl- or 1-ethyl-4-carbometh-

87

R = Me or Et

88

[395]For reviews of solvent polarity scales, see Abraham; Grellier; Abboud; Doherty; Taft *Can. J. Chem.* **1988**, *66*, 2673-2686; Kamlet; Abboud; Taft *Prog. Phys. Org. Chem.* **1981**, *13*, 485-630; Shorter *Correlation Analysis of Organic Reactivity*; Wiley: New York, 1982, pp. 127-172; Reichardt, Ref. 386; Reichardt; Dimroth, Ref. 386; Abraham *Prog. Phys. Org. Chem.* **1974**, *11*, 1-87; Koppel; Palm, in Chapman; Shorter *Advances in Linear Free Energy Relationships*; Plenum: New York, 1972, pp. 203-280; Ref. 384. See also Chastrette; Carretto *Tetrahedron* **1982**, *38*, 1615; Chastrette; Rajzmann; Chanon; Purcell *J. Am. Chem. Soc.* **1985**, *107*, 1.

oxypyridinium ion was dependent on the polarity of the solvent.[396] From these peaks, which are very easy to measure, Kosower calculated transition energies that he called Z values. Z 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 **88** in various solvents.[397] Solvent polarity values on this scale are called $E_T(30)$[398] values. $E_T(30)$ values are related to Z values by the expression[399]

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

Table 10.13 shows that Z and $E_T(30)$ values are generally in the same order as Y values. Other scales, the π^* scale,[400] the π^*_{azo} scale,[401] and the Py scale,[402] are also based on spectral data.[403]

The effect of solvent on nucleophilicity has already been discussed (pp. 349-350).

Phase Transfer Catalysis and Ultrasound

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 difficulty is to use a solvent that will dissolve both species. As we saw on p. 358, a dipolar aprotic solvent may serve this purpose. Another way, which is used very often, is *phase transfer catalysis*.[404]

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

[396]Kosower *J. Am. Chem. Soc.* **1958**, *80*, 3253, 3261, 3267; Kosower; Wu; Sorensen *J. Am. Chem. Soc.* **1961**, *83*, 3147. See also Larsen; Edwards; Dobi *J. Am. Chem. Soc.* **1980**, *102*, 6780.

[397]Dimroth; Reichardt; Siepmann; Bohlmann *Liebigs Ann. Chem.* **1963**, *661*, 1; Dimroth; Reichardt *Liebigs Ann. Chem.* **1969**, *727*, 93. See also Haak; Engberts *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 307.

[398]The symbol E_T comes from *energy, transition*. The (30) is used because the ion **88** bore this number in the first paper of Ref. 397. Values based on other ions have also been reported: See, for example Reichardt; Harbusch-Görnert *Liebigs Ann. Chem.* **1983**, 839.

[399]Reichardt; Dimroth, Ref. 386, p. 32.

[400]Kamlet; Abboud; Taft *J. Am. Chem. Soc.* **1977**, *99*, 6027; Doherty; Abraham; Harris; Taft; Kamlet *J. Org. Chem.* **1986**, *51*, 4872; Kamlet; Doherty; Abboud; Abraham; Taft *CHEMTECH* **1986**, 566-576, and other papers in this series. See also Doan; Drago *J. Am. Chem. Soc.* **1982**, *104*, 4524; Kamlet; Abboud; Taft, Ref. 395; Bekárek *J. Chem. Soc., Perkin Trans. 2* **1986**, 1425; Abe *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2328.

[401]Buncel; Rajagopal *J. Org. Chem.* **1989**, *54*, 798.

[402]Dong; Winnik *Can. J. Chem.* **1984**, *62*, 2560.

[403]For a review of such scales, see Buncel; Rajagopal *Acc. Chem. Res.* **1990**, *23*, 226-231.

[404]For monographs, see Dehmlow; Dehmlow *Phase Transfer Catalysis*, 2nd ed.; Verlag Chemie: Deerfield Beach, FL, 1983; Starks; Liotta *Phase Transfer Catalysis*; Academic Press: New York, 1978; Weber; Gokel *Phase Transfer Catalysis in Organic Synthesis*; Springer: New York, 1977. For reviews, see Mąkosza; Fedoryński *Adv. Catal.* **1987**, *35*, 375-422; Gallo; Mąkosza; Dou; Hassanaly *Adv. Heterocycl. Chem.* **1984**, *36*, 175-234; Montanari; Landini; Rolla *Top. Curr. Chem.* **1982**, *101*, 147-200; Alper *Adv. Organomet. Chem.* **1981**, *19*, 183-211; Gallo; Dou; Hassanaly *Bull. Soc. Chim. Belg.* **1981**, *90*, 849-879; Dehmlow *Chimia* **1980**, *34*, 12-20, *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 493-505, **1974**, *13*, 170-174 [*Angew. Chem. 89*, 521-533; *86*, 187-196]; Mąkosza *Surv. Prog. Chem.* **1980**, *9*, 1-53; Starks, *CHEMTECH* **1980**, 110-117; Sjöberg *Aldrichimica Acta* **1980**, *13*, 55-58; McIntosh *J. Chem. Educ.* **1978**, *55*, 235-238; Gokel; Weber *J. Chem. Educ.* **1978**, *55*, 350-354; Weber; Gokel *J. Chem. Educ.* **1978**, *55*, 429-433; Liotta, in Izatt; Christensen *Synthetic Multidentate Macrocyclic Compounds*; Academic Press: New York, 1978, pp. 111-205; Brändström *Adv. Phys. Org. Chem.* **1977**, *15*, 267-330; Jones *Aldrichimica Acta* **1976**, *9*, 35-45; Dockx *Synthesis* **1973**, 441-456.

is quantitatively formed in about 2 hr.[405] There are two principal types of phase transfer catalyst. Though 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 t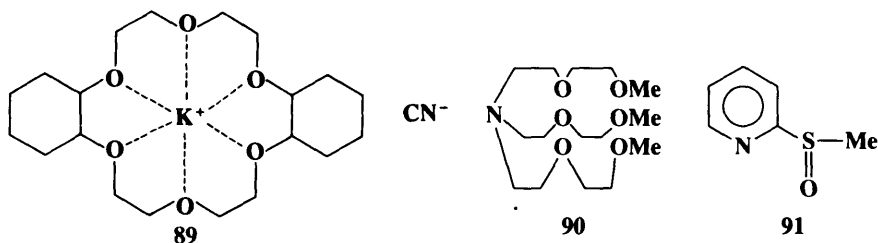o Na^+ ions, quaternary ammonium (R_4N^+)[406] and phosphonium (R_4P^+) ions with sufficiently large R groups are poorly solvated in water and prefer organic solvents. If a small amount of such a salt is added, three equilibria are set up:

Organic phase $\quad Q^+CN^- + RCl \xrightarrow{\ 4\ } RCN + Q^+Cl^-$

$$Q^+ = R_4N^+ \text{ or } R_4P^+$$

Aqueous phase $\quad Q^+CN^- + Na^+Cl^- \rightleftharpoons Na^+CN^- + Q^+Cl^-$

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. All the equilibria are normally reached much faster than the actual reaction (4), 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.[407] 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.[408] 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.[409]

2. *Crown ethers and other cryptands.*[410] 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 (**89**) whose anion is the same, but whose cation is now a much larger species with the positive charge spread over a large volume and hence much less

89   90   91

[405]Starks; Liotta, Ref. 404, p. 2.
[406]Bis-quaternary ammonium salts have also been used: Lissel; Feldman; Nir; Rabinovitz *Tetrahedron Lett.* **1989**, *30*, 1683.
[407]Landini; Maia; Montanari *J. Chem. Soc. Commun.* **1977**, 112, *J. Am. Chem. Soc.* **1978**, *100*, 2796.
[408]For a review, see Rabinovitz; Cohen; Halpern *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 960-970 [*Angew. Chem. 98*, 958-968].
[409]This mechanism was proposed by Mąkosza *Pure Appl. Chem.* **1975**, *43*, 439. See also Dehmlow; Thieser; Sasson; Pross *Tetrahedron* **1985**, *41*, 2927; Mason; Magdassi; Sasson *J. Org. Chem.* **1990**, *55*, 2714.
[410]For a review of this type of phase transfer catalysis, see Liotta, in Patai, Ref. 336, pp. 157-174.

concentrated. This larger cation is much less solubilized by water than K$^+$ and much more attracted to organic solvents. Though KCN is generally insoluble inorganic 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. Suitable cryptands have been used to increase greatly the rates of reactions where F$^-$, Br$^-$, I$^-$, OAc$^-$, and CN$^-$ are nucleophiles.[411] Certain compounds that are not cryptands can act in a similar manner. One example is the podand tris(3,6-dioxaheptyl)amine (**90**), also called TDA-1.[412] Another, not related to the crown ethers, is the pyridyl sulfoxide **91**.[413]

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. 350). 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 shall 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,[414] radicals, and molecules.[415] 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.[416]

The catalysts mentioned above are soluble. Certain cross-linked polystyrene resins, as well as alumina[417] and silica gel, have been used as insoluble phase transfer catalysts. These, called *triphase catalysts*,[418] have the advantage of simplified product work-up and easy and quantitative catalyst recovery, since the catalyst can easily be separated from the product by filtration.

Another technique used to increase reaction rates is *ultrasound.*[419] 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

[411]See, for example, Liotta; Harris; McDermott; Gonzalez; Smith *Tetrahedron Lett.* **1974**, 2417; Sam; Simmons *J. Am. Chem. Soc.* **1974**, *96*, 2252; Durst *Tetrahedron Lett.* **1974**, 2421.

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

[413]Furukawa; Ogawa; Kawai; Oae *J. Chem. Soc., Perkin Trans. 1* **1984**, 1833. See also Fujihara; Imaoka; Furukawa; Oae *J. Chem. Soc., Perkin Trans. 1* **1986**, 333.

[414]See Armstrong; Godat *J. Am. Chem. Soc.* **1979**, *101*, 2489; Iwamoto; Yoshimura; Sonoda; Kobayashi *Bull. Chem. Soc. Jpn.* **1983**, *56*, 796.

[415]See, for example, Dehmlow; Slopianka *Chem. Ber.* **1979**, *112*, 2765.

[416]Mathias; Vaidya *J. Am. Chem. Soc.* **1986**, *108*, 1093; Fife; Xin *J. Am. Chem. Soc.* **1987**, *109*, 1278.

[417]Quici; Regen *J. Org. Chem.* **1979**, *44*, 3436.

[418]For reviews, see Regen *Nouv. J. Chim.* **1982**, *6*, 629-637; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 421-429 [*Angew. Chem. 91*, 464-472]. See also Molinari; Montanari; Quici; Tundo *J. Am. Chem. Soc.* **1979**, *101*, 3920; Bogatskii; Luk'yanenko; Pastushok; Parfenova *Doklad. Chem.* **1985**, *283*, 210; Pugia; Czech; Czech; Bartsch *J. Org. Chem.* **1986**, *51*, 2945.

[419]For monographs, see Ley; Low *Ultrasound in Synthesis*; Springer: New York, 1989; Mason; Lorimer *Sonochemistry*; Wiley: New York, 1988; Suslick *Ultrasound*; VCH: New York, 1988. For reviews, see Giguere *Org. Synth. Theory Appl.* **1989**, *1*, 103-172; Einhorn; Einhorn; Luche *Synthesis* **1989**, 787-813; Goldberg; Sturkovich; Lukevics *Heterocycles* **1989**, *29*, 597-627; Abdulla *Aldrichimica Acta* **1988**, *21*, 31-42; Moon *CHEMTECH* **1987**, 434-437; Lorimer; Mason *Chem. Soc. Rev.* **1987**, *16*, 239-274; Lindley; Mason *Chem. Soc. Rev.* **1987**, *16*, 275-311; Boudjouk *J. Chem. Educ.* **1986**, *63*, 427; Bremner *Chem. Br.* **1986**, 633-638; Suslick *Adv. Organomet. Chem.* **1986**, *25*, 73-119; *Mod. Synth. Methods* **1986**, *4*, 1-60. See also the series *Advances in Sonochemistry*.

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.[420] 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. It has been postulated that ultrasound has its best results with reactions that proceed, at least partially, through free-radical intermediates.[421]

Ambident 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*.[422] In most cases a nucleophile with two potentially attacking atoms can attack with either of them, depending on conditions, and mixtures are often obtained, though this is not always the case. For example, the nucleophile NCO⁻ usually gives only isocyanates RNCO and not the isomeric cyanates ROCN.[423] 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*[424] (compare the definitions of stereoselective, p. 137 and enantioselective, p. 119). Some important ambident nucleophiles are:

1. *Ions of the type* —CO—C̄R—CO—. These ions, which are derived by removal of a proton from malonic esters, β-keto esters, β-diketones, etc., are resonance hybrids:

$$\text{—C—C̄R—C—} \longleftrightarrow \text{—C=CR—C—} \longleftrightarrow \text{—C—CR=C—}$$

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

$$\text{—C—CR=C—} \xleftarrow{\text{R'X}} \text{—C—C̄R—C—} \xrightarrow{\text{R'X}} \text{—C—CR—C—}$$

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.

[420]Reaction rates can also be increased by running reactions in a microwave oven. For reviews, see Mingos; Baghurst *Chem. Soc. Rev.* **1991**, *20*, 1-47; Giguere, Ref. 419.
[421]See Einhorn; Einhorn; Dickens; Luche *Tetrahedron Lett.* **1990**, *31*, 4129.
[422]For a monograph, see Reutov; Beletskaya; Kurts *Ambident Anions*; Plenum: New York, 1983. For a review, see Black *Org. Prep. Proceed. Int.* **1989**, *21*, 179-217.
[423]Both cyanates and isocyanates have been isolated in treatment of secondary alkyl iodides with NCO⁻: Holm; Wentrup *Acta Chem. Scand.* **1966**, *20*, 2123.
[424]This term was introduced by Hassner *J. Org. Chem.* **1968**, *33*, 2684.

2. Compounds of the type CH_3CO-CH_2-CO- can give up two protons, if treated with 2 moles of a strong enough base, to give dicarbanions:

$$CH_3-CO-CH_2-CO- \xrightarrow[\text{of base}]{\text{2 moles}} \quad ^{\ominus}\overline{C}H_2-CO-\overset{\ominus}{\overline{C}}H-CO-$$

$$\textbf{92}$$

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.[425] 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 **92** 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 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.[426] For example, ethyl acetoacetate can be alkylated at either the methyl or the methylene group (0-94):

3. *The CN⁻ ion.* This nucleophile can give nitriles RCN (**0-101**) or isocyanides $RN{\equiv}C$.
4. *The nitrite ion.* This ion can give nitrite esters $R-O-N{=}O$ (**0-32**) or nitro compounds RNO_2 (**0-60**), which are not esters.
5. Phenoxide ions (which are analogous to enolate ions) can undergo C-alkylation or O-alkylation:

[425]For an exception, see Trimitsis; Hinkley; TenBrink; Faburada; Anderson; Poli; Christian; Gustafson; Erdman; Rop *J. Org. Chem.* **1983**, *48*, 2957.
[426]The use of this principle was first reported by Hauser; Harris *J. Am. Chem. Soc.* **1958**, *80*, 6360. It has since been applied many times. For reviews, see Thompson; Green *Tetrahedron* **1991**, *47*, 4223-4285; Kaiser; Petty; Knutson *Synthesis* **1977**, 509-550; Harris; Harris *Org. React.* **1969**, *17*, 155-211.

6. Removal of a proton from an aliphatic nitro compound gives a carbanion $(R_2\overset{\ominus}{C}-NO_2)$ that can be alkylated at oxygen or carbon.[427] O-Alkylation gives nitronic esters, which are generally unstable to heat but break down to give an oxime and an aldehyde or ketone.

$$R_2C=\underset{\oplus}{N}-O-\underset{\underset{R''}{|}}{CH}-R' \longrightarrow R_2C=NOH + R'-\underset{\underset{O}{\|}}{C}-R''$$

There are many other ambident nucleophiles.

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.[428] 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. 214), the principal product is usually the one in which the atom of higher basicity has attacked (i.e., $C > N > O > S$).[429] 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. 348), 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. 263). In an SN1 mechanism the nucleophile attacks a carbocation, which is a hard acid. In an SN2 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 SN1-like to SN2-like, an ambident nucleophile becomes more likely to attack with its less electronegative atom.[430] Therefore, changing from SN1 to SN2 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 SN1 mechanism, are attacked by the oxygen atom. However, this does not mean that attack is by the less electronegative atom in all SN2 reactions and by the more electronegative atom in all SN1 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 SN2 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. 359), rather than the more usual Na^+ or K^+, then the transition state is more SN1-like. Therefore

[427]For a review, see Erashko; Shevelev; Fainzil'berg *Russ. Chem. Rev.* **1966**, *35*, 719-732.

[428]For reviews, see Jackman; Lange *Tetrahedron* **1977**, *33*, 2737-2769; Reutov; Kurts *Russ. Chem. Rev.* **1977**, *46*, 1040-1056; Gompper; Wagner *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 321-333 [*Angew. Chem. 88*, 389-401]; Shevelev *Russ. Chem. Rev.* **1970**, *39*, 844-858.

[429]For an example, see Bégué; Charpentier-Morize; Née *J. Chem. Soc., Chem. Commun.* **1989**, 83.

[430]This principle, sometimes called *Kornblum's rule*, was first stated by Kornblum; Smiley; Blackwood; Iffland *J. Am. Chem. Soc.* **1955**, *77*, 6269.
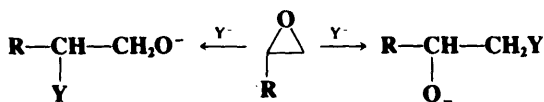
the use of Ag^+ promotes attack at the more electronegative atom. For example, alkyl halides treated with NaCN generally give mostly RCN, but the use of AgCN increases the yield of isocyanides RNC.[431]

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.[432] Changing the cation from Li^+ to Na^+ to K^+ (in nonpolar solvents) also favors O- over C-alkylation[433] 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. 82).[434] Alkylation of the enolate ion of cyclohexanone in the gas phase, where the nucleophile is completely free, showed only O-alkylation and no C-alkylation.[435]

4. In extreme cases, steric effects can govern the regioselectivity.[436]

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 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. 327). The other is the epoxy (or the similar aziridine or episulfide) substrate.[437]

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

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

[433]Kornblum; Seltzer; Haberfield, Ref. 432; Kurts; Beletskaya; Masias; Reutov *Tetrahedron Lett.* **1968**, 3679. See, however, Sarthou; Bram; Guibe *Can. J. Chem.* **1980**, *58*, 786.

[434]Smith; Hanson *J. Org. Chem.* **1971**, *36*, 1931; Kurts; Dem'yanov; Beletskaya; Reutov *J. Org. Chem. USSR* **1973**, *9*, 1341; Cambillau; Sarthou; Bram *Tetrahedron Lett.* **1976**, 281; Akabori; Tuji *Bull. Chem. Soc. Jpn.* **1978**, *51*, 1197. See also Zook; Russo; Ferrand; Stotz *J. Org. Chem.* **1968**, *33*, 2222; le Noble; Palit *Tetrahedron Lett.* **1972**, 493.

[435]Jones; Kass; Filley; Barkley; Ellison *J. Am. Chem. Soc.* **1985**, *107*, 109.

[436]See, for example O'Neill; Hegarty *J. Org. Chem.* **1987**, *52*, 2113.

[437]For reviews of SN reactions at such substrates, see Rao; Paknikar; Kirtane *Tetrahedron* **1983**, *39*, 2323-2367; Behrens; Sharpless *Aldrichimica Acta* **1983**, *16*, 67-79; Enikolopiyan *Pure Appl. Chem.* **1976**, *48*, 317-328; Fokin; Kolomiets *Russ. Chem. Rev.* **1976**, *45*, 25-42; Wohl *Chimia* **1974**, *28*, 1-5; Kirk *Chem. Ind. (London)* **1973**, 109-116; Buchanan; Sable *Sel. Org. Transform.* **1972**, *2*, 1-95; Dermer; Ham *Ethylenimine and Other Aziridines*; Academic Press: New York, 1969, pp. 206-273; Akhrem; Moiseenkov; Dobrynin *Russ. Chem. Rev.* **1968**, *37*, 448-462; Gritter, in Patai, Ref. 333, pp. 390-400.

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.[438] 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.[439] When an epoxide ring is fused to a cyclohexane ring, S_N2 ring opening invariably gives diaxial rather than diequatorial ring opening.[440]

Cyclic sulfates (**93**), prepared from 1,2-diols, react in the same manner as epoxides, but usually more rapidly:[441]

93

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 (such as **0-76**), 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.

[438]Addy; Parker *J. Chem. Soc.* **1963**, 915; Biggs; Chapman; Finch; Wray *J. Chem. Soc. B* **1971**, 55.

[439]Caron; Sharpless *J. Org. Chem.* **1985**, *50*, 1557. See also Chong; Sharpless *J. Org. Chem.* **1985**, *50*, 1560; Behrens; Sharpless *J. Org. Chem.* **1985**, *50*, 5696.

[440]Murphy; Alumbaugh; Rickborn *J. Am. Chem. Soc.* **1969**, *91*, 2649. For a method of overriding this preference, see McKittrick; Ganem *J. Org. Chem.* **1985**, *50*, 5897.

[441]Gao; Sharpless *J. Am. Chem. Soc.* **1988**, *110*, 7538; Kim; Sharpless *Tetrahedron Lett.* **1989**, *30*, 655.

Oxygen Nucleophiles

A. Attack by OH at an Alkyl Carbon

0-1 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, except that especially active substrates such as allylic or benzylic types can be hydrolyzed by water. Ordinary halides can also be hydrolyzed by water,[442] if the solvent is HMPA or N-methyl-2-pyrrolidone.[443] In contrast to most nucleophilic substitutions at saturated carbons, this reaction can be performed on tertiary substrates without significant interference from elimination side reactions. The reaction is not frequently used for synthetic purposes, because alkyl halides are usually obtained from alcohols.

Vinylic halides are unreactive (p. 341), 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.[444] Primary bromides and iodides give alcohols when treated with bis(tributyltin)oxide $Bu_3Sn—O—SnBu_3$ in the presence of silver salts.[445]

OS **II**, 408; **III**, 434; **IV**, 128; **VI**, 142, 1037.

0-2 Hydrolysis of *gem*-Dihalides
Oxo-de-dihalo-bisubstitution

[442]It has been proposed that the mechanism of the reaction of primary halides with water is not the ordinary SN2 mechanism, but that the rate-determining process involves a fluctuation of solvent configuration: Kurz; Kurz *Isr. J. Chem.* **1985**, *26*, 339; Kurz; Lee; Love; Rhodes *J. Am. Chem. Soc.* **1986**, *108*, 2960.

[443]Hutchins; Taffer *J. Org. Chem.* **1983**, *48*, 1360.

[444]Martin; Chou *Tetrahedron Lett.* **1978**, 1943; Yoshioka; Takasaki; Kobayashi; Matsumoto *Tetrahedron Lett.* **1979**, 3489.

[445]Gingras; Chan *Tetrahedron Lett.* **1989**, *30*, 279.

gem-Dihalides can be hydrolyzed with either acid or basic catalysis to give aldehydes or ketones.[446] 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, strong bases cannot be used, because the product undergoes the aldol reaction (**6-39**) or the Cannizzaro reaction (**9-69**).

OS **I**, 95; **II**, 89, 133, 244, 549; **III**, 538, 788; **IV**, 110, 423, 807. Also see OS **III**, 737.

0-3   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, though these compounds can be prepared by addition of CCl_4 and similar compounds to double bonds (**5-33**) and by the free-radical halogenation of methyl groups on aromatic rings (**4-1**). When the hydrolysis is carried out in the presence of an alcohol, a carboxylic ester can be obtained directly.[447] 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,[448] though exceptions are known.[449]

Aryl 1,1,1-trihalomethanes can be converted to acyl halides by treatment with sulfur trioxide.[450]

$$ArCCl_3 + SO_3 \longrightarrow Ar—\underset{\underset{O}{\|}}{C}—Cl + (ClSO_2)_2O$$

Chloroform is more rapidly hydrolyzed with base than dichloromethane or carbon tetrachloride and gives not only formic acid but also carbon monoxide.[451] Hine[452] has shown that the mechanism of chloroform hydrolysis is quite different from that of dichloromethane or carbon tetrachloride, though 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.

$$HCCl_3 \overset{OH^-}{\rightleftharpoons} CCl_3^- \overset{-Cl^-}{\longrightarrow} \overline{C}Cl_2 \overset{H_2O}{\longrightarrow} HCOOH \text{ or } CO$$

This is an example of an S~N~1cB mechanism (p. 356). 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.

[446]For a review, see Salomaa, in Patai *The Chemistry of the Carbonyl Group*, vol. 1; Wiley: New York, 1966, pp. 177-210.
[447]See, for example, Le Fave; Scheurer *J. Am. Chem. Soc.* **1950**, *72*, 2464.
[448]Sheppard; Sharts *Organic Fluorine Chemistry*; W.A. Benjamin: New York, 1969, pp. 410-411; Hudlický, *Chemistry of Organic Fluorine Compounds*, 2nd ed.; Ellis Horwood: Chichester, 1976, pp. 273-274.
[449]See, for example, Kobayashi; Kumadaki *Acc. Chem. Res.* **1978**, *11*, 197-204.
[450]Rondestvedt *J. Org. Chem.* **1976**, *41*, 3569, 3574, 3576. For another method, see Nakano; Ohkawa; Matsumoto; Nagai *J. Chem. Soc., Chem. Commun.* **1977**, 808.
[451]For a review, see Kirmse *Carbene Chemistry*, 2nd ed.; Academic Press: New York, 1971, pp. 129-141.
[452]Hine *J. Am. Chem. Soc.* **1950**, *72*, 2438. Also see le Noble *J. Am. Chem. Soc.* **1965**, *87*, 2434.

0-4   Hydrolysis of Alkyl Esters of Inorganic Acids
Hydroxy-de-sulfonyloxy-substitution, etc.

$$
\left.
\begin{array}{l}
R—OSO_2R' \\
R—OSO_2OH \\
R—OSO_2OR' \\
R—OSOR' \\
R—ONO_2 \\
R—ONO \\
R—OPO(OH)_2 \\
R—OPO(OR')_2 \\
R—OB(OH)_2 \\
\text{and others}
\end{array}
\right\} \xrightarrow{H_2O} R—OH
$$

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.

$$R_2C{=}CH—X \xrightarrow{H_2O} R_2C{=}CH—OH \longrightarrow R_2CH—CHO$$

These reactions are all considered at one place because they are formally similar, but though 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.[453] 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,[454] while nitrous acid esters RONO usually give N—O cleavage.[455] Esters of sulfonic acids that are frequently hydrolyzed are mentioned on p. 353. For hydrolysis of sulfonic acid esters, see also **0-114.**

OS **VI**, 852. See also OS **67**, 13.

0-5   Hydrolysis of Diazo Ketones
Hydro,hydroxy-de-diazo-bisubstitution

$$R—\underset{\substack{\| \\ O}}{C}—CHN_2 + H_2O \xrightarrow{H^+} R—\underset{\substack{\| \\ O}}{C}—CH_2OH$$

Diazo ketones are relatively easy to prepare (see **0-112**). 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.[456] Relatively good yields of α-hydroxy ketones can be prepared in this

[453]Bunton; Hendy *J. Chem. Soc.* **1963**, 627. For another example, see Batts *J. Chem. Soc. B* **1966**, 551.

[454]Barnard; Robertson *Can. J. Chem.* **1961**, *39*, 881. See also Drabicky; Myhre; Reich; Schmittou *J. Org. Chem.* **1976**, *41*, 1472.

[455]For a discussion of the mechanism of hydrolysis of alkyl nitrites, see Williams *Nitrosation*; Cambridge University Press: Cambridge, 1988, pp. 162-163.

[456]Dahn; Gold *Helv. Chim. Acta* **1963**, *46*, 983; Thomas; Leveson *Int. J. Chem. Kinet.* **1983**, *15*, 25. For a review of the acid-promoted decomposition of diazo ketones, see Smith; Dieter *Tetrahedron* **1981**, *37*, 2407-2439.

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.

0-6 Hydrolysis of Acetals, Enol Ethers, and Similar Compounds[457]

$$-C=C-OR \xrightarrow[H_2O]{H^+} -CH-\underset{\underset{O}{\|}}{C} + ROH \quad \textbf{3/Hydro-de-\textit{O}-alkylation}$$

$$R-\underset{\underset{OR'}{|}}{\overset{\overset{R}{|}}{C}}-OR' \xrightarrow[H_2O]{H^+} R-\overset{\overset{R}{|}}{C}=O + 2R'OH \quad \textbf{\textit{O}-Alkyl-\textit{C}-alkoxy-elimination}$$

$$R-\underset{\underset{OR'}{|}}{\overset{\overset{OR'}{|}}{C}}-OR' \xrightarrow[H_2O]{H^+} R-\underset{\underset{O}{\|}}{C}-OR' \text{ or } R-\underset{\underset{O}{\|}}{C}-OH + 2 \text{ or } 3R'OH$$

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,[458] the only acids used preparatively for this purpose are HBr and HI (**0-68**). However, acetals, ketals, and ortho esters[459] are easily cleaved by dilute acids. These compounds are hydrolyzed with greater facility because carbocations of the type $RO-\overset{\oplus}{\underset{|}{C}}-$ are greatly stabilized by resonance (p. 170). The reactions therefore proceed by the SN1 mechanism,[460] as shown for acetals:[461]

$$RCH(OR')_2 \rightleftharpoons^{H^+} \underset{|}{\overset{\overset{\oplus}{HOR'}}{RCH}}-OR' \underset{-R'OH}{\overset{slow}{\rightleftharpoons}} \overset{\oplus}{RCH}-OR' \overset{H_2O}{\rightleftharpoons} \underset{|}{\overset{\overset{\oplus}{OH_2}}{RCH}}-OR' \overset{-H^+}{\rightleftharpoons}$$

94

$$\underset{|}{\overset{\overset{OH}{|}}{RCH}}-OR' \rightleftharpoons^{H^+} \underset{|}{\overset{\overset{OH}{|}}{RCH}}-\overset{\oplus}{OR'H} \overset{-R'OH}{\rightleftharpoons} \overset{\oplus}{RCH}-OH \rightleftharpoons^{-H^+} RCH=O$$

hemiacetal

This mechanism (which is an SN1cA or A1 mechanism) is the reverse of that for acetal formation by reaction of an aldehyde and an alcohol (**6-6**). Among the facts supporting the

[457]For reviews, see Bergstrom, in Patai, Ref. 336, pp. 881-902; Cockerill; Harrison, in Patai *The Chemistry of Functional Groups, Supplement A*, pt. 1; Wiley: New York, 1977, pp. 149-329; Cordes; Bull *Chem. Rev.* **1974**, *74*, 581-603; Cordes *Prog. Phys. Org. Chem.* **1967**, *4*, 1-44; Salomaa, Ref. 446, pp. 184-198; Pindur; Müller; Flo; Witzel *Chem. Soc. Rev.* **1987**, *16*, 75-87 (ortho esters); Cordes, in Patai, Ref. 197, pp. 632-656 (ortho esters); DeWolfe *Carboxylic Ortho Acid Derivatives*; Academic Press: New York, 1970, pp. 134-146 (ortho esters); Rekasheva *Russ. Chem. Rev.* **1968**, *37*, 1009-1022 (enol ethers).
[458]Jaques; Leisten *J. Chem. Soc.* **1964**, 2683. See also Olah; O'Brien *J. Am. Chem. Soc.* **1967**, *89*, 1725.
[459]For a review of the reactions of ortho esters, see Pavlova; Davidovich; Rogozhin *Russ. Chem. Rev.* **1986**, *55*, 1026-1041.
[460]For a review of the mechanisms of hydrolysis of acetals and thioacetals, see Satchell; Satchell *Chem. Soc. Rev.* **1990**, *19*, 55-81.
[461]Kreevoy; Taft *J. Am. Chem. Soc.* **1955**, 77, 3146, 5590.

mechanism are:[462] (1) The reaction proceeds with *specific* H_3O^+ catalysis (see p. 259). (2) It is faster in D_2O. (3) Optically active ROH are not racemized. (4) E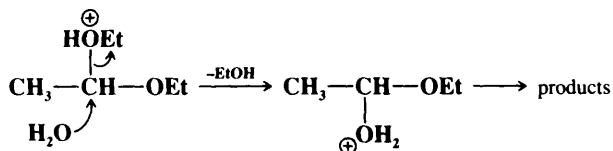ven with *t*-butyl alcohol the R—O bond does not cleave, as shown by ^{18}O labeling.[463] (5) In the case of acetophenone ketals, the intermediate corresponding to **94** [$Ar\overset{\oplus}{C}Me(OR)_2$] could be trapped with sulfite ions (SO_3^{2-}).[464] (6) Trapping of this ion did not affect the hydrolysis rate,[464] so the rate-determining step must come earlier. (7) In the case of 1,1-dialkoxyalkanes, intermediates corresponding to **94** were isolated as stable ions in super-acid solution at $-75°C$, where their spectra could be studied.[465] (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. Formation of **94** 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.[466] Rate-determining addition of water to **94** has also been reported.[467]

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.[468] In one of these mechanisms the second and third of the above steps are concerted, so that the mechanism is SN2cA (or A2). This has been shown, for example, in the hydrolysis of 1,1-diethoxyethane, by isotope effect studies:[469]

$$CH_3-\underset{\underset{H_2O}{}}{\overset{\overset{\oplus}{HOEt}}{CH}}-OEt \xrightarrow{-EtOH} CH_3-\underset{\underset{\oplus}{OH_2}}{CH}-OEt \longrightarrow products$$

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[470] demonstrating that the substrate is protonated in the rate-determining step (p. 259). Reactions in which a substrate is protonated in the rate-determining step are called A-SE2 reactions.[471] 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. 259). 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

[462]For a discussion of these, and of other evidence, see Cordes *Prog. Phys. Org. Chem.*, Ref. 457.

[463]Cawley; Westheimer *Chem. Ind. (London)* **1960**, 656.

[464]Young; Jencks *J. Am. Chem. Soc.* **1977**, *99*, 8238. See also Jencks *Acc. Chem. Res.* **1980**, *13*, 161-169; McClelland; Ahmad *J. Am. Chem. Soc.* **1978**, *100*, 7027, 7031; Young; Bogseth; Rietz *J. Am. Chem. Soc.* **1980**, *102*, 6268. However, in the case of simple aliphatic acetals, **94** could not be trapped: Amyes; Jencks *J. Am. Chem. Soc.* **1988**, *110*, 3677.

[465]See White; Olah *J. Am. Chem. Soc.* **1969**, *91*, 2943; Akhmatdinov; Kantor; Imashev; Yasman; Rakhmankulov *J. Org. Chem. USSR* **1981**, *17*, 626.

[466]Jensen; Lenz *J. Am. Chem. Soc.* **1978**, *100*, 1291; Finley; Kubler; McClelland *J. Org. Chem.* **1980**, *45*, 644; Przystas; Fife *J. Am. Chem. Soc.* **1981**, *103*, 4884; Chiang; Kresge *J. Org. Chem.* **1985**, *50*, 5038; Fife; Natarajan *J. Am. Chem. Soc.* **1986**, *108*, 2425, 8050; McClelland; Sørensen *Acta Chem. Scand.* **1990**, *44*, 1082.

[467]Toullec; El-Alaoui *J. Org. Chem.* **1985**, *50*, 4928; Fife; Natarajan, Ref. 466.

[468]For a review, see Fife *Acc. Chem. Res.* **1972**, *5*, 264-272. For a discussion, see Wann; Kreevoy *J. Org. Chem.* **1981**, *46*, 419.

[469]Kresge; Weeks *J. Am. Chem. Soc.* **1984**, *106*, 7140. See also Fife *J. Am. Chem. Soc.* **1967**, *89*, 3228; Craze; Kirby; Osborne *J. Chem. Soc., Perkin Trans. 2* **1978**, 357; Amyes; Jencks *J. Am. Chem. Soc.* **1989**, *111*, 7888, 7900.

[470]Fife; Jao *J. Am. Chem. Soc.* **1968**, *90*, 4081; Fife; Brod *J. Am. Chem. Soc.* **1970**, *92*, 1681. For other examples, see Kankaanperä; Lahti *Acta Chem. Scand.* **1969**, *23*, 2465; Mori; Schaleger *J. Am. Chem. Soc.* **1972**, *94*, 5039; Capon; Nimmo *J. Chem. Soc., Perkin Trans. 2* **1975**, 1113; Eliason; Kreevoy *J. Am. Chem. Soc.* **1978**, *100*, 7037; Jensen; Herold; Lenz; Trusty; Sergi; Bell; Rogers *J. Am. Chem. Soc.* **1979**, *101*, 4672.

[471]For a review of A-SE2 reactions, see Williams; Kreevoy *Adv. Phys. Org. Chem.* **1968**, *6*, 63-101.

about halfway. This can be explained if the basicity of the substrate is increased by partial breaking of the C—O bond. The conclusion is thus drawn that steps 1 and 2 are concerted. The hydrolysis of ortho esters in most cases is also subject to general acid catalysis.[472]

The hydrolysis of acetals and ortho esters is governed by the stereoelectronic control factor previously discussed (see **A** and **B** on p. 334)[473] though the effect can generally be seen only in systems where conformational mobility is limited, especially in cyclic systems.

Particularly convenient reagents for acetals are wet silica gel[474] and Amberlyst-15 (a sulfonic acid-based polystyrene cation exchange resin).[475] Acetals and ketals can be converted to ketones under nonaqueous conditions by treatment with BF_3 etherate-I^- in $CHCl_3$ or $MeCN$,[476] with triphenylphosphine dibromide PPh_3Br_2,[477] with $SmCl_3$–Me_3SiCl,[478] or with Me_3SiI in CH_2Cl_2 or $CHCl_3$.[479] They can also be hydrolyzed with $LiBF_4$ in wet $MeCN$.[480]

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 (**6-6**), and then can be cleaved with acid. 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. Thioacetals $RCH(SR')_2$ and thioketals $R_2C(SR')_2$ are among those compounds generally resistant to acid hydrolysis. Because conversion to these compounds (**6-11**) 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[481] used for this purpose are $HgCl_2$,[482] H_2O_2–HCl,[483] *t*-BuBr–Me_2SO,[484] Me_2SO–HCl–dioxane,[485] $Cu(NO_3)_2$ on clay (claycop),[486] $CuSO_4$ on silica gel,[487] *m*-chloroperoxybenzoic acid and CF_3COOH in CH_2Cl_2,[488] $GaCl_3$–H_2O,[489] phenyl dichlorophosphate–DMF–NaI,[490] bis(triflouroacetoxy)iodobenzene $(CF_3CO_2)_2IPh$,[491] diphosphorus tetraiodide P_2I_4 in Ac_2O,[492] and benzeneseleninic anhydride $(PhSeO)_2O$.[493] Electrochemical methods have also been used.[494]

[472]See Bergstrom; Cashen; Chiang; Kresge *J. Org. Chem.* **1979**, *44*, 1639; Ahmad; Bergstrom; Cashen; Chiang; Kresge; McClelland; Powell *J. Am. Chem. Soc.* **1979**, *101*, 2669; Chiang; Kresge; Lahti; Weeks *J. Am. Chem. Soc.* **1983**, *105*, 6852; Santry; McClelland *J. Am. Chem. Soc.* **1983**, *105*, 6138; Fife; Przystas *J. Chem. Soc., Perkin Trans.* 2 **1987**, 143.
[473]See, for example, Kirby *Acc. Chem. Res.* **1984**, *17*, 305-311; Bouab; Lamaty; Moreau *Can. J. Chem.* **1985**, *63*, 816. See, however, Ratcliffe; Mootoo; Andrews; Fraser-Reid *J. Am. Chem. Soc.* **1989**, *111*, 7661.
[474]Huet; Lechevallier; Pellet; Conia *Synthesis* **1978**, 63.
[475]Coppola *Synthesis* **1984**, 1021.
[476]Mandal; Shrotri; Ghogare *Synthesis* **1986**, 221.
[477]Wagner; Heitz; Mioskowski *J. Chem. Soc., Chem. Commun.* **1989**, 1619.
[478]Ukaji; Koumoto; Fujisawa *Chem. Lett.* **1989**, 1623.
[479]Jung; Andrus; Ornstein *Tetrahedron Lett.* **1977**, 4175. See also Balme; Goré *J. Org. Chem.* **1983**, *48*, 3336.
[480]Lipshutz; Harvey *Synth. Commun.* **1982**, *12*, 267.
[481]For references to other reagents, see Gröbel; Seebach *Synthesis* **1977**, 357-402, pp. 359-367; Cussans; Ley; Barton *J. Chem. Soc., Perkin Trans. 1* **1980**, 1654.
[482]Corey; Erickson *J. Org. Chem.* **1971**, *36*, 3553. For a mechanistic study, see Satchell; Satchell *J. Chem. Soc., Perkin Trans. 2* **1987**, 513.
[483]Olah; Narang; Salem *Synthesis* **1980**, 657, 659.
[484]Olah; Mehrotra; Narang *Synthesis* **1982**, 151.
[485]Prato; Quintily; Scorrano; Sturaro *Synthesis* **1982**, 679.
[486]Laszlo; Cornélis *Aldrichimica Acta* **1988**, *21*, 97-103, p. 101.
[487]Caballero; Gros *J. Chem. Res. (S)* **1989**, 320.
[488]Cossy *Synthesis* **1987**, 1113.
[489]Saigo; Hashimoto; Kihara; Umehara; Hasegawa *Chem. Lett.* **1990**, 831.
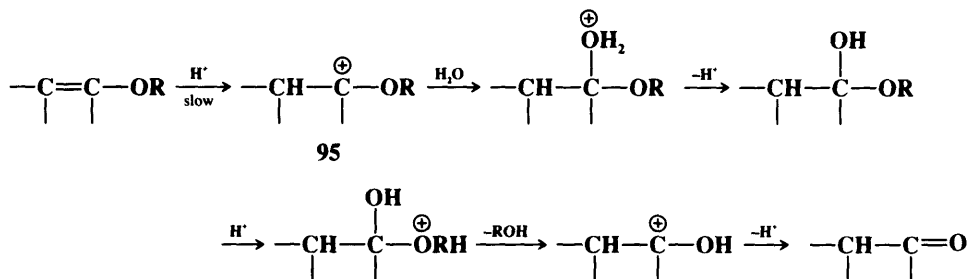[490]Liu; Wiszniewski *Tetrahedron Lett.* **1988**, *29*, 5471.
[491]Stork; Zhao *Tetrahedron Lett.* **1989**, *30*, 287.
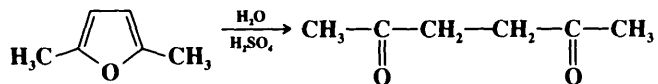[492]Shigemasa; Ogawa; Sashiwa; Saimoto *Tetrahedron Lett.* **1989**, *30*, 1277.
[493]Cussans; Ley; Barton, Ref. 481.
[494]See Platen; Steckhan *Chem. Ber.* **1984**, *117*, 1679; Schulz-von Itter; Steckhan *Tetrahedron* **1987**, *43*, 2475.
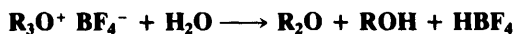
Enol ethers are readily hydrolyzed by acids; the rate-determining step is protonation of the substrate. However, protonation does not take place at the oxygen but at the β carbon,[495] because that gives rise to the stable carbocation **95**.[496] After that the mechanism is similar to the A1 mechanism given above for the hydrolysis of acetals.

$$\text{—C}{=}\text{C—OR} \xrightarrow[\text{slow}]{\text{H}^{\cdot}} \text{—CH—}\overset{\oplus}{\text{C}}\text{—OR} \xrightarrow{\text{H}_2\text{O}} \text{—CH—}\overset{\overset{\oplus}{\text{OH}_2}}{\underset{}{\text{C}}}\text{—OR} \xrightarrow{\text{-H}^{\cdot}} \text{—CH—}\overset{\text{OH}}{\underset{}{\text{C}}}\text{—OR}$$

95

$$\xrightarrow{\text{H}^{\cdot}} \text{—CH—}\overset{\text{OH}}{\underset{}{\overset{\oplus}{\text{C}}}}\text{—ORH} \xrightarrow{\text{-ROH}} \text{—CH—}\overset{\oplus}{\text{C}}\text{—OH} \xrightarrow{\text{-H}^{\cdot}} \text{—CH—C}{=}\text{O}$$

Among the facts supporting this mechanism (which is an A-S$_E$2 mechanism because the substrate is protonated in the rate-determining step) are: (1) ^{18}O labeling shows that in ROCH=CH$_2$ it is the vinyl-oxygen bond and not the RO bond that cleaves;[497] (2) the reaction is subject to general acid catalysis;[498] (3) there is a solvent isotope effect when D$_2$O is used.[498] Enamines are also hydrolyzed by acids (see **6-2**); the mechanism is similar. Ketene dithioacetals R$_2$C=C(SR')$_2$ also hydrolyze by a similar mechanism, except that the initial protonation step is partially reversible.[499] Furans represent a special case of enol ethers that are cleaved by acid to give 1,4 diones. Thus

$$\text{H}_3\text{C}\underset{\text{O}}{\diagdown\diagup}\text{CH}_3 \xrightarrow[\text{H}_2\text{SO}_4]{\text{H}_2\text{O}} \text{CH}_3\text{—}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{—CH}_2\text{—CH}_2\text{—}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{—CH}_3$$

Oxonium ions are cleaved by water to give an alcohol and an ether:

$$\text{R}_3\text{O}^+ \text{ BF}_4^- + \text{H}_2\text{O} \longrightarrow \text{R}_2\text{O} + \text{ROH} + \text{HBF}_4$$

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; **68**, 25, 92; **69**, 31, 55, 148.

0-7 Hydrolysis of Epoxides
(3)*OC-seco*-**hydroxy-de-alkoxy-substitution**

$$\overset{\text{O}}{\diagup\!\!\!\diagdown} + \text{H}_2\text{O} \xrightarrow[\text{OH}^-]{\text{H}^{\cdot} \text{ or}} \text{—}\overset{\text{HO}}{\overset{|}{\text{C}}}\text{—}\overset{\text{OH}}{\overset{|}{\text{C}}}\text{—}$$

[495]Jones; Wood *J. Chem. Soc.* **1964**, 5400; Okuyama; Fueno; Furukawa *Bull. Chem. Soc. Jpn.* **1970**, *43*, 3256; Kreevoy; Eliason *J. Phys. Chem.* **1969**, *72*, 1313; Lienhard; Wang *J. Am. Chem. Soc.* **1969**, *91*, 1146; Kresge; Chen *J. Am. Chem. Soc.* **1972**, *94*, 2818; Burt; Chiang; Kresge; Szilagyi *Can. J. Chem.* **1984**, *62*, 74.
[496]See Chwang; Kresge; Wiseman *J. Am. Chem. Soc.* **1979**, *101*, 6972.
[497]Kiprianova; Rekasheva *Dokl. Akad. Nauk SSSR* **1962**, *142*, 589.
[498]Fife *J. Am. Chem. Soc.* **1965**, *87*, 1084; Salomaa; Kankaanperä; Lajunen *Acta Chem. Scand.* **1966**, *20*, 1790; Kresge; Chiang *J. Chem. Soc. B* **1967**, 53, 58; Kresge; Yin *Can. J. Chem.* **1987**, *65*, 1753.
[499]For a review, see Okuyama *Acc. Chem. Res.* **1986**, *19*, 370-376.

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. 369). Among acid catalysts the reagent of choice is perchloric acid, since side reactions are minimized with this reagent.[500] Dimethyl sulfoxide is a superior solvent for the alkaline hydrolysis of epoxides.[501]

OS V, 414.

B. Attack by OH at an Acyl Carbon

0-8 Hydrolysis of Acyl Halides
Hydroxy-de-halogenation

$$RCOCl + H_2O \longrightarrow RCOOH$$

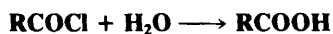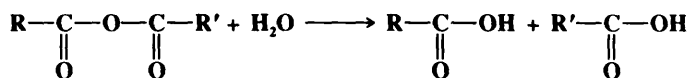Acyl halides are so reactive that hydrolysis is easily carried out. In fact, most simple acyl halides must be stored under anhydrous conditions lest they react with water in the air. Consequently, water is usually a strong enough nucleophile for the reaction, though in difficult cases hydroxide ion may be required. The reaction is seldom synthetically useful, because acyl halides are normally prepared from acids. The reactivity order is F < Cl < Br < I.[502] If a carboxylic acid is used as the nucleophile, an exchange may take place (see **0-74**). The mechanism[502] of hydrolysis can be either SN1 or tetrahedral, the former occurring in highly polar solvents and in the absence of strong nucleophiles.[503] There is also evidence for the SN2 mechanism in some cases.[504]

Hydrolysis of acyl halides is not usually catalyzed by acids, except for acyl fluorides, where hydrogen bonding can assist in the removal of F.[505]

OS II, 74.

0-9 Hydrolysis of Anhydrides
Hydroxy-de-acyloxy-substitution

$$\underset{\substack{\| \\ O}}{R-C}-O-\underset{\substack{\| \\ O}}{C-R'} + H_2O \longrightarrow \underset{\substack{\| \\ O}}{R-C}-OH + \underset{\substack{\| \\ O}}{R'-C}-OH$$

Anhydrides are somewhat more difficult to hydrolyze than acyl halides, but here too water is usually a strong enough nucleophile. The mechanism is usually tetrahedral. Only under acid catalysis does the SN1 mechanism occur and seldom even then.[506] Anhydride hydrolysis can also be catalyzed by bases. Of course, OH⁻ attacks more readily than water, but other bases can also catalyze the reaction. This phenomenon, called *nucleophilic catalysis* (p. 334), is actually the result of two successive tetrahedral mechanisms. For example, pyridine catalyzes the hydrolysis of acetic anhydride in this manner.[507]

[500]Fieser; Fieser *Reagents for Organic Synthesis*, vol. 1; Wiley: New York, 1967, p. 796.
[501]Berti; Macchia; Macchia *Tetrahedron Lett.* **1965**, 3421.
[502]For a review, see Talbot, Ref. 197, pp. 226-257. For a review of the mechanisms of reactions of acyl halides with water, alcohols, and amines, see Kivinen, in Patai *The Chemistry of Acyl Halides*; Wiley: New York, 1972, pp. 177-230.
[503]Bender; Chen *J. Am. Chem. Soc.* **1963**, *85*, 30. See also Song; Jencks *J. Am. Chem. Soc.* **1989**, *111*, 8470; Bentley; Koo; Norman *J. Org. Chem.* **1991**, *56*, 1604.
[504]Bentley; Carter; Harris, Ref. 198; Guthrie; Pike, Ref. 198. See also Lee; Sung; Uhm; Ryu *J. Chem. Soc., Perkin Trans. 2* **1989**, 1697.
[505]Bevan; Hudson *J. Chem. Soc.* **1953**, 2187; Satchell *J. Chem. Soc.* **1963**, 555.
[506]Satchell *Q. Rev., Chem. Soc.* **1963**, *17*, 160-203, pp. 172-173. For a review of the mechanism, see Talbot, Ref. 197, pp. 280-287.
[507]Butler; Gold *J. Chem. Soc.* **1961**, 4362; Fersht; Jencks *J. Am. Chem. Soc.* **1970**, *92*, 5432, 5442; Deady; Finlayson *Aust. J. Chem.* **1983**, *36*, 1951.

$$CH_3\!-\!\underset{\underset{O}{\|}}{C}\!-\!O\!-\!\underset{\underset{O}{\|}}{C}\!-\!CH_3 + \overset{\bigcirc}{\underset{N}{\bigcirc}} \longrightarrow CH_3\!-\!\underset{\underset{O}{\|}}{C}\!-\!\overset{\oplus}{N}\!\overset{\bigcirc}{\bigcirc} + \overset{\ominus}{O}\!-\!\underset{\underset{O}{\|}}{C}\!-\!CH_3$$

$$CH_3\!-\!\underset{\underset{O}{\|}}{C}\!-\!\overset{\oplus}{N}\!\overset{\bigcirc}{\bigcirc} + H_2O \longrightarrow CH_3\!-\!\underset{\underset{O}{\|}}{C}\!-\!\overset{\oplus}{O}H_2 + \overset{\bigcirc}{\underset{N}{\bigcirc}}$$

Many other nucleophiles similarly catalyze the reaction.
OS **I**, 408; **II**, 140, 368, 382; **IV**, 766; **V**, 8, 813.

0-10 Hydrolysis of Carboxylic Esters
Hydroxy-de-alkoxylation

$$R\!-\!\underset{\underset{O}{\|}}{C}\!-\!OR' \underset{\underset{H_2O}{\overset{OH}{\searrow}}}{\overset{\overset{H_2O}{\nearrow}}{}} \begin{array}{l} RCOOH + R'OH \\[1em] RCOO^- + R'OH \end{array}$$

Ester hydrolysis is usually catalyzed by acids or bases. Since OR is a much poorer leaving group than halide or OCOR, water alone does not hydrolyze most esters. When bases catalyze the reaction, the attacking species is the more powerful nucleophile OH⁻. This reaction is called *saponification* and gives the salt of the acid. Acids catalyze the reaction by making the carbonyl carbon more positive and therefore more susceptible to attack by the nucleophile. Both reactions are equili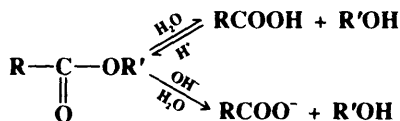brium reactions, so they are practicable only when there is a way of shifting the equilibrium to the right. Since formation of the salt does just this, ester hydrolysis is almost always done for preparative purposes in basic solution, unless the compound is base-sensitive. Ester hydrolysis can also be catalyzed[508] by metal ions, by cyclodextrins,[509] by enzymes,[510] and by nucleophiles (see **0-9**).[197] Among other compounds used to cleave carboxylic esters have been methanesulfonic acid,[511] guanidine,[512] Dowex-50,[513] Me₃SiI,[514] MeSiCl₃–NaI,[515] and KOSiMe₃.[516] Phenolic esters can be similarly cleaved; in fact the reaction is usually faster for these compounds.[517] Lactones also undergo the reaction[518] (though if the lactone is five- or six-membered, the hydroxy acid often spontaneously relactonizes) and thiol esters (RCOSR') give thiols R'SH. Sterically hindered esters are hydrolyzed with difficulty (p. 340), though this can be accomplished at room temperature with "anhydrous hydroxide," generated via the reaction of 2 moles of *t*-BuOK with 1 mole

[508]For a list of catalysts and reagents that have been used to convert carboxylic esters to acids, with references, see Larock *Comprehensive Organic Transformations*; VCH: New York, 1989, pp. 981-985.
[509]See Bender; Komiyama *Cyclodextrin Chemistry*; Springer: New York, 1978, pp. 34-41. The mechanism is shown in Saenger *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 344-362 [*Angew. Chem. 92*, 343-361].
[510]For reviews of ester hydrolysis catalyzed by pig liver esterase, see Zhu; Tedford *Tetrahedron* **1990**, *46*, 6587-6611; Ohno; Otsuka *Org. React.* **1989**, *37*, 1-55. For reviews of enzymes as catalysts in synthetic organic chemistry, see Wong *Chemtracts: Org. Chem.* **1990**, *3*, 91-111, *Science* **1989**, *244*, 1145-1152; Whitesides; Wong *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 617-638 [*Angew. Chem. 97*, 617-638].
[511]Loev *Chem. Ind. (London)* **1964**, 193.
[512]Kunesch; Miet; Poisson *Tetrahedron Lett.* **1987**, *28*, 3569.
[513]Basu; Sarkar; Ranu *Synth. Commun.* **1989**, *19*, 627.
[514]Ho; Olah *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 774 [*Angew. Chem. 88*, 847]; Jung; Lyster *J. Am. Chem. Soc.* **1977**, *99*, 968. For a review of this reagent, see Olah; Narang *Tetrahedron* **1982**, *38*, 2225-2277.
[515]Olah; Husain; Singh; Mehrotra *J. Org. Chem.* **1983**, *48*, 3667.
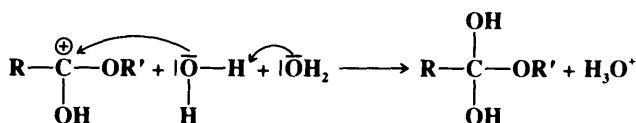[516]Laganis; Chenard *Tetrahedron Lett.* **1984**, *25*, 5831.
[517]For a method of hydrolyzing phenolic esters in the presence of other esters, see Blay; Cardona; Garcia; Pedro *Synthesis* **1989**, 438.
[518]For a review of the mechanisms of lactone hydrolysis, see Kaiser; Kézdy *Prog. Bioorg. Chem.* **1976**, *4*, 239-267, pp. 254-265.

of water.[519] Hindered esters can also be cleaved with *n*-propyllithium.[520] For esters insoluble in water the rate of two-phase ester saponification can be greatly increased by the application of ultrasound.[521] Phase-transfer techniques have also been applied.[522]

Ingold[523] has classified the acid- and base-catalyzed hydrolyses of esters (and the formation of esters, since these are reversible reactions and thus have the same mechanisms) into eight possible mechanisms (Table 10.14), depending on the following criteria: (1) acid- or base-catalyzed, (2) unimolecular or bimolecular, and (3) acyl cleavage or alkyl cleavage.[525] All eight of these are SN1, SN2, or tetrahedral mechanisms. The acid-catalyzed mechanisms are shown with reversible arrows. They are not only reversible but symmetrical; that is, the mechanisms for ester formation are exactly the same as for hydrolysis, except that H replaces R. Internal proton transfers, such as shown for **B** and **C**, may not actually be direct but may take place through the solvent. There is much physical evidence to show that esters are initially protonated on the carbonyl and not on the alkyl oxygen (Chapter 8, Ref. 17). We have nevertheless shown the AAc1 mechanism as proceeding through the ether-protonated intermediate **A**, since it is difficult to envision OR′ as a leaving group here. It is of course possible for a reaction to proceed through an intermediate even if only a tiny concentration is present. The designations AAc1, etc., are those of Ingold. The AAc2 and AAc1 mechanisms are also called A2 and A1, respectively. It may be noted that the AAc1 mechanism is actually the same as the SN1cA mechanism for this type of substrate and that AAL2 is analogous to SN2cA. Some authors use A1 and A2 to refer to all types of nucleophilic substitution in which the leaving group first acquires a proton. The base-catalyzed reactions are not shown with reversible arrows, since they are reversible only in theory and not in practice. Hydrolyses taking place under neutral conditions are classified as B mechanisms.

Of the eight mechanisms, seven have actually been observed in hydrolysis of carboxylic esters. The one that has not been observed is the BAc1 mechanism.[526] The most common mechanisms are the BAc2 for basic catalysis and the AAc2[527] for acid catalysis, that is, the two tetrahedral mechanisms. Both involve acyl-oxygen cleavage. The evidence is: (1) hydrolysis with $H_2^{18}O$ results in the ^{18}O appearing in the acid and not in the alcohol;[528] (2) esters with chiral R′ groups give alcohols with *retention* of configuration;[529] (3) allylic R′ gives no allylic rearrangement;[530] (4) neopentyl R′ gives no rearrangement;[531] all these facts indicate that the O—R′ bond is not broken. It has been concluded that two molecules of water are required in the AAc2 mechanism.

$$R{-}\overset{\displaystyle OH}{\underset{\displaystyle OH}{\overset{\oplus}{C}}}{-}OR' + I\bar{O}{-}H + I\overset{+}{O}H_2 \longrightarrow R{-}\overset{\displaystyle OH}{\underset{\displaystyle OH}{C}}{-}OR' + H_3O^+$$

[519]Gassman; Schenk *J. Org. Chem.* **1977**, *42*, 918.
[520]Lion; Dubois; MacPhee; Bonzougou *Tetrahedron* **1979**, *35*, 2077.
[521]Moon; Duchin; Cooney *Tetrahedron Lett.* **1979**, 3917.
[522]Dehmlow; Naranjo *J. Chem. Res.*, *(S)* **1979**, 238; Loupy; Pedoussaut; Sansoulet *J. Org. Chem.* **1986**, *51*, 740.
[523]Ingold, Ref. 366, pp. 1129-1131.
[524]As given here, the IUPAC designations for BAc1 and BAL1 are the same, but Rule A.2 adds further symbols so that they can be distinguished: Su-AL for BAL1 and Su-AC for BAc1. See the IUPAC rules: Guthrie *Pure Appl. Chem.* **1989**, *61*, 23-56, p. 49.
[525]For reviews of the mechanisms of ester hydrolysis and formation, see Kirby, in Bamford; Tipper, Ref. 178, vol. 10, 1972, pp. 57-207; Euranto, in Patai, Ref. 197, pp. 505-588.
[526]This is an SN1 mechanism with OR′ as leaving group, which does not happen.
[527]For a discussion of this mechanism with specific attention to the proton transfers involved, see Zimmermann; Rudolph *Angew. Chem. Int. Ed. Engl.* **1965**, *4*, 40-49 [*Angew. Chem. 77*, 65-74].
[528]For one of several examples, see Polanyi; Szabo *Trans. Faraday Soc.* **1934**, *30*, 508.
[529]Holmberg *Ber.* **1912**, *45*, 2997.
[530]Ingold; Ingold *J. Chem. Soc.* **1932**, 758.
[531]Norton; Quayle *J. Am. Chem. Soc.* **1940**, *62*, 1170.

TABLE 10.14 Classification of the eight mechanisms for ester hydrolysis and formation[523]

Ingold	Name IUPAC[524]	Type	Mechanism
			Acid catalysis — Acyl cleavage
AAc1	$A_h + D_N + A_N + D_h$	SN1	$R-\overset{\|\|}{\underset{O}{C}}-OR' \overset{H^+}{\rightleftharpoons} R-\overset{+}{\underset{O}{C}}-\underset{H}{OR'} \overset{slow}{\underset{R'OH}{\rightleftharpoons}} R-\overset{\oplus}{\underset{O}{C}} \overset{H_2O}{\underset{slow}{\rightleftharpoons}} R-\underset{OH}{\overset{+}{C}}-OH \rightleftharpoons R-\overset{\|\|}{\underset{O}{C}}-OH \overset{}{\underset{H^+}{\rightleftharpoons}} R-\overset{\|\|}{\underset{O}{C}}-OH$ (A)
AAc2	$A_h + A_N + A_N D_h + D_N + D_h$	Tetra-hedral	$R-\overset{\|\|}{\underset{O}{C}}-OR' \overset{H^+}{\rightleftharpoons} R-\overset{+}{\underset{OH}{C}}-OR' \overset{\overset{+}{OH_2}}{\underset{slow}{\rightleftharpoons}} R-\overset{OH}{\underset{OH}{C}}-OR' \rightleftharpoons R-\overset{\oplus OR'}{\underset{H}{C}}-OH \overset{R'OH}{\underset{slow}{\rightleftharpoons}} R-\overset{+}{\underset{OH}{C}}-OH \overset{}{\underset{H^+}{\rightleftharpoons}} R-\overset{\|\|}{\underset{O}{C}}-OH$ (B) (C)
			Acid catalysis — Alkyl cleavage
AAl1	$A_h + D_N + A_N + D_h$	SN1	$R-\overset{\|\|}{\underset{O}{C}}-OR' \overset{H^+}{\rightleftharpoons} R-\overset{+}{\underset{OH}{C}}-OR' \overset{slow}{\underset{H_2O}{\rightleftharpoons}} R-C=O + R'^+ \overset{H_2O}{\underset{slow}{\rightleftharpoons}} R-\overset{\oplus}{C}=O + R'OH_2^+ \rightleftharpoons R'OH$
AAl2	$A_h + A_N D_N + D_h$	SN2	$R-\overset{\|\|}{\underset{O}{C}}-OR' \overset{H^+}{\rightleftharpoons} R-\overset{+}{\underset{OH}{C}}-OR' \overset{H_2O}{\rightleftharpoons} R-\overset{\|\|}{\underset{O}{C}}-OH + R'OH_2^+ \overset{}{\underset{H^+}{\rightleftharpoons}} R'OH$
			Basic catalysis — Acyl cleavage
BAc1	$D_N + A_N + A_{xh}D_h$	SN1	$R-\overset{\|\|}{\underset{O}{C}}-OR' \overset{slow}{\longrightarrow} R-C^{\oplus} + OR'^- \overset{OH^-}{\longrightarrow} R-\overset{\|\|}{\underset{O}{C}}-OH + OR'^- \longrightarrow R-\overset{\|\|}{\underset{O}{C}}-O^- + R'OH$
BAc2	$A_N + D_N + A_{xh}D_h$	Tetra-hedral	$R-\overset{\|\|}{\underset{O}{C}}-OR' \overset{OH^-}{\underset{slow}{\longrightarrow}} R-\overset{OH}{\underset{O\ominus}{C}}-OR' \overset{slow}{\longrightarrow} R-\overset{\|\|}{\underset{O}{C}}-OH + OR'^- \longrightarrow R-\overset{\|\|}{\underset{O}{C}}-O^- + R'OH$
			Basic catalysis — Alkyl cleavage
BAl1	$D_N + A_N + A_{xh}D_h$	SN1	$R-\overset{\|\|}{\underset{O}{C}}-OR' \overset{slow}{\longrightarrow} R-\overset{\|\|}{\underset{O}{C}}-O^- + R''^+ \overset{}{\underset{H_2O}{\longrightarrow}} R'OH_2^+ \overset{}{\underset{OH^-}{\longrightarrow}} R'OH$
BAl2	$A_N D_N$	SN2	$R-\overset{\|\|}{\underset{O}{C}}-OR' \overset{OH^-}{\longrightarrow} R-\overset{\|\|}{\underset{O}{C}}-O^- + R'OH$

If this is so, the protonated derivatives **B** and **C** would not appear at all. This conclusion stems from a value of w (see p. 257) of about 5, indicating that water acts as a proton donor here as well as a nucleophile.[532] Termolecular processes are rare, but in this case the two water molecules are already connected by a hydrogen bond. (A similar mechanism, called B$_{AC}$3, also involving two molecules of water, has been found for esters that hydrolyze without a catalyst.[533] Such esters are mostly those containing halogen atoms in the R group.)
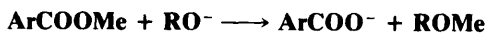
The other mechanism involving acyl cleavage is the A$_{AC}$1 mechanism. This is rare, being found only where R is very bulky, so that bimolecular attack is sterically hindered, and only in ionizing solvents. The mechanism has been demonstrated for esters of 2,4,6-trimethyl-benzoic acid (mesitoic acid). This acid depresses the freezing point of sulfuric acid four times as much as would be predicted from its molecular weight, which is evidence for the equilibrium

$$ArCOOH + 2H_2SO_4 \rightleftharpoons ArCO^\oplus + H_3O^+ + 2HSO_4^-$$

In a comparable solution of benzoic acid the freezing point is depressed only twice the predicted amount, indicating only a normal acid–base reaction. Further, a sulfuric acid solution of methyl mesitoate when poured into water gave mesitoic acid, while a similar solution of methyl benzoate similarly treated did not.[534] The A$_{AC}$1 mechanism is also found when acetates of phenols or of primary alcohols are hydrolyzed in concentrated (more than 90%) H_2SO_4 (the mechanism under the more usual dilute acid conditions is the normal A$_{AC}$2).[535]

The mechanisms involving alkyl-oxygen cleavage are ordinary S$_N$1 and S$_N$2 mechanisms in which OCOR (an acyloxy group) or its conjugate acid is the leaving group. Two of the four mechanisms, the B$_{AL}$1 and A$_{AL}$1 mechanisms, occur most readily when R' comes off as a stable carbocation, that is, when R' is tertiary alkyl, allylic, benzylic, etc. For acid catalysis, most esters with this type of alkyl group (especially tertiary alkyl) cleave by this mechanism, but even for these substrates, the B$_{AL}$1 mechanism occurs only in neutral or weakly basic solution, where the rate of attack by OH$^-$ is so slowed that the normally slow (by comparison) unimolecular cleavage takes over. These two mechanisms have been established by kinetic studies, [18]O labeling, and isomerization of R'.[536] Secondary and benzylic acetates hydrolyze by the A$_{AC}$2 mechanism in dilute H_2SO_4, but in concentrated acid the mechanism changes to A$_{AL}$1.[535] Despite its designation, the B$_{AL}$1 mechanism is actually uncatalyzed (as is the unknown B$_{AC}$1 mechanism).

The two remaining mechanisms, B$_{AL}$2 and A$_{AL}$2, are very rare, the B$_{AL}$2 because it requires OH$^-$ to attack an alkyl carbon when an acyl carbon is also available, and the A$_{AL}$2 because it requires water to be a nucleophile in an S$_N$2 process. Both have been observed, however. The B$_{AL}$2 has been seen in the hydrolysis of β-lactones under neutral conditions[537] (because cleavage of the C—O bond in the transition state opens the four-membered ring and relieves strain), the alkaline hydrolysis of methyl 2,4,6-tri-t-butyl benzoate,[538] and in the unusual reaction[539]

$$ArCOOMe + RO^- \longrightarrow ArCOO^- + ROMe$$

[532]Martin *J. Am. Chem. Soc.* **1962**, *84*, 4130. See also Lane; Cheung; Dorsey *J. Am. Chem. Soc.* **1968**, *90*, 6492; Yates; McClelland *J. Am. Chem. Soc.* **1967**, *89*, 2686; Yates *Acc. Chem. Res.* **1971**, *6*, 136-144; Huskey; Warren; Hogg *J. Org. Chem.* **1981**, *46*, 59.

[533]Euranto; Kanerva; Cleve *J. Chem. Soc., Perkin Trans. 2* **1984**, 2085; Neuvonen *J. Chem. Soc., Perkin Trans. 2* **1986**, 1141; Euranto; Kanerva *Acta Chem. Scand., Ser. B* **1988**, *42* 717.

[534]Treffers; Hammett *J. Am. Chem. Soc.* **1937**, *59*, 1708. For other evidence for this mechanism, see Bender; Chen *J. Am. Chem. Soc.* **1963**, *85*, 37.

[535]Yates, Ref. 532; Al-Shalchi; Selwood; Tillett *J. Chem. Res. (S)* **1985**, 10.

[536]For discussions, see Kirby, Ref. 525, pp. 86-101; Ingold, Ref. 366, pp. 1137-1142, 1157-1163.

[537]Cowdrey; Hughes; Ingold; Masterman; Scott *J. Chem. Soc.* **1937**, 1264; Long; Purchase *J. Am. Chem. Soc.* **1950**, *73*, 3267.

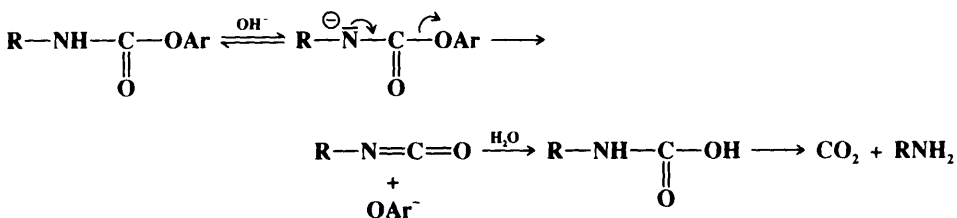[538]Barclay; Hall; Cooke *Can. J. Chem.* **1962**, *40*, 1981.

[539]Sneen; Rosenberg *J. Org. Chem.* **1961**, *26*, 2099. See also Müller; Siegfried *Helv. Chim. Acta* **1974**, *57*, 987.

When it does occur, the BAL2 mechanism is easy to detect, since it is the only one of the base-catalyzed mechanisms that requires inversion at R'. However, in the last example given, the mechanism is evident from the nature of the product, since the ether could have been formed in no other way. The AAL2 mechanism has been reported in the acid cleavage of γ-lactones.[539a]

To sum up the acid-catalysis mechanisms, AAC2 and AAL1 are the common mechanisms, the latter for R' that give stable carbocations, the former for practically all the rest. AAC1 is rare, being found mostly with strong acids and sterically hindered R. AAL2 is even rarer. For basic catalysis, BAC2 is almost universal; BAL1 occurs only with R' that give stable carbocations and then only in weakly basic or neutral solutions; BAL2 is very rare; and BAC1 has never been observed.

The above results pertain to reactions in solution. In the gas phase[540] reactions can take a different course, as illustrated by the reaction of carboxylic esters with MeO⁻, which in the gas phase was shown to take place only by the BAL2 mechanism,[541] even with aryl esters,[542] where this means that an S_N2 mechanism takes place at an aryl substrate. However, when the gas-phase reaction of aryl esters was carried out with MeO⁻ ions, each of which was solvated with a single molecule of MeOH or H_2O, the BAC2 mechanism was observed.[542]

In the special case of alkaline hydrolysis of N-substituted aryl carbamates, there is another mechanism[543] involving elimination–addition:[544]

$$R-NH-\underset{\underset{O}{\|}}{C}-OAr \overset{OH^-}{\rightleftharpoons} R-\overset{\ominus}{N}-\underset{\underset{O}{\|}}{C}-OAr \longrightarrow$$

$$R-N{=}C{=}O \overset{H_2O}{\longrightarrow} R-NH-\underset{\underset{O}{\|}}{C}-OH \longrightarrow CO_2 + RNH_2$$
$$+$$
$$OAr^-$$

This mechanism does not apply to unsubstituted or N,N-disubstituted aryl carbamates, which hydrolyze by the normal mechanisms. Carboxylic esters substituted in the α position by an electron-withdrawing group (e.g., CN or COOEt) can also hydrolyze by a similar mechanism involving a ketene intermediate.[545] These elimination–addition mechanisms usually are referred to as E1cB mechanisms, because that is the name given to the elimination portion of the mechanism (p. 991).

The acid-catalyzed hydrolysis of enol esters $RCOOCR'{=}CR_2''$ can take place either by the normal AAC2 mechanism or by a mechanism involving initial protonation on the double-bond carbon, similar to the mechanism for the hydrolysis of enol ethers given in **0-6**,[546]

[539a]Moore; Schwab *Tetrahedron Lett.* **1991,** *32,* 2331.
[540]Takashima; José; do Amaral; Riveros *J. Chem. Soc. Chem. Commun.* **1983,** 1255.
[541]Comisarow *Can. J. Chem.* **1977,** *55,* 171.
[542]Fukuda; McIver *J. Am. Chem. Soc.* **1979,** *101,* 2498.
[543]For a review of elimination–addition mechanisms at a carbonyl carbon, see Williams; Douglas *Chem. Rev.* **1975,** *75,* 627-649.
[544]Bender; Homer *J. Org. Chem.* **1965,** *30,* 3975; Williams *J. Chem. Soc., Perkin Trans. 2* **1972,** 808, **1973,** 1244; Hegarty; Frost *J. Chem. Soc., Perkin Trans. 2* **1973,** 1719; Menger; Glass *J. Org. Chem.* **1974,** *39,* 2469; Sartoré; Bergon; Calmon *J. Chem. Soc., Perkin Trans. 2* **1977,** 650; Moravcová; Večeřa *Collect. Czech. Chem. Commun.* **1977,** *42,* 3048; Broxton; Chung *J. Org. Chem.* **1986,** *51,* 3112.
[545]Casanova; Werner; Kiefer *J. Am. Chem. Soc.* **1967,** *89,* 2411; Holmquist; Bruice *J. Am. Chem. Soc.* **1969,** *91,* 2993, 3003; Campbell; Lawrie *Chem. Commun.* **1971,** 355; Kirby; Lloyd *J. Chem. Soc., Perkin Trans. 2* **1976,** 1762; Broxton; Duddy *J. Org. Chem.* **1981,** *46,* 1186; Inoue; Bruice *J. Am. Chem. Soc.* **1982,** *104,* 1644, *J. Org. Chem.* **1983,** *48,* 3559, **1986,** *51,* 959; Alborz; Douglas *J. Chem. Soc., Perkin Trans. 2* **1982,** 331; Thea; Cevasco; Guanti; Kashefi-Naini; Williams *J. Org. Chem.* **1985,** *50,* 1867; Isaacs; Najem *Can. J. Chem.* **1986,** *64,* 1140, *J. Chem. Soc., Perkin Trans. 2* **1988,** 557.
[546]Alkynyl esters also hydrolyze by this mechanism; see Allen; Kitamura; Roberts; Stang; Tidwell *J. Am. Chem. Soc.* **1988,** *110,* 622.

depending on reaction conditions.[547] In either case, the products are the carboxylic acid RCOOH and the aldehyde or ketone $R_2'CHCOR'$.

OS **I**, 351, 360, 366, 379, 391, 418, 523; **II**, 1, 5, 53, 93, 194, 214, 258, 299, 416, 422, 474, 531, 549; **III**, 3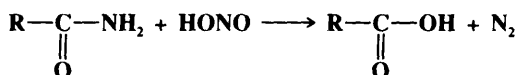, 33, 101, 209, 213, 234, 267, 272, 281, 300, 495, 510, 526, 531, 615, 637, 652, 705, 737, 774, 785, 809 (but see OS **V**, 1050), 833, 835; **IV**, 15, 55, 169, 317, 417, 444, 532, 549, 555, 582, 590, 608, 616, 628, 630, 633, 635, 804; **V**, 8, 445, 509, 687, 762, 887, 985, 1031; **VI**, 75, 121, 560, 690, 824, 913, 1024; **VII**, 4, 190, 210, 297, 319, 323, 356, 411; **65**, 203; **66**, 37, 87, 173; **67**, 76, 170; **68**, 175, 198; **69**, 1, 19. Ester hydrolyses with concomitant decarboxylation are listed at reaction **2-40**.

0-11   Hydrolysis of Amides
         Hydroxy-de-amination

Unsubstituted amides ($RCONH_2$) can be hydrolyzed with either acidic or basic catalysis, the products being, respectively, the free acid and the ammonium ion or the salt of the acid and ammonia. N-Substituted ($RCONHR'$) and N,N-disubstituted ($RCONR_2''$) amides can be hydrolyzed analogously, with the primary or secondary amine, respectively (or their salts), being obtained instead of ammonia. Lactams, imides, cyclic imides, hydrazides, etc., also undergo the reaction. Water alone is not sufficient to hydrolyze most amides, since NH_2 is even a poorer leaving group than OR.[548] Prolonged heating is often required, even with acidic or basic catalysts.[549] In difficult cases, nitrous acid, NOCl, N_2O_4,[550] or a similar compound can be used (unsubstituted amides only[551]).

These reactions involve a diazonium ion (see **2-49**) and are much faster than ordinary hydrolysis; for benzamide the nitrous acid reaction took place 2.5×10^7 times faster than ordinary hydrolysis.[552] Another procedure for difficult cases involves treatment with aqueous sodium peroxide.[553] In still another method, the amide is treated with water and *t*-BuOK at room temperature.[554] The strong base removes the proton from **96**, thus preventing the reaction marked k_{-1}. Amide hydrolysis can also be catalyzed by nucleophiles (see p. 334).

[547]See, for example, Noyce; Pollack *J. Am. Chem. Soc.* **1969**, *91*, 119, 7158; Monthéard; Camps; Chatzopoulos; Benzaïd *Bull. Soc. Chim. Fr.* **1984**, 11-109. For a discussion, see Euranto *Pure Appl. Chem.* **1977**, *49*, 1009-1020.

[548]The very low rate of amide hydrolysis by water alone has been measured: Kahne; Still *J. Am. Chem. Soc.* **1988**, *110*, 7529.

[549]For a list of catalysts and reagents that have been used to hydrolyze amides, with references, see Ref. 508, pp. 988-989.

[550]Kim; Kim; Park *Tetrahedron Lett.* **1990**, *31*, 3893.

[551]N-Substituted amides can be converted to N-nitrosoamides, which are more easily hydrolyzable than the original amide. For example, see Rull; Serratosa; Vilarrasa *Tetrahedron Lett.* **1977**, 4549. For another method of hydrolyzing N-substituted amides, see Flynn; Zelle; Grieco *J. Org. Chem.* **1983**, *48*, 2424.

[552]Ladenheim; Bender *J. Am. Chem. Soc.* **1960**, *82*, 1895.

[553]Vaughan; Robbins *J. Org. Chem.* **1975**, *40*, 1187.

[554]Gassman; Hodgson; Balchunis *J. Am. Chem. Soc.* **1976**, *98*, 1275.

The same framework of eight possible mechanisms that was discussed for ester hydrolysis can also be applied to amide hydrolysis.[555] Both the acid- and base-catalyzed hydrolyses are essentially irreversible, since salts are formed in both cases. For basic catalysis[556] the mechanism is $B_{AC}2$.

$$R-\underset{\underset{O}{\|}}{C}-NR_2' + OH^- \underset{k_{-1}}{\overset{\underset{slow}{k_1}}{\rightleftharpoons}} R-\underset{\underset{\underset{\ominus}{O}}{|}}{\overset{\overset{OH}{|}}{C}}-NR_2' \overset{k_2}{\longrightarrow}$$

96

$$R-\underset{\underset{O}{\|}}{C}-OH + NR_2'^- \longrightarrow R-\underset{\underset{O}{\|}}{C}-O^- + R_2'NH$$

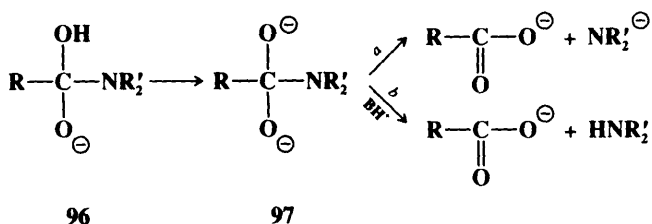There is much evidence for this mechanism, similar to that discussed for ester hydrolysis. In certain cases, kinetic studies have shown that the reaction is second order in OH^-, indicating that **96** can lose a proton to give **97**.[557] Depending on the nature of R', **97** can

$$R-\underset{\underset{\underset{\ominus}{O}}{|}}{\overset{\overset{OH}{|}}{C}}-NR_2' \longrightarrow R-\underset{\underset{\underset{\ominus}{O}}{|}}{\overset{\overset{O^\ominus}{|}}{C}}-NR_2' \overset{a}{\underset{b}{\diagdown}} \begin{array}{l} R-\underset{\underset{O}{\|}}{C}-O^\ominus + NR_2'^\ominus \\ \\ R-\underset{\underset{O}{\|}}{C}-O^\ominus + HNR_2' \end{array}$$

96   **97**

cleave directly to give the two negative ions (path *a*) or become N-protonated prior to or during the act of cleavage (path *b*), in which case the products are obtained directly and a final proton transfer is not necessary.[558] Studies of the effect, on the rate of hydrolysis and on the ratio k_{-1}/k_2, of substituents on the aromatic rings in a series of amides $CH_3CONHAr$ led to the conclusion that path *a* is taken when Ar contains electron-withdrawing substituents and path *b* when electron-donating groups are present.[559] The presence of electron-withdrawing groups helps stabilize the negative charge on the nitrogen, so that $NR_2'^-$ can be a leaving group (path *a*). Otherwise, the C—N bond does not cleave until the nitrogen is protonated (either prior to or in the act of cleavage), so that the leaving group, *even in the base-catalyzed reaction*, is not $NR_2'^-$ but the conjugate NHR_2' (path *b*). Though we have shown formation of **96** as the rate-determining step in the $B_{AC}2$ mechanism, this is true

[555]For reviews, see O'Connor *Q. Rev., Chem. Soc.* **1970**, *24*, 553-564; Talbot, Ref. 197, pp. 257-280; Challis; Challis, in Zabicky *The Chemistry of Amides*; Wiley: New York, 1970, pp. 731-857.

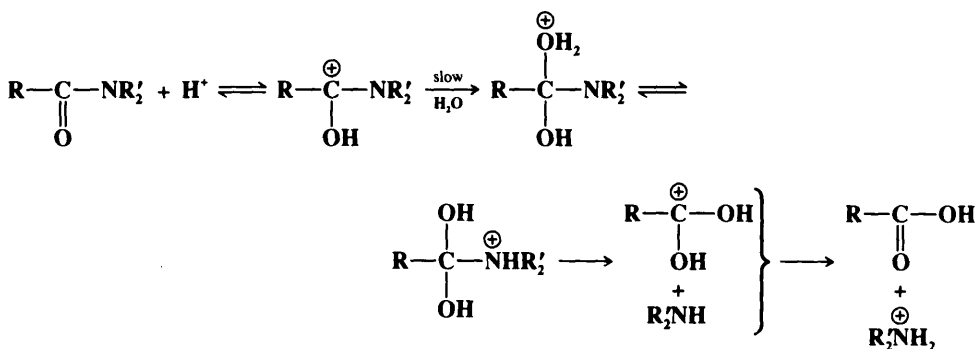[556]For a comprehensive list of references, see DeWolfe; Newcomb *J. Org. Chem.* **1971**, *36*, 3870.

[557]Biechler; Taft *J. Am. Chem. Soc.* **1957**, *79*, 4927. For evidence that a similar intermediate can arise in base-catalyzed ester hydrolysis, see Khan; Olagbemiro *J. Org. Chem.* **1982**, *47*, 3695.

[558]Eriksson; Holst *Acta Chem. Scand.* **1966**, *20*, 1892; Eriksson *Acta Chem. Scand.* **1968**, *22*, 892, *Acta Pharm. Suec.* **1969**, *6*, 139-162.

[559]Bender; Thomas *J. Am. Chem. Soc.* **1961**, *83*, 4183; Pollack; Bender *J. Am. Chem. Soc.* **1970**, *92*, 7190; Kershner; Schowen *J. Am. Chem. Soc.* **1971**, *93*, 2014; Schowen; Hopper; Bazikian *J. Am. Chem. Soc.* **1972**, *94*, 3095. See also Ref. 556; Gani; Viout *Tetrahedron Lett.* **1972**, 5241; Menger; Donohue *J. Am. Chem. Soc.* **1973**, *95*, 432; Pollack; Dumsha *J. Am. Chem. Soc.* **1973**, *95*, 4463; Kijima; Sekiguchi *J. Chem. Soc., Perkin Trans. 2* **1987**, 1203.

only at high base concentrations. At lower concentrations of base, the cleavage of **96** or **97** becomes rate-determining.[560]
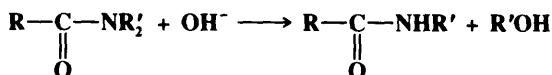
For acid catalysis, matters are less clear. The reaction is generally second order, and it is known that amides are primarily protonated on the oxygen (Chapter 8, Ref. 17). Because of these facts it has been generally agreed that most acid-catalyzed amide hydrolysis takes place by the A$_{AC}$2 mechanism.

$$R-\underset{\underset{O}{\parallel}}{C}-NR'_2 + H^+ \rightleftharpoons R-\underset{\underset{OH}{|}}{\overset{\oplus}{C}}-NR'_2 \xrightarrow[H_2O]{slow} R-\underset{\underset{OH}{|}}{\overset{\overset{\oplus}{OH_2}}{C}}-NR'_2 \rightleftharpoons$$

$$R-\underset{\underset{OH}{|}}{\overset{\overset{OH}{|}}{C}}-\overset{\oplus}{N}HR'_2 \longrightarrow \left.\begin{array}{c} R-\overset{\overset{\oplus}{C}}{\underset{\underset{+}{\underset{OH}{|}}}{}}-OH \\ R'_2NH \end{array}\right\} \longrightarrow \begin{array}{c} R-\underset{\underset{O}{\parallel}}{C}-OH \\ + \\ \overset{\oplus}{R'_2}NH_2 \end{array}$$

Further evidence for this mechanism is that a small but detectable amount of ^{18}O exchange (see p. 332) has been found in the acid-catalyzed hydrolysis of benzamide.[561] (^{18}O exchange has also been detected for the base-catalyzed process,[562] in accord with the B$_{AC}$2 mechanism). Kinetic data have shown that three molecules of water are involved in the rate-determining step,[563] suggesting that, as in the A$_{AC}$2 mechanism for ester hydrolysis (**0-10**), additional water molecules take part in a process such as

$$\begin{array}{c} H_2O\text{-----}H \\ \phantom{H_2O\text{-----}}\searrow O \curvearrowright \overset{\overset{R}{\overset{|}{\oplus}}}{\underset{\underset{OH}{|}}{C}}-NR'_2 \\ H_2O\text{-----}H \nearrow \end{array}$$

The four mechanisms involving alkyl—N cleavage (the AL mechanisms) do not apply to this reaction. They are not possible for unsubstituted amides, since the only N—C bond is the acyl bond. They are possible for N-substituted and N,N-disubstituted amides, but in these cases they give entirely different products and are not amide hydrolyses at all.

$$R-\underset{\underset{O}{\parallel}}{C}-NR'_2 + OH^- \longrightarrow R-\underset{\underset{O}{\parallel}}{C}-NHR' + R'OH$$

This reaction, while rare, has been observed for various N-t-butyl amides in 98% sulfuric acid, where the mechanism was the A$_{AL}$1 mechanism,[564] and for certain amides containing

[560]Schowen; Jayaraman; Kershner *J. Am. Chem. Soc.* **1966,** *88,* 3373. See also Gani; Viout *Tetrahedron* **1976,** *32,* 1669, 2883; Bowden; Bromley *J. Chem. Soc., Perkin Trans. 2* **1990,** 2103.

[561]McClelland *J. Am. Chem. Soc.* **1975,** *97,* 5281; Bennet; Ślebocka-Tilk; Brown; Guthrie; Jodhan *J. Am. Chem. Soc.* **1990,** *112,* 8497.

[562]Bender; Thomas, Ref. 559, Bunton; Nayak; O'Connor *J. Org. Chem.* **1968,** *33,* 572; Ślebocka-Tilk; Bennet; Hogg; Brown *J. Am. Chem. Soc.* **1991,** *113,* 1288; Ref. 561.

[563]Moodie; Wale; Whaite *J. Chem. Soc.,* **1963,** 4273; Yates; Stevens *Can. J. Chem.* **1965,** *43,* 529; Yates; Riordan *Can. J. Chem.* **1965,** *43,* 2328.

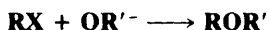[564]Lacey *J. Chem. Soc.* **1960,** 1633; Druet; Yates *Can. J. Chem.* **1984,** *62,* 2401.

an azo group, where a BAL1 mechanism was postulated.[565] Of the two first-order acyl cleavage mechanisms, only the AAc1 has been observed, in concentrated sulfuric acid solutions.[566] Of course, the diazotization of unsubstituted amides might be expected to follow this mechanism, and there is evidence that this is true.[552]

OS **I**, 14, 111, 194, 201, 286; **II**, 19, 25, 28, 49, 76, 208, 330, 374, 384, 457, 462, 491, 503, 519, 612; **III**, 66, 88, 154, 256, 410, 456, 586, 591, 661, 735, 768, 813; **IV**, 39, 42, 55, 58, 420, 441, 496, 664; **V**, 27, 96, 341, 471, 612, 627; **VI**, 56, 252, 507, 951, 967; **VII**, 4, 287; **65**, 119, 173; **67**, 52; **68**, 83; **69**, 55.

The oxidation of aldehydes to carboxylic acids can proceed by a nucleophilic mechanism, but more often it does not. The reaction is considered in Chapter 14 (**4-6**). Basic cleavage of β-keto esters and the haloform reaction could be considered at this point, but they are also electrophilic substitutions and are treated in Chapter 12 (**2-43** and **2-44**).

C.   Attack by OR at an Alkyl Carbon

0-12   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 ethers or, for that matter, symmetrical ones.[567] The reaction can also be carried out with aromatic R′, though C-alkylation is sometimes a side reaction (see p. 366).[568] The normal method involves treatment of the halide with alkoxide or aroxide ion prepared from an alcohol or phenol, but it is also possible to mix the halide and alcohol or phenol directly with solid KOH in Me_2SO[569] or with HgO and HBF_4 in CH_2Cl_2.[570] The reaction is not successful for tertiary R (because of elimination), and low yields are obtained with secondary R. Many other 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 (**0-14**) with a tertiary alkoxide $R'O^-$, which is prepared by removal of a proton from a tertiary alcohol with methylsulfinyl carbanion,[571] or with a copper(I) tertiary alkoxide.[572] Di-*t*-butyl ether was prepared in high yield by direct attack by *t*-BuOH on the *t*-butyl cation (at $-80°C$ in SO_2ClF).[573] Di-*t*-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.[574] Active halides such as Ar_3CX may react directly with the alcohol without the need for the more powerful nucleophile alkoxide ion.[575] Even tertiary halides have been converted to ethers in this way, with no elimination.[576] The mechanism is these cases is of course SN1. *t*-Butyl halides can be converted to aryl *t*-butyl ethers by treatment

[565]Stodola *J. Org. Chem.* **1972**, *37*, 178.
[566]Duffy; Leisten *J. Chem. Soc.* **1960**, 545, 853; Barnett; O'Connor *J. Chem. Soc., Chem. Commun.* **1972**, 525, *J. Chem. Soc., Perkin Trans. 2* **1972**, 2378.
[567]For a review, see Feuer; Hooz, in Patai, Ref. 333, pp. 446-450, 460-468.
[568]For a list of reagents used to convert alcohols and phenols to ethers, see Ref. 508, pp. 446-448.
[569]Benedict; Bianchi; Cate *Synthesis* **1979**, 428; Johnstone; Rose *Tetrahedron* **1979**, *35*, 2169. See also Loupy; Sansoulet; Vaziri-Zand *Bull. Soc. Chim. Fr.* **1987**, 1027.
[570]Barluenga; Alonso-Cires; Campos; Asensio *Synthesis* **1983**, 53.
[571]Sjöberg; Sjöberg *Acta Chem. Scand.* **1972**, *26*, 275.
[572]Whitesides; Sadowski; Lilburn *J. Am. Chem. Soc.* **1974**, *96*, 2829.
[573]Olah; Halpern; Lin *Synthesis* **1975**, 315. For another synthesis of di-*t*-butyl ether, see Masada; Yonemitsu; Hirota *Tetrahedron Lett.* **1979**, 1315.
[574]Masada; Sakajiri *Bull. Chem. Soc. Jpn.* **1978**, *51*, 866.
[575]For a review of reactions in which alcohols serve as nucleophiles, see Salomaa; Kankaanperä; Pihlaja, in Patai *The Chemistry of the Hydroxyl Group*, pt. 1; Wiley: New York, 1971, pp. 454-466.
[576]Biordi; Moelwyn-Hughes, *J. Chem. Soc.* **1962**, 4291.

with phenols and an amine such as pyridine.[577] 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.[578]

gem-Dihalides react with alkoxides to give acetals, and 1,1,1-trihalides give ortho esters.[579] Both aryl alkyl and dialkyl ethers can be efficiently prepared with the use of phase transfer catalysis (p. 362)[580] and with micellar catalysis.[581]

Hydroxy groups can be protected[582] 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 (**0-6**). Another protecting group, the 2-methoxyethoxymethyl group (the MEM group), is formed in a similar manner: $RO^- + MeOCH_2CH_2OCH_2Cl \rightarrow ROCH_2OCH_2CH_2OMe$. Both MOM and MEM groups can be cleaved with dialkyl- and diarylboron halides such as Me_2BBr.[583] Phenacyl bromides ($ArCOCH_2Br$) have also been used to protect hydroxy groups.[584] The resulting ethers can easily be hydrolyzed with zinc and acetic acid.
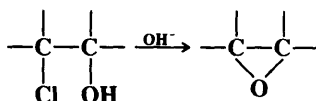
Aryl cyanates[585] can be prepared by reaction of phenols with cyanogen halides in the presence of a base: $ArO^- + ClCN \rightarrow ArOCN + Cl^-$.[586] This reaction has also been applied to certain alkyl cyanates.[587]

Though most Williamson reactions proceed by the S_N2 mechanism, there is evidence (see p. 308) that in some cases the SET mechanism can take place, especially with alkyl iodides.[588]

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; **65,** 68, 173; **68,** 92; **69,** 148.

0-13   Epoxide Formation
         (3)*OC-cyclo*-Alkoxy-de-halogenation

[577]Masada; Oishi *Chem. Lett.* 57, 1978. For another method, see Camps; Coll; Moretó. *Synthesis* **1982,** 186.
[578]Banerjee; Gupta; Singh *J. Chem. Soc., Chem. Commun.* **1982,** 815.
[579]For a review of the formation of ortho esters by this method, see DeWolfe, Ref. 457, pp. 12-18.
[580]For reviews, see Starks; Liotta, Ref. 404, pp. 128-138; Weber; Gokel *Phase Transfer Catalysis in Organic Synthesis*, Ref. 404, pp. 73-84. For the use of phase transfer catalysis to convert, selectively, one OH group of a diol or triol to an ether, see de la Zerda; Barak; Sasson *Tetrahedron* **1989,** *45,* 1533.
[581]Juršić *Tetrahedron* **1988,** *44,* 6677.
[582]For other protecting groups for OH, see Greene, *Protective Groups in Organic Synthesis*; Wiley: New York, 1981, pp. 10-113; Corey; Gras; Ulrich *Tetrahedron Lett.* **1976,** 809 and references cited therein.
[583]Guindon; Yoakim; Morton *J. Org. Chem.* **1984,** *49,* 3912. For other methods, see Williams; Sakdarat *Tetrahedron Lett.* **1983,** *24,* 3965; Hanessian; Delorme; Dufresne *Tetrahedron Lett.* **1984,** *25,* 2515; Rigby; Wilson *Tetrahedron Lett.* **1984,** *25,* 1429.
[584]Hendrickson; Kandall *Tetrahedron Lett.* **1970,** 343.
[585]For reviews of alkyl and aryl cyanates, see Jensen; Holm in Patai *The Chemistry of Cyanates and Their Thio Derivatives,* pt. 1; Wiley: New York, 1977, pp. 569-618; Grigat; Pütter *Angew. Chem. Int. Ed. Engl.* **1967,** *6,* 206-218 [*Angew. Chem.* 79, 219-231].
[586]Grigat; Pütter *Chem. Ber.* **1964,** 97, 3012; Martin; Bauer *Org. Synth. VII,* 435.
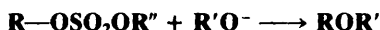[587]Kauer; Henderson *J. Am. Chem. Soc.* **1964,** 86, 4732.
[588]Ashby; Bae; Park; Depriest; Su *Tetrahedron Lett.* **1984,** *25,* 5107.

This is a special case of **0-12**. The base removes the proton from the OH group and the epoxide then attacks in an internal SN2 reaction.[589] Many epoxides have been made in this way.[590] The method can also be used to prepare larger cyclic ethers: five- and six-membered rings. Additional treatment with base yields the glycol (**0-7**).

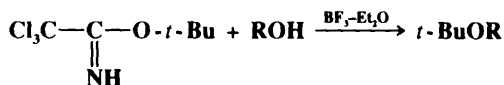OS **I**, 185, 233; **II**, 256; **III**, 835; **VI**, 560; **VII**, 164, 356; **66**, 160.

0-14   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 **0-12** in mechanism and scope. Other inorganic esters can also be used. One of the most common usages of the reaction is the formation of methyl ethers of alcohols and phenols by treatment of alkoxides or aroxides with methyl sulfate. The alcohol or phenol can be methylated directly, by treatment with dimethyl sulfate and alumina in cyclohexane.[591] Carboxylic esters sometimes give ethers when treated with alkoxides (BAL2 mechanism, p. 381) in a very similar process (see also **0-23**).
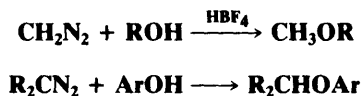
t-Butyl ethers can be prepared by treating the compound *t*-butyl 2,2,2-trichloroacetimidate with an alcohol or phenol in the presence of boron trifluoride etherate.[592]

$$Cl_3C—\overset{\underset{\parallel}{NH}}{C}—O\text{-}t\text{-}Bu + ROH \xrightarrow{BF_3-Et_2O} t\text{-}BuOR$$

OS **I**, 58, 537; **II**, 387, 619; **III**, 127, 564, 800; **IV**, 588; **VI**, 737, 859, **VII**, 41. Also see OS **V**, 431.

0-15   Alkylation with Diazo Compounds
Hydro,alkoxy-de-diazo-bisubstitution

$$CH_2N_2 + ROH \xrightarrow{HBF_4} CH_3OR$$

$$R_2CN_2 + ArOH \longrightarrow R_2CHOAr$$

Reaction with alcohols is general for diazo compounds, but it is most often performed with diazomethane to produce methyl ethers or with diazo ketones to produce α-keto ethers, since these kinds of diazo compounds are most readily available. With diazomethane[593] the method is expensive and requires great caution. It is used chiefly to methylate alcohols and phenols that are expensive or available in small amounts, since the conditions are mild and high yields are obtained. Hydroxy compounds react better as their acidity increases; ordinary alcohols do not react at all unless a catalyst such as HBF_4[594] or silica gel[595] is present. The more acidic phenols react very well in the absence of a catalyst. Oximes, and ketones that

[589]See, for example, Swain; Ketley; Bader *J. Am. Chem. Soc.* **1959**, *81*, 2353; Knipe *J. Chem. Soc., Perkin Trans. 2* **1973**, 589.
[590]For a review, see Berti *Top. Stereochem.* **1973**, 7, 93-251, pp. 187-209.
[591]Ogawa; Ichimura; Chihara; Teratani; Taya *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2481.
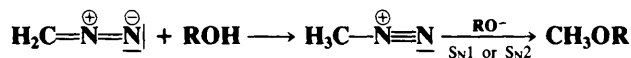[592]Armstrong; Brackenridge; Jackson; Kirk *Tetrahedron Lett.* **1988**, *29*, 2483.
[593]For a review of diazomethane, see Pizey *Synthetic Reagents*, vol. 2; Wiley: New York, 1974, pp. 65-142.
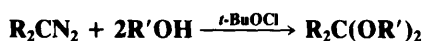[594]Neeman; Caserio; Roberts; Johnson *Tetrahedron* **1959**, *6*, 36.
[595]Ohno; Nishiyama; Nagase *Tetrahedron Lett.* **1979**, 4405; Ogawa; Hagiwara; Chihara; Teratani; Taya *Bull. Chem. Soc. Jpn.* **1987**, *60*, 627.

have substantial enolic contributions, give O-alkylation to form, respectively, O-alkyl oximes and enol ethers. The mechanism[596] is as in **0-5**:

$$H_2C\overset{\oplus}{=}N\overset{\ominus}{=}\underline{N}| + ROH \longrightarrow H_3C\overset{\oplus}{-}N\equiv N \xrightarrow[-\ S_N1\ or\ S_N2]{RO^-} CH_3OR$$
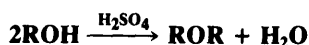
Diazoalkanes can also be converted to ethers by thermal or photochemical cleavage in the presence of an alcohol. These are carbene or carbenoid reactions.[597] Similar intermediates are involved when diazoalkanes react with alcohols in the presence of t-BuOCl to give acetals.[598]
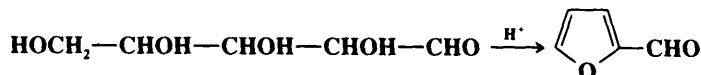
$$R_2CN_2 + 2R'OH \xrightarrow{\ t\text{-BuOCl}\ } R_2C(OR')_2$$

OS **V**, 245. Also see OS **V**, 1099.

0-16   Dehydration of Alcohols
       Alkoxy-de-hydroxylation

$$2ROH \xrightarrow{\ H_2SO_4\ } ROR + H_2O$$

The dehydration of alcohols to form ethers[599] is analogous to **0-12** and **0-14**, 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.[600]

The ether prepared is symmetrical. Mixed 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.[601] If one group is not tertiary, the reaction of a mixture of two alcohols leads to all three possible ethers. Diols can be converted to cyclic ethers,[602] though the reaction is most successful for five-membered rings. Thus, 1,6-hexanediol gives mostly 2-ethyltetrahydrofuran. However, 5-, 6-, and 7-membered rings have been prepared with $AlPO_4$–Al_2O_3,[603] with $BuSnCl_3$,[604] and with a Nafion-H acid catalyst[605] (the last-named reagent was also used to make an 8-membered ring). This reaction is also important in preparing furfural derivatives from aldoses, with concurrent elimination:

$$HOCH_2—CHOH—CHOH—CHOH—CHO \xrightarrow{\ H^+\ } \underset{O}{\underset{\fbox{}}{}}-CHO$$

[596]Kreevoy; Thomas *J. Org. Chem.* **1977**, *42*, 3979. See also McGarrity; Smyth *J. Am. Chem. Soc.* **1980**, *102*, 7303.

[597]Bethell; Howard *J. Chem. Soc. B* **1969**, 745; Bethell; Newall; Whittaker *J. Chem. Soc. B* **1971**, 23; Noels; Demonceau; Petiniot; Hubert; Teyssié *Tetrahedron* **1982**, *38*, 2733.

[598]Baganz; May *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 420 [*Angew. Chem. 78*, 448].

[599]For a review, see Ref. 567, pp. 457-460, 468-470.

[600]Toda; Takumi; Akehi *J. Chem. Soc., Perkin Trans. 2* **1990**, 1270.

[601]See, for example, Jenner *Tetrahedron Lett.* **1988**, *29*, 2445.

[602]For a list of reagents, with references, see Ref. 508, pp. 449-450.

[603]Costa; Riego *Synth. Commun.* **1987**, *17*, 1373.

[604]Tagliavini; Marton; Furlani *Tetrahedron* **1989**, *45*, 1187.

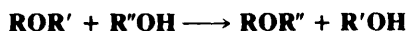[605]Olah; Fung; Malhotra *Synthesis* **1981**, 474.

Phenols and primary alcohols form ethers when heated with dicyclohexylcarbo-diimide[606] (see **0-22**). 1,2-Diols can be converted to epoxides by treatment with dimethylformamide dimethyl acetal [$(MeO)_2CHNMe_2$],[607] with diethyl azodicarboxylate [$EtOOCN\!=\!NCOOEt$] and Ph_3P,[608] with a dialkoxytriphenylphosphorane,[609] or with $TsCl-NaOH-PhCH_2NEt_3{}^+ Cl^-$.[610]

OS **I**, 280; **II**, 126; **IV**, 25, 72, 266, 350, 393, 534; **V**, 539, 1024; **VI**, 887; **69**, 205. Also see OS **V**, 721.

0-17 Transetherification
Hydroxy-de-alkoxylation
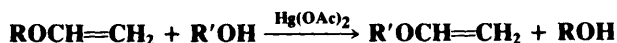**Alkoxy-de-hydroxylation**

$$ROR' + R''OH \longrightarrow ROR'' + R'OH$$

The exchange of one alkoxy group for another is very rare for *ethers*, though it has been accomplished with reactive R, for example, diphenylmethyl with *p*-toluenesulfonic acid as a catalyst,[611] and by treatment of alkyl aryl ethers with alkoxide ions: $ROAr + R'O^- \rightarrow ROR' + ArO^-$.[612] However, acetals and ortho esters undergo transetherification readily,[613] for example,[614]

$$ClCH_2\overset{\displaystyle OEt}{\underset{\displaystyle OEt}{CH}} + \underset{\underset{\displaystyle OH}{|}}{CH_2}\!-\!\underset{\underset{\displaystyle OH}{|}}{CH_2} \longrightarrow ClCH_2\overset{\displaystyle O\!-\!CH_2}{\underset{\displaystyle O\!-\!CH_2}{CH}} + 2EtOH$$

because, as we have seen (**0-6**), departure of the leaving group from an acetal gives a particularly stable carbocation. 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,[615] e.g.,

$$ROCH\!=\!CH_2 + R'OH \xrightarrow{\ Hg(OAc)_2\ } R'OCH\!=\!CH_2 + ROH$$

1,2-Diketones can be converted to α-keto enol ethers by treatment with an alkoxytrimethylsilane $ROSiMe_3$.[616]

OS **VI**, 298, 491, 584, 606, 869; **VII**, 334; **65**, 32; **68**, 92. Also see OS **V**, 1080, 1096.

[606]Vowinkel *Chem. Ber.* **1962**, *95*, 2997, **1963**, *96*, 1702, **1966**, *99*, 42.
[607]Neumann *Chimia* **1969**, *23*, 267.
[608]Guthrie; Jenkins; Yamasaki; Skelton; White *J. Chem. Soc., Perkin Trans. 1* **1981**, 2328 and references cited therein. For a review of diethyl azodicarboxylate-Ph_3P, see Mitsunobu *Synthesis* **1981**, 1-28.
[609]Robinson; Barry; Kelly; Evans *J. Am. Chem. Soc.* **1985**, *107*, 5210; Kelly; Evans *J. Org. Chem.* **1986**, *51*, 5490. See also Hendrickson; Hussoin *Synlett* **1990**, 423.
[610]Szeja *Synthesis* **1985**, 983.
[611]Pratt; Draper *J. Am. Chem. Soc.* **1949**, *71*, 2846.
[612]Zoltewicz; Sale *J. Org. Chem.* **1970**, *35*, 3462.
[613]For reviews, see Ref. 575, pp. 458-463; DeWolfe, Ref. 457, pp. 18-29, 146-148.
[614]McElvain; Curry *J. Am. Chem. Soc.* **1948**, *70*, 3781.
[615]Watanabe; Conlon *J. Am. Chem. Soc.* **1957**, *79*, 2828; Büchi; White *J. Am. Chem. Soc.* **1964**, *86*, 2884. For a review, see Shostakovskii; Trofimov; Atavin; Lavrov *Russ. Chem. Rev.* **1968**, *37*, 907-919. For a discussion of the mechanism, see Gareev *J. Org. Chem. USSR* **1982**, *18*, 36.
[616]Ponaras; Meah *Tetrahedron Lett.* **1986**, *27*, 4953.

0-18   Alcoholysis of Epoxides
    (3)OC-seco-Alkoxy-de-alkoxylation

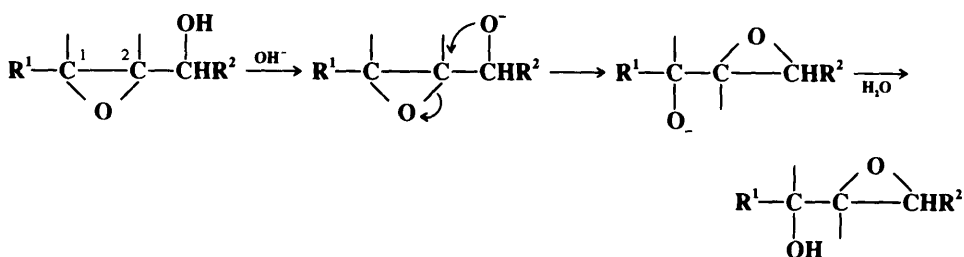$$-\overset{|}{\underset{\underset{O}{\diagup}}{C}}-\overset{|}{\underset{}{C}}- \; + \; \underset{ROH}{\overset{RO^-}{\text{or}}} \longrightarrow -\overset{|}{\underset{\underset{OH}{|}}{C}}-\overset{|}{\underset{OR}{|}}{C}-$$

This reaction is analogous to **0-7**. It may be acid, base, or alumina[617] catalyzed, and may occur by either an S_N1 or S_N2 mechanism. Many of the β-hydroxy ethers produced in this way are valuable solvents, for example, diethylene glycol, Cellosolve, etc. Aziridines can similarly be converted to β-amino ethers.[618]

$$-\overset{|}{\underset{\underset{N}{\diagup}}{C}}-\overset{|}{\underset{}{C}}- \; \xrightarrow[ROH]{H^+} \; -\overset{|}{\underset{\underset{\oplus}{|}}{C}}-\overset{|}{\underset{OR}{|}}{C}- \; \xrightarrow{-H^+} \; -\overset{|}{\underset{\underset{NH_2}{|}}{C}}-\overset{|}{\underset{OR}{|}}{C}-$$

In the *Payne rearrangement*, a 2,3-epoxy alcohol is converted to an isomeric one, by treatment with aqueous base:[619]

$$R^1-\overset{|}{\underset{\underset{O}{\diagup}}{C}}-\overset{2}{\underset{}{C}}-\overset{OH}{\underset{}{CHR^2}} \xrightarrow{OH^-} R^1-\overset{|}{C}-\overset{O^-}{\underset{\underset{O}{\diagup}}{C}}-CHR^2 \longrightarrow R^1-\overset{|}{\underset{\underset{O_-}{|}}{C}}-\overset{O}{\underset{}{\diagup}}\overset{O}{\diagdown}{C}-CHR^2 \xrightarrow{H_2O}$$

$$R^1-\overset{|}{\underset{\underset{OH}{|}}{C}}-\overset{O}{\underset{}{\diagup}}\overset{O}{\diagdown}{C}-CHR^2$$

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.

0-19   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.[620] Quaternary ammonium salts can sometimes also be used.[621]
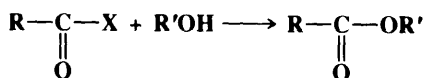   OS **65**, 140; **66**, 29.

[617]See Posner; Rogers *J. Am. Chem. Soc.* **1977**, *99*, 8208, 8214.
[618]For a review, see Dermer; Ham, Ref. 437, pp. 224-227, 256-257.
[619]Payne *J. Org. Chem.* **1962**, *27*, 3819; Behrens; Ko; Sharpless; Walker *J. Org. Chem.* **1985**, *50*, 5687.
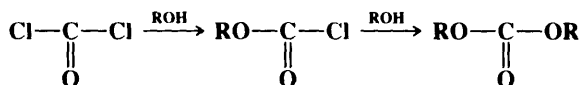[620]Granik; Pyatin; Glushkov, Ref. 339, p. 749.
[621]For an example, see Vogel; Büchi *Org. Synth.* **66**, 29.

D.   Attack by OR at an Acyl Carbon

0-20   Alcoholysis of Acyl Halides
Alkoxy-de-halogenation

$$R-\underset{\underset{O}{\|}}{C}-X + R'OH \longrightarrow R-\underset{\underset{O}{\|}}{C}-OR'$$

The reaction between acyl halides and alcohols or phenols is the best general method for the preparation of carboxylic esters. The reaction is of wide scope, and many functional groups do not interfere. A base is frequently added to combine with the HX formed. When aqueous alkali is used, this is called the *Schotten–Baumann procedure*, but pyridine is also frequently used. Both R and R' may be primary, secondary, or tertiary alkyl or aryl. Enolic esters can also be prepared by this method, though C-acylation competes in these cases. In difficult cases, especially with hindered acids or tertiary R', the alkoxide can be used instead of the alcohol.[622] Activated alumina has also been used as a catalyst, for tertiary R'.[623] Thallium salts of phenols give very high yields of phenolic esters.[624] Phase transfer catalysis has been used for hindered phenols.[625]
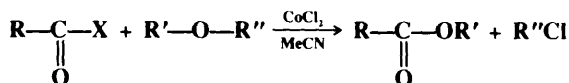
When phosgene is the acyl halide, haloformic esters or carbonates can be obtained.

$$Cl-\underset{\underset{O}{\|}}{C}-Cl \xrightarrow{ROH} RO-\underset{\underset{O}{\|}}{C}-Cl \xrightarrow{ROH} RO-\underset{\underset{O}{\|}}{C}-OR$$

An important example is the preparation of carbobenzoxy chloride ($PhCH_2OCOCl$) from phosgene and benzyl alcohol. This compound is widely used for protection of amino groups during peptide synthesis (see **0-52**).
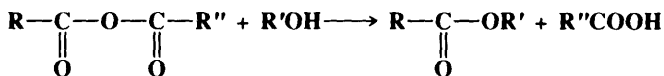
As with **0-8**, the mechanism can be S_N1 or tetrahedral.[502] Pyridine catalyzes the reaction by the nucleophilic catalysis route (see **0-9**).

Acyl halides can also be converted to carboxylic acids by using ethers instead of alcohols, in MeCN in the presence of certain catalysts such as cobalt(II) chloride.[626]

$$R-\underset{\underset{O}{\|}}{C}-X + R'-O-R'' \xrightarrow[\text{MeCN}]{CoCl_2} R-\underset{\underset{O}{\|}}{C}-OR' + R''Cl$$

This is a method for the cleavage of ethers (see also **0-68**).

OS **I**, 12; **III**, 142, 144, 167, 187, 623, 714; **IV**, 84, 263, 478, 479, 608, 616, 788; **V**, 1, 166, 168, 171; **VI**, 199, 259, 312, 824. **VII**, 190; **65**, 203; **69**, 1.

0-21   Alcoholysis of Anhydrides
Alkoxy-de-acyloxy-substitution

$$R-\underset{\underset{O}{\|}}{C}-O-\underset{\underset{O}{\|}}{C}-R'' + R'OH \longrightarrow R-\underset{\underset{O}{\|}}{C}-OR' + R''COOH$$

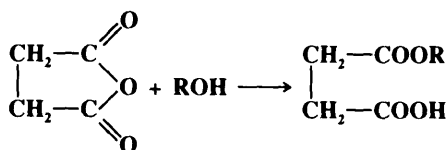[622]For an example, see Kaiser; Woodruff, *J. Org. Chem.* **1970**, *35*, 1198.
[623]Nagasawa; Yoshitake; Amiya; Ito *Synth. Commun.* **1990**, *20*, 2033.
[624]Taylor, McLay; McKillop *J. Am. Chem. Soc.* **1968**, *90*, 2422.
[625]Illi, *Tetrahedron Lett.* **1979**, 2431. For another method, see Nekhoroshev; Ivakhnenko; Okhlobystin *J. Org. Chem. USSR* **1977**, *13*, 608.
[626]See Ahmad; Iqbal *Chem. Lett.* **1987**, 953, and references cited therein.

The scope of this reaction is similar to that of **0-20**. Though anhydrides are somewhat less reactive than acyl halides, they are often used to prepare carboxylic esters. Acids, Lewis acids, and bases are often used as catalysts—most often, pyridine.[627] Catalysis by pyridine is of the nucleophilic type (see **0-9**). 4-(N,N-Dimethylamino)pyridine is a better catalyst than pyridine and can be used in cases where pyridine fails.[628] A nonbasic catalyst is cobalt(II) chloride.[629] Formic anhydride is not a stable compound but esters of formic acid can be prepared by treating alcohols[630] or phenols[631] with acetic–formic anhydride. Cyclic anhydrides give monoesterified dicarboxylic acids, for example,
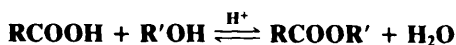
$$
\begin{array}{l}
CH_2-C\diagup^{\textstyle O}\diagdown_{\textstyle O} \\
\qquad\qquad\qquad + \ ROH \ \longrightarrow \\
CH_2-C\diagdown_{\textstyle O}
\end{array}
\qquad
\begin{array}{l}
CH_2-COOR \\
\ | \\
CH_2-COOH
\end{array}
$$

Alcohols can also be acylated by mixed organic-inorganic anhydrides, such as acetic-phosphoric anhydride $MeCOOPO(OH)_2$[632] (see **0-33**).

OS **I**, 285, 418; **II**, 69, 124; **III**, 11, 127, 141, 169, 237, 281, 428, 432, 690, 833; **IV**, 15, 242, 304; **V**, 8, 459, 591, 887; **VI**, 121, 245, 560, 692; **67**, 76; **69,** 19.

0-22   Esterification of Carboxylic Acids
Alkoxy-de-hydroxylation

$$
\textbf{RCOOH + R'OH} \xrightleftharpoons{\ H^+\ } \textbf{RCOOR' + H}_2\textbf{O}
$$

The esterification of carboxylic acids with alcohols[633] is the reverse of **0-11** and can be accomplished only if a means is available to drive the equilibrium to the right.[634] There are many ways of doing this, among which are: (1) addition of an excess of one of the reactants, usually the alcohol; (2) removal of the ester or the water by distillation; (3) removal of water by azeotropic distillation; and (4) removal of water by use of a dehydrating agent or a molecular sieve. When R' is methyl, the most common way of driving the equilibrium is by adding excess MeOH; when R' is ethyl, it is preferable to remove water by azeotropic distillation.[635] The most common catalysts are H_2SO_4 and TsOH, though some reactive acids (e.g., formic,[636] trifluoroacetic[637]) do not require a catalyst. Besides methyl and ethyl, R' may be other primary or secondary alkyl groups, but tertiary alcohols usually give carbocations and elimination. Phenols can sometimes be used to prepare phenolic esters, but yields are generally very low.

[627]For a list of catalysts, with references, see Ref. 508, pp. 980-981.
[628]For reviews, see Scriven *Chem. Soc. Rev.* **1983**, *12*, 129-161; Höfle; Steglich; Vorbrüggen *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 569-583 [*Angew. Chem. 90*, 602-615].
[629]Ahmad; Iqbal *J. Chem. Soc., Chem. Commun.* **1987**, 114.
[630]For example, see Stevens; van Es *Recl. Trav. Chim. Pays-Bas*, **1964**, *83*, 1287; van Es; Stevens *Recl. Trav. Chim. Pays-Bas* **1965**, *84*, 704.
[631]For example, see Stevens; van Es *Recl. Trav. Chim. Pays-Bas* **1964**, *83*, 1294; Sōfuku; Muramatsu; Hagitani *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2942.
[632]Fatiadi *Carbohydr. Res.* **1968**, *6*, 237.
[633]For a review of some methods, see Haslam *Tetrahedron* **1980**, *36*, 2409-2433.
[634]For a list of reagents, with references, see Ref. 508, pp. 966-972.
[635]Newman *An Advanced Organic Laboratory Course*; Macmillan: New York, 1972, pp. 8-10.
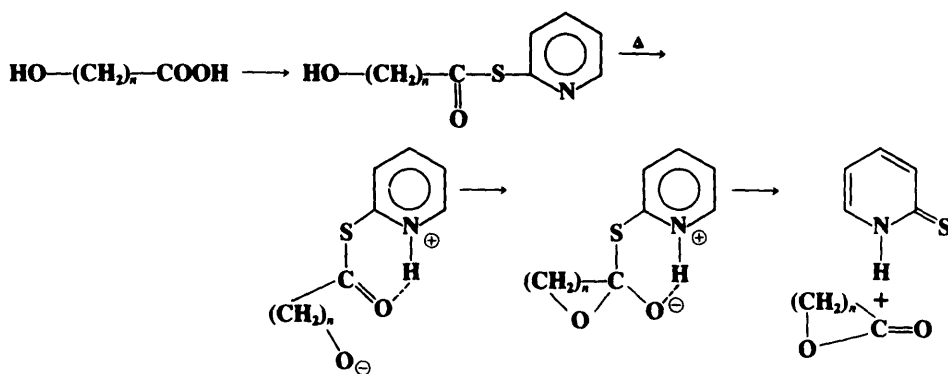[636]Formates can be prepared if diisopropyl ether is used to remove water by azeotropic distillation: Werner, *J. Chem. Res. (S)* **1980**, 196.
[637]Johnston; Knipe; Watts *Tetrahedron Lett.* **1979**, 4225.

γ- and δ-hydroxy acids are easily lactonized by treatment with acids, or often simply on standing, but larger and smaller lactone rings cannot be made in this manner, because

$$CH_3-CH-CH_2-CH_2-COOH \longrightarrow$$
$$\quad\quad\quad |$$
$$\quad\quad OH$$

polyester formation occurs more readily.[638] Often the conversion of a group such as keto or halogen, γ or δ to a carboxyl group, to a hydroxyl group gives the lactone directly, since the hydroxy acid cyclizes too rapidly for isolation. β-Substituted β-hydroxy acids can be converted to β-lactones by treatment with benzenesulfonyl chloride in pyridine at 0 to 5°C.[639] ε-Lactones (seven-membered rings) have been made by cyclization of ε-hydroxy acids at high dilution.[640] Macrocyclic lactones[641] can be prepared indirectly in very good yields by conversion of the hydroxy acids to 2-pyridinethiol esters and adding these to refluxing xylene.[642]

$$HO-(CH_2)_n-COOH \longrightarrow$$

A closely related method, which often gives higher yields, involves treatment of the hydroxy acids with 1-methyl- or 1-phenyl-2-halopyridinium salts, especially 1-methyl-2-chloropyridinium iodide (*Mukaiyama's reagent*).[643] Another method uses organotin oxides.[644]

[638]For a review of the synthesis of lactones and lactams, see Wolfe; Ogliaruso, in Patai *The Chemistry of Acid Derivatives*, pt. 2; Wiley: New York, 1979, pp. 1062-1330. For a list of methods for converting hydroxy acids to lactones, with references, see Ref. 508, pp. 941-943.

[639]Adam; Baeza; Liu *J. Am. Chem. Soc.* **1972**, *94*, 2000. For other methods of converting β-hydroxy acids to β-lactones, see Merger *Chem. Ber.* **1968**, *101*, 2413; Blume *Tetrahedron Lett.* **1969**, 1047.

[640]Lardelli; Lamberti; Weller; de Jonge *Recl. Trav. Chim. Pays-Bas* **1967**, *86*, 481.

[641]For reviews on the synthesis of macrocyclic lactones, see Nicolaou *Tetrahedron* **1977**, *33*, 683-710; Back *Tetrahedron* **1977**, *33*, 3041-3059; Masamune; Bates; Corcoran *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 585-607 [*Angew. Chem. 89*, 602-624].
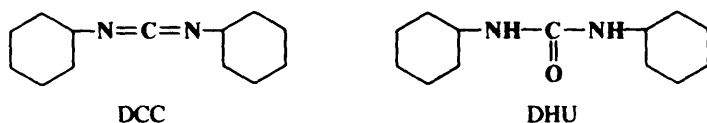
[642]Corey; Nicolaou; Melvin *J. Am. Chem. Soc.* **1975**, *97*, 653, 655; Corey; Brunelle; Stork *Tetrahedron Lett.* **1976**, 3405; Corey; Brunelle; *Tetrahedron Lett.* **1976**, 3409; Wollenberg; Nimitz; Gokcek *Tetrahedron Lett.* **1980**, *21*, 2791; Thalmann; Oertle; Gerlach *Org. Synth. VII*, 470. See also Schmidt; Heermann *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 308 [*Angew. Chem. 91*, 330].

[643]For a review of reactions with this and related methods, see Mukaiyama *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 707-721 [*Angew. Chem. 91*, 798-812].
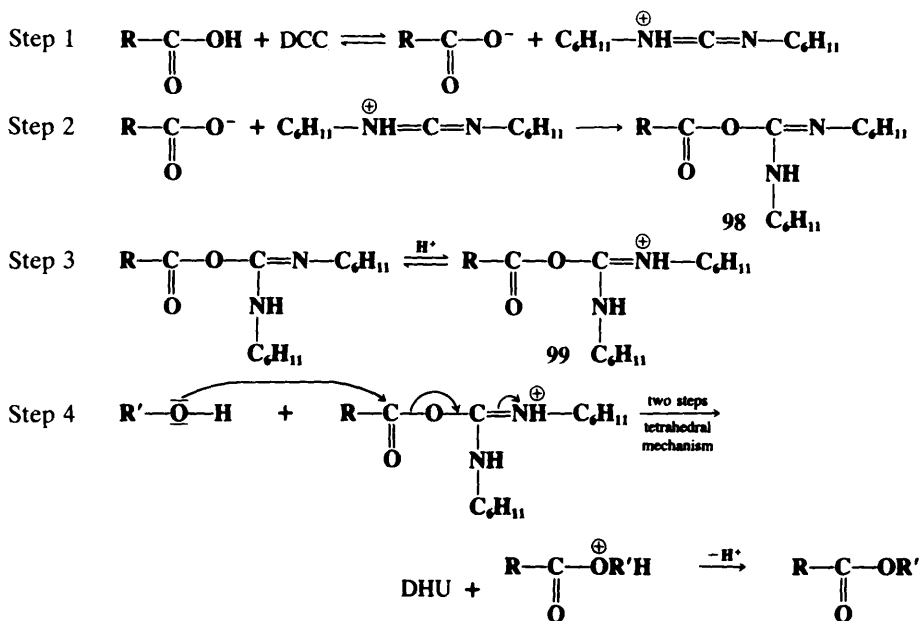
[644]Steliou; Szczygielska-Nowosielska; Favre; Poupart; Hanessian *J. Am. Chem. Soc.* **1980**, *102*, 7578; Steliou; Poupart *J. Am. Chem. Soc.* **1983**, *105*, 7130. For some other methods, see Masamune; Kamata; Schilling *J. Am. Chem. Soc.* **1975**, *97*, 3515; Scott; Naples *Synthesis* **1976**, 738; Kurihara; Nakajima; Mitsunobu *Tetrahedron Lett.* **1976**, 2455; Corey; Brunelle; Nicolaou *J. Am. Chem. Soc.* **1977**, *99*, 7359; Vorbrüggen; Krolikiewicz *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 876 [*Angew. Chem. 89*, 914]; Nimitz; Wollenberg *Tetrahedron Lett.* **1978**, 3523; Inanaga; Hirata; Saeki; Katsuki; Yamaguchi *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989; Venkataraman; Wagle *Tetrahedron Lett.* **1980**, *21*, 1893; Schmidt; Dietsche *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 771 [*Angew. Chem. 93*, 786]; Taniguchi; Kinoshita; Inomata; Kotake *Chem. Lett.* **1984**, 1347; Cossy; Pete *Bull. Soc. Chim. Fr.* **1988**, 989.

Esterification is catalyzed by acids (not bases) in ways that were discussed on p. 379.[525] The mechanisms are usually $A_{AC}2$, but $A_{AC}1$ and $A_{AL}1$ have also been observed.[645] Certain acids, such as 2,6-di-ortho-substituted benzoic acids, cannot be esterified by the $A_{AC}2$ mechanism because of steric hindrance (p. 340). In such cases, esterification can be accomplished by dissolving the acid in 100% H_2SO_4 (forming the ion RCO^+) and pouring the solution into the alcohol ($A_{AC}1$ mechanism). The reluctance of hindered acids to undergo the normal $A_{AC}2$ mechanism can sometimes be put to advantage when, in a molecule containing two COOH groups, only the less hindered one is esterified. The $A_{AC}1$ pathway cannot be applied to unhindered carboxylic acids.

Another way to esterify a carboxylic acid is to treat it with an alcohol in the presence of a dehydrating agent.[634] One of these is dicyclohexylcarbodiimide (DCC), which is converted

in the process to dicyclohexylurea (DHU). The mechanism[646] has much in common with the nucleophilic catalysis mechanism; the acid is converted to a compound with a better leaving group. However, the conversion is not by a tetrahedral mechanism (as it is in nucleophilic catalysis), since the C—O bond remains intact during this step:

Evidence for this mechanism was the preparation of O-acylureas similar to **98** and the finding that when catalyzed by acids they react with alcohols to give esters.[647]

[645]For a review of aspects of the mechanism, see Ref. 575, pp. 466-481.
[646]Smith; Moffatt; Khorana *J. Am. Chem. Soc.* **1958**, *80*, 6204; Balcom; Petersen *J. Org. Chem.* **1989**, *54*, 1922.
[647]Doleschall; Lempert *Tetrahedron Lett.* **1963**, 1195.

However, there are limitations to the use of DCC; yields are variable and N-acyl-ureas are side products. Many other dehydrating agents[648] have been used, including an alkyl chloroformate and Et₃N,[649] pyridinium salts–Bu₃N,[643] phenyl dichlorophos-phate PhOPOCl₂,[650] DCC and an aminopyridine,[651] 2-chloro-1,3,5-trinitrobenzene and pyridine,[652] di-2-pyridyl carbonate,[653] polystyryl diphenylphosphine,[654] (trimethyl-silyl)ethoxyacetylene,[655] 1,1'-carbonylbis(3-methylimidazolium) triflate (CBMIT),[656] Am-berlyst-15,[657] diethyl azodicarboxylate EtOOCN=NCOOEt and Ph₃P[658] (when these re-agents are used the procedure is called the *Mitsunobu esterification reaction*[659]), chlorosulfonyl isocyanate ClSO₂NCO,[660] chlorosilanes,[661] MeSO₂Cl–Et₃N,[662] Ph₃P–CCl₄–

100   **101**

Et₃N,[663] and N,N'-carbonyldiimidazole (**100**).[664] In the latter case easily alcoholyzed im-idazolides (**101**) are intermediates. BF₃ promotes the esterification by converting the acid to RCO⁺ BF₃OH⁻, so the reaction proceeds by an AAc1 type of mechanism. The use of BF₃–etherate is simple and gives high yields.[665] Carboxylic esters can also be prepared by treating carboxylic acids with *t*-butyl ethers and acid catalysts.[666]

$$\text{RCOOH} + t\text{-Bu-OR}' \longrightarrow \text{RCOOR}' + \text{H}_2\text{C}=\text{CMe}_2 + \text{H}_2\text{O}$$

Carboxylic acids can be converted to *t*-butyl esters by treatment with *t*-butyl 2,2,2-trichlo-roacetimidate (see **0-14**) and BF₃–Et₂O.[592]

OS **I**, 42, 138, 237, 241, 246, 254, 261, 451; **II**, 260, 264, 276, 292, 365, 414, 526; **III**, 46, 203, 237, 381, 413, 526, 531, 610; **IV**, 169, 178, 302, 329, 390, 398, 427, 506, 532, 635, 677; **V**, 80, 762, 946; **VI**, 471, 797; **VII**, 93, 99, 210, 319, 356, 386, 470; **66**, 22, 142; **67**, 76. Also see OS **III**, 536, 742.

[648]For a list of many of these with references, see Arrieta; García; Lago; Palomo *Synth. Commun.* **1983**, *13*, 471.
[649]Kim; Lee; Kim *J. Org. Chem.* **1985**, *50*, 560.
[650]Liu; Chan; Lee *Tetrahedron Lett.* **1978**, 4461. García; Arrieta; Palomo *Synth. Commun.* **1982**, *12*, 681. See also Ueda; Oikawa *J. Org. Chem.* **1985**, *50*, 760.
[651]Hassner; Alexanian *Tetrahedron Lett.* **1978**, 4475; Neises; Steglich *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 522 [*Angew. Chem. 90*, 556]; Boden; Keck *J. Org. Chem.* **1985**, *50*, 2394.
[652]Takimoto; Inanaga; Katsuki; Yamaguchi *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1470. See also Kim; Yang *Synth. Commun.* **1981**, *11*, 121; Takimoto; Abe; Kodera; Ohta *Bull. Chem. Soc. Jpn.* **1983**, *56*, 639.
[653]Kim; Lee; Ko *Tetrahedron Lett.* **1984**, *25*, 4943. For a review of 2-pyridyl reagents, see Kim *Org. Prep. Proced. Int.* **1988**, *20*, 145-172.
[654]Caputo; Corrado; Ferreri; Palumbo *Synth. Commun.* **1986**, *16*, 1081.
[655]Kita; Akai; Yamamoto; Taniguchi; Tamura *Synthesis* **1989**, 334.
[656]Saha; Schultz; Rapoport *J. Am. Chem. Soc.* **1989**, *111*, 4856.
[657]Petrini; Ballini; Marcantoni; Rosini *Synth. Commun.* **1988**, *18*, 847.
[658]Mitsunobu; Yamada *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380; Camp; Jenkins *Aust. J. Chem.* **1988**, *41*, 1835.
[659]For discussions of the mechanism, see Varasi; Walker; Maddox *J. Org. Chem.* **1987**, *52*, 4235; Hughes; Reamer; Bergan; Grabowski *J. Am. Chem. Soc.* **1988**, *110*, 6487; Crich; Dyker; Harris *J. Org. Chem.* **1989**, *54*, 257; Camp; Jenkins *J. Org. Chem.* **1989**, *54*, 3045, 3049.
[660]Keshavamurthy; Vankar; Dhar *Synthesis* **1982**, 506. For a review of ClSO₂NCO, see Dhar; Murthy *Synthesis* **1988**, 437-450.
[661]Nakao; Oka; Fukumoto *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1267; Brook; Chan *Synthesis* **1983**, 201.
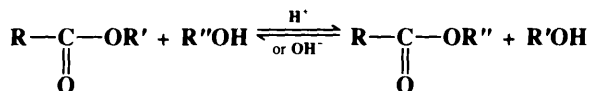[662]Chandrasekaran; Turner *Synth. Commun.* **1982**, *12*, 727.
[663]Hashimoto; Furukawa *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2227; Ramaiah *J. Org. Chem.* **1985**, *50*, 4991.
[664]For a review, see Staab; Rohr *Newer Methods Prep. Org. Chem.* **1968**, *5*, 61-108. See also Morton; Mangroo; Gerber *Can. J. Chem.* **1988**, *66*, 1701.
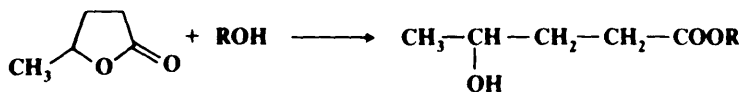[665]For examples, see Marshall; Erickson; Folsom *Tetrahedron Lett.* **1970**, 4011; Kadaba *Synthesis* **1972**, 628, *Synth. Commun.* **1974**, *4*, 167.
[666]Derevitskaya; Klimov; Kochetkov *Tetrahedron Lett.* **1970**, 4269. See also Mohacsi *Synth. Commun.* **1982**, *12*, 453.

0-23   Alcoholysis of Carboxylic Esters. Transesterification
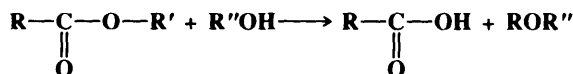**Alkoxy-de-alkoxylation**

$$R\text{—}\underset{\underset{O}{\|}}{C}\text{—}OR' + R''OH \underset{\text{or OH}^-}{\overset{H^{\cdot}}{\rightleftharpoons}} R\text{—}\underset{\underset{O}{\|}}{C}\text{—}OR'' + R'OH$$

Transesterification is catalyzed[667] by acids or bases.[668] It is an equilibrium reaction and must be shifted in the desired direction. In many cases low-boiling esters can be converted to higher-boiling ones by the distillation of the lower-boiling alcohol as fast as it is formed. This reaction has been used as a method for the acylation of a primary OH in the presence of a secondary OH: The diol is treated with ethyl acetate in the presence of Woelm neutral alumina.[669] Regioselectivity has also been accomplished by using enzymes (lipases) as catalysts.[670] Lactones are easily opened by treatment with alcohols to give open-chain hydroxy esters:

$$\underset{CH_3}{\overset{\diagdown}{\bigcirc}}\!\!\!\diagup\!\!\!\diagdown_O\!\!\diagup\!\!\!\diagdown_O + ROH \longrightarrow CH_3\text{—}\underset{\underset{OH}{|}}{CH}\text{—}CH_2\text{—}CH_2\text{—}COOR$$

Transesterification has been caried out with phase-transfer catalysis, without an added solvent.[671] In another procedure, RCOOR' are converted to RCOOR'' by treatment of the ester and an alcohol R''OH with n-BuLi, which converts the R''OH to R''OLi.[672]

Transesterification occurs by mechanisms[673] that are identical with those of ester hydrolysis—except that ROH replaces HOH—that is, by the acyl–oxygen fission mechanisms. When alkyl fission takes place, the products are the *acid* and the *ether*:

$$R\text{—}\underset{\underset{O}{\|}}{C}\text{—}O\text{—}R' + R''OH \longrightarrow R\text{—}\underset{\underset{O}{\|}}{C}\text{—}OH + ROR''$$

Therefore, transesterification reactions frequently fail when R' is tertiary, since this type of substrate most often reacts by alkyl–oxygen cleavage. In such cases, the reaction is of the Williamson type with OCOR as the leaving group (see **0-14**).

With enol esters, the free alcohol is the enol of a ketone, so such esters easily undergo the reaction

$$CH_2\!\!=\!\!\underset{\underset{CH_3}{|}}{C}\text{—}OCOR + R'OH \longrightarrow RCOOR' + CH_2\!\!=\!\!\underset{\underset{CH_3}{|}}{C}\text{—}OH \rightleftharpoons CH_3\text{—}\underset{\underset{CH_3}{|}}{C}\!\!=\!\!O$$

[667]For a list of catalysts, with references, see Ref. 508, pp. 985-987.
[668]For some methods of transesterification under neutral conditions, see Bittner, Barneis; Felix *Tetrahedron Lett.* **1975**, 3871; Hashimoto; Furukawa; Kuroda *Tetrahedron Lett.* **1980**, *21*, 2857; Olah; Narang; Salem; Gupta *Synthesis* **1981**, 142; Otera; Yano; Kawabata; Nozaki *Tetrahedron Lett.* **1986**, *27*, 2383; Imwinkelried; Schiess; Seebach *Org. Synth.* **65**, 230.
[669]Posner; Oda *Tetrahedron Lett.* **1981**, *22*, 5003; Rana; Barlow; Matta *Tetrahedron Lett.* **1981**, *22*, 5007. See also Costa; Riego *Can. J. Chem.* **1987**, *65*, 2327.
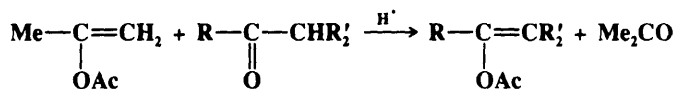[670]Therisod; Klibanov *J. Am. Chem. Soc.* **1987**, *109*, 3977. See also Wang; Lalonde; Momongan; Bergbreiter; Wong *J. Am. Chem. Soc.* **1988**, *110*, 7200.
[671]Barry; Bram; Petit *Tetrahedron Lett.* **1988**, *29*, 4567. See also Nishiguchi; Taya *J. Chem. Soc., Perkin Trans. 1* **1990**, 172.
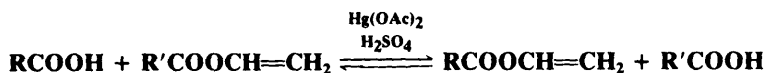[672]Meth-Cohn *J. Chem. Soc., Chem. Commun.* **1986**, 695.
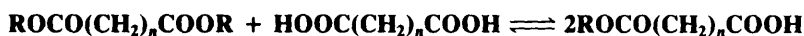[673]For a review, see Koskikallio, in Patai, Ref. 197, pp. 103-136.

Hence, enol esters such as isopropenyl acetate are good acylating agents for alcohols.[674] Isopropenyl acetate can also be used to convert other ketones to the corresponding enol acetates in an exchange reaction:[675]

$$\underset{\underset{OAc}{|}}{Me-C}=CH_2 \; + \; \underset{\underset{O}{||}}{R-C}-CHR'_2 \; \xrightarrow{H^+} \; \underset{\underset{OAc}{|}}{R-C}=CR'_2 \; + \; Me_2CO$$

Enol esters can also be prepared in the opposite type of exchange reaction, catalyzed by mercuric acetate[676] or Pd(II) chloride,[677] e.g.,

$$RCOOH \; + \; R'COOCH=CH_2 \; \underset{\underset{H_2SO_4}{\overset{Hg(OAc)_2}{\rightleftharpoons}}}{} \; RCOOCH=CH_2 \; + \; R'COOH$$

A closely related reaction is equilibration of a dicarboxylic acid and its diester to produce monoesters:

$$ROCO(CH_2)_nCOOR \; + \; HOOC(CH_2)_nCOOH \; \rightleftharpoons \; 2ROCO(CH_2)_nCOOH$$
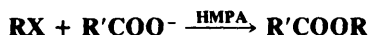
OS II, 5, 122, 360; III, 123, 146, 165, 231, 281, 581, 605; IV, 10, 549, 630, 977; V, 155, 545, 863; VI, 278; VII, 4, 164, 411; 65, 98, 230; 67, 170; 68, 77, 92, 155, 210. See also OS VII, 87; 66, 108.

Alcoholysis of amides is possible but is seldom performed,[678] except for the imidazolide type of amide (101).

E.   Attack by OCOR at an Alkyl Carbon

0-24   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.[679] The mechanism is S_N2. Another method uses phase transfer catalysis.[680] With this method good yields of esters have been obtained from primary, secondary, benzylic, allylic, and phenacyl halides.[681] In another procedure, which is applicable to long-chain primary halides, the dry carboxylate salt and the halide, impregnated on alumina as a solid support, are subjected to irradiation by microwaves in a commercial microwave oven.[682] In still another method, carboxylic acids

[674]Jeffery; Satchell *J. Chem. Soc.* **1962**, 1906; Rothman; Hecht; Pfeffer; Silbert *J. Org. Chem.* **1972**, *37*, 3551.

[675]For examples, see Deghenghi; Engel *J. Am. Chem. Soc.* **1960**, *82*, 3201; House; Trost *J. Org. Chem.* **1965**, *30*, 2502.

[676]For example, see Hopff; Osman *Tetrahedron* **1968**, *24*, 2205, 3887; Mondal; van der Meer; German; Heikens *Tetrahedron* **1974**, *30*, 4205.

[677]Henry *J. Am. Chem. Soc.* **1971**, *93*, 3853, *Acc. Chem. Res.* **1973**, *6*, 16-24.

[678]For example, see Czarnik *Tetrahedron Lett.* **1984**, *25*, 4875. For a list of references, see Ref. 508, pp. 989-990.

[679]Parker, *Adv. Org. Chem.* **1965**, *5*, 1-46, p. 37; Alvarez; Watt *J. Org. Chem.* **1968**, *33*, 2143; Mehta *Synthesis* **1972**, 262; Shaw; Kunerth *J. Org. Chem.* **1974**, *39*, 1968; Larock *J. Org. Chem.* **1974**, *39*, 3721; Pfeffer; Silbert *J. Org. Chem.* **1976**, *41*, 1373.

[680]For reviews of phase transfer catalysis of this reaction, see Starks; Liotta, Ref. 404, pp. 140-155; Weber; Gokel *Phase Transfer Catalysis in Organic Synthesis*, Ref. 404, pp. 85-95.

[681]For an alternative method for phenacyl halides, see Clark; Miller *Tetrahedron Lett.* **1977**, 599.

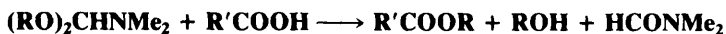[682]Bram; Loupy; Majdoub; Gutierrez; Ruiz-Hitzky *Tetrahedron* **1990**, *46*, 5167. See also Barry; Bram; Decodts; Loupy; Orange; Petit; Sansoulet *Synthesis* **1985**, 40; Arrad; Sasson *J. Am. Chem. Soc.* **1988**, *110*, 185; Dakka; Sasson; Khawaled; Bram; Loupy *J. Chem. Soc., Chem. Commun.* **1991**, 853.

have been esterified by treatment with primary or secondary halides in benzene in the presence of DBU (p. 1023).[683] In most cases good yields of esters can be obtained only with one of these methods. Without phase transfer catalysts and in protic solvents, the reaction is useful only for fairly active R, such as benzylic, allylic, etc. (SN1 mechanism), but not for tertiary alkyl, since elimination occurs instead.[684] Sodium salts are often used, but potassium, silver, cesium,[685] and substituted ammonium salts have also been used. Lactones can be prepared from halo acids by treatment with base (see **0-22**). This has most often been accomplished with γ and δ lactones, but macrocyclic lactones (e.g., 11 to 17 members) have also been prepared in this way.[686]

Cooper(I) carboxylates give esters with primary (including neopentyl without rearrangement), secondary, and tertiary alkyl, allylic, and vinylic halides.[687] A simple SN 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.[688]

A carboxylic acid (not the salt) can be the nucleophile if F⁻ is present.[689] Dihalides have been converted to diesters by this method.[689] A COOH group can be conveniently protected by reaction of its ion with a phenacyl bromide (ArCOCH₂Br).[584] The resulting ester is easily cleaved when desired with zinc and acetic acid. Dialkyl carbonates can be prepared without phosgene (see **0-20**) by phase-transfer catalyzed treatment of primary akyl halides with dry KHCO₃ and K₂CO₃.[690]

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. The use of dimethyl sulfate[691] or trimethyl phosphate[692] allows sterically hindered COOH groups to be methylated. With certain substrates, carboxylic acids are strong enough nucleophiles for the reaction. Examples of such substrates are trialkyl phosphites P(OR)₃[693] and acetals of dimethylformamide.[694]

$$(RO)_2CHNMe_2 + R'COOH \longrightarrow R'COOR + ROH + HCONMe_2$$

This is an SN2 process, since inversion is found at R. Another good leaving group is NTs₂; ditosylamines react quite well with acetate ion in dipolar aprotic solvents:[695] RNTs₂ + OAc⁻ → ROAc. Ordinary primary amines have been converted to acetates and benzoates by the Katritzky pyrylium–pyridinium method (p. 354).[696] Quaternary ammonium salts can be cleaved by heating with AcO⁻ in an aprotic solvent.[697] Oxonium ions can also be used as substrates:[698] R₃O⁺ + R'COO⁻ → R'COOR + R₂O.

[683]Ono; Yamada; Saito; Tanaka; Kaji *Bull. Chem. Soc. Jpn.* **1978**, *51*, 2401; Mal *Synth. Commun.* **1986**, *16*, 331.

[684]See, however, Moore; Foglia; McGahan *J. Org. Chem.* **1979**, *44*, 2425.

[685]See Kruizinga; Strijtveen; Kellogg *J. Org. Chem.* **1981**, *46*, 4321; Dijkstra; Kruizinga; Kellogg *J. Org. Chem.* **1987**, *52*, 4230.

[686]For example, see Galli; Mandolini *Org. Synth. VI*, 698; Kruizinga; Kellogg *J. Chem. Soc. Chem. Commun.* **1979**, 286; *J. Am. Chem. Soc.* **1981**, *103*, 5183; Regen; Kimura *J. Am. Chem. Soc.* **1982**, *104*, 2064; Kimura; Regen *J. Org. Chem.* **1983**, *48*, 1533.

[687]Lewin; Goldberg *Tetrahedron Lett.* **1972**, 491; Klumpp; Bos; Schakel; Schmitz; Vrielink *Tetrahedron Lett.* **1975**, 3429.

[688]Kohll; van Helden *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 481; Volger *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 501; Yamaji; Fujiwara; Asano; Teranishi *Bull. Chem. Soc. Jpn.* **1973**, *46*, 90.

[689]Clark; Emsley; Hoyte *J. Chem. Soc. Perkin Trans. 1* **1977**, 1091. See also Barluenga; Alonso-Cires; Campos; Ascensio *Synthesis* **1983**, 649.

[690]Lissel; Dehmlow *Chem. Ber.* **1981**, *114*, 1210.

[691]Grundy; James; Pattenden *Tetrahedron Lett.* **1972**, 757.

[692]Harris; Patel *Chem. Ind. (London)* **1973**, 1002.

[693]Szmuszkovicz *Org. Prep. Proceed. Int.* **1972**, *4*, 51.

[694]Vorbrüggen *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 211 [*Angew. Chem. 75*, 296]; Brechbühler; Büchi; Hatz; Schreiber; Eschenmoser *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 212 [*Angew. Chem. 75*, 296].

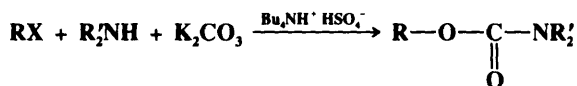[695]Andersen; Uh *Synth. Commun.* **1972**, *2*, 297; Curtis; Schwartz; Hartman; Pick; Kolar; Baumgarten *Tetrahedron Lett* **1977**, 1969.

[696]See Katritzky; Gruntz; Kenny; Rezende; Sheikh *J. Chem. Soc., Perkin Trans 1* **1979**, 430.

[697]Wilson; Joule *Tetrahedron* **1968**, *24*, 5493.

[698]Raber; Gariano; Brod; Gariano; Guida; Guida; Herbst *J. Org. Chem.* **1979**, *44*, 1149.

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.[699]
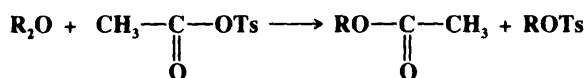
$$RX + R_2'NH + K_2CO_3 \xrightarrow{Bu_4NH^+\ HSO_4^-} R—O—\underset{\underset{O}{\|}}{C}—NR_2'$$

OS **II**, 5; **III**, 650; **IV**, 582; **V**, 580; **VI**, 273, 576, 698.

0-25   Cleavage of Ethers with Acetic Anhydride
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.[700] In this reaction both R groups are converted to acetates. Yields are moderate to high. Ethers can also be cleaved by the mixed anhydride acetyl tosylate:[701]

$$R_2O + CH_3—\underset{\underset{O}{\|}}{C}—OTs \longrightarrow RO—\underset{\underset{O}{\|}}{C}—CH_3 + ROTs$$

Epoxides give β-hydroxyalkyl carboxylates when treated with a carboxylic acid or a carboxylate ion and a suitable catalyst.[702]

OS **67**, 114.

0-26   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 **0-15**. 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, the diazo compounds most often used are diazomethane[593] (for methyl esters)
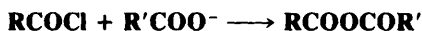
$$CH_2N_2 + RCOOH \longrightarrow RCOOCH_3$$

and diazo ketones. The mechanism is as shown in **0-15**.

OS **V**, 797.

F.   Attack by OCOR at an Acyl Carbon

0-27   Acylation of Carboxylic Acids with Acyl Halides
Acyloxy-de-halogenation

$$RCOCl + R'COO^- \longrightarrow RCOOCOR'$$

[699]Gómez-Parra; Sánchez; Torres *Synthesis* **1985**, 282, *J. Chem. Soc., Perkin Trans. 2* **1987**, 695. For another method, with lower yields, see Yoshida; Ishii; Yamashita *Chem. Lett.* **1984**, 1571.
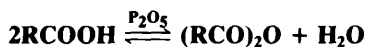[700]Ganem; Small *J. Org. Chem.* **1974**, *39*, 3728.
[701]Karger; Mazur *J. Am. Chem. Soc.* **1968**, *90*, 3878. See also Coffi-Nketsia; Kergomard; Tautou *Bull. Soc. Chim. Fr.* **1967**, 2788.
[702]See Otera; Matsuzaki *Synthesis* **1986**, 1019; Deardorff; Myles *Org. Synth.* **67**, 114.
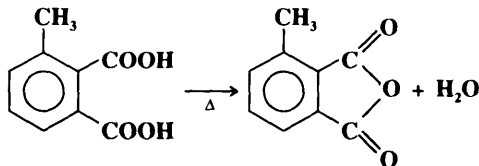
Unsymmetrical as well as symmetrical anhydrides are often prepared by the treatment of an acyl halide with a carboxylic acid salt. If a metallic salt is used, Na^+, K^+, or Ag^+ are the most common cations, but more often pyridine or another tertiary amine is added to the free acid and the salt thus formed is treated with the acyl halide. Mixed formic anhydrides are prepared from sodium formate and an aryl halide, by use of a solid-phase copolymer of pyridine-1-oxide.[703] Symmetrical anhydrides can be prepared by reaction of the acyl halide with aqueous NaOH or $NaHCO_3$ under phase transfer conditions.[704]

OS **III**, 28, 422, 488; **IV**, 285; **VI**, 8, 910; **66**, 132. See also OS **VI**, 418.

0-28   Acylation of Carboxylic Acids with Carboxylic Acids
        Acyloxy-de-hydroxylation

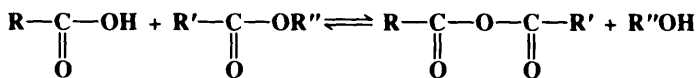$$2RCOOH \overset{P_2O_5}{\rightleftharpoons} (RCO)_2O + H_2O$$

Anhydrides can be formed from two molecules of an ordinary carboxylic acid only if a dehydrating agent is present so that the equilibrium can be driven to the right. Common dehydrating agents[705] are acetic anhydride, trifluoroacetic anhydride, dicyclohexylcarbodiimide,[706] methoxyacetylene,[707] and P_2O_5. Among other reagents used have been trimethylsilylethoxyacetylene $Me_3SiC{\equiv}COEt$,[708] tetracyanoethylene and a base,[709] 1,1,1-trichloro-3,3,3-trifluoroacetone and pyridine,[710] diphenyl phosphorochloridate $(PhO)_2POCl$,[711] and phenyl N-phenylphosphoramidochloridate $(PhO)(PhNH)POCl$.[711]The method is very poor for the formation of mixed anhydrides, which in any case generally undergo disproportionation to the two simple anhydrides when they are heated. However, simple heating of dicarboxylic acids does give cyclic anhydrides, provided that the ring formed contains five, six, or seven members, e.g.,

Malonic acid and its derivatives, which would give four-membered cyclic anhydrides, do not give this reaction when heated but undergo decarboxylation (**2-40**) instead.

Carboxylic acids exchange with amides and esters; these methods are sometimes used to prepare anhydrides if the equilibrium can be shifted, e.g.,

[703]Fife; Zhang *J. Org. Chem.* **1986,** *51*, 3744. See also Fife; Zhang *Tetrahedron Lett.* **1986,** *27*, 4933, 4937. For a review of acetic formic anhydride see Strazzolini; Giumanini; Cauci *Tetrahedron* **1990,** *46* 1081-1118.

[704]Plusquellec; Roulleau; Lefeuvre; Brown *Tetrahedron* **1988,** *44*, 2471; Wang; Hu; Cui *J. Chem. Res. (S)* **1990,** 84.

[705]For lists of other dehydrating agents with references, see Ref. 508, pp. 965-966; Ogliaruso; Wolfe, in Patai, Ref. 638, pt. 1, pp. 437-438.

[706]For example, see Schüssler; Zahn *Chem. Ber.* **1962,** *95*, 1076; Rammler; Khorana *J. Am. Chem. Soc.* **1963,** *85*, 1997. See also Hata; Tajima; Mukaiyama *Bull. Chem. Soc. Jpn.* **1968,** *41*, 2746.

[707]See, for example, Eglinton; Jones; Shaw; Whiting *J. Chem. Soc.* **1954,** 1860; Arens; Doornbos *Recl. Trav. Chim. Pays-Bas* **1955,** *74*, 79.
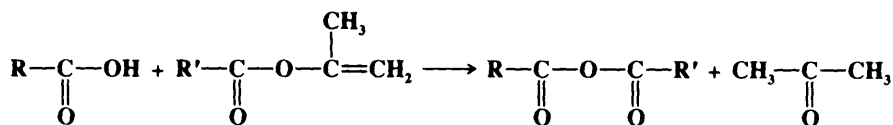
[708]Kita; Akai; Yoshigi; Nakajima; Yasuda; Tamura *Tetrahedron Lett.* **1984,** *25*, 6027.

[709]Voisin; Gastambide *Tetrahedron Lett.* **1985,** *26*, 1503.

[710]Abdel-Baky; Giese *J. Org. Chem.* **1986,** *51*, 3390.

[711]Mestres; Palomo *Synthesis* **1981,** 218.

Enolic esters are especially good for this purpose, because the equilibrium is shifted by formation of the ketone.

$$R-\underset{\underset{O}{\|}}{C}-OH \; + \; R'-\underset{\underset{O}{\|}}{C}-O-\underset{\underset{CH_3}{|}}{C}=CH_2 \; \longrightarrow \; R-\underset{\underset{O}{\|}}{C}-O-\underset{\underset{O}{\|}}{C}-R' \; + \; CH_3-\underset{\underset{O}{\|}}{C}-CH_3$$

Carboxylic acids also exchange with anhydrides; indeed, this is how acetic anhydride acts as a dehydrating agent in this reaction.

Anhydrides can be formed from certain carboxylic acid salts; for example, by treatment of trimethylammonium carboxylates with phosgene:[712]

$$2RCOO^{\ominus} \; \overset{\oplus}{N}HEt_3 \; \xrightarrow{COCl_2} \; RCOOCOR \; + \; 2\overset{\oplus}{N}HEt_3 \; Cl^- \; + \; CO_2$$

or of thallium(I) carboxylates with thionyl chloride,[624] or of sodium carboxylates with CCl_4 and a catalyst such as CuCl or $FeCl_2$.[713]
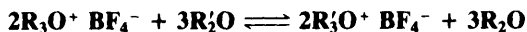
OS **I**, 91, 410; **II**, 194, 368, 560; **III**, 164, 449; **IV**, 242, 630, 790; **V**, 8, 822. Also see OS **VI**, 757; **VII**, 506.

G.   Other Oxygen Nucleophiles

0-29   Formation of Oxonium Salts

$$RX \; + \; R_2O \; \xrightarrow{AgBF_4} \; R_3O^+ \quad BF_4^- \; + \; AgX \quad \textbf{Dialkyloxonio-de-halogenation}$$

$$RX \; + \; R_2'CO \; \xrightarrow{AgBF_4} \; R_2'C{=}\overset{\oplus}{O}{-}R \quad BF_4^- \; + \; AgX$$
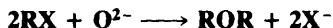
Alkyl halides can be alkylated by ethers or ketones to give oxonium salts, if a very weak, negatively charged nucleophile is present to serve as a counterion and a Lewis acid is present to combine with X^-.[714] A typical procedure consists of treating the halide with the ether or the ketone in the presence 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, e.g., R_2O—BF_3 + RF → R_3O^+ BF_4^-, though 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:

$$2R_3O^+ \; BF_4^- \; + \; 3R_2'O \; \rightleftharpoons \; 2R_3'O^+ \; BF_4^- \; + \; 3R_2O$$

OS **V**, 1080, 1096, 1099; **VI**, 1019.

0-30   Reaction of Halides with Oxide Ion
   Oxy-de-dihalo-*aggre*-substitution

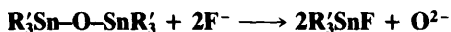$$2RX \; + \; O^{2-} \; \longrightarrow \; ROR \; + \; 2X^-$$

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[712]Rinderknecht; Ma *Helv. Chim. Acta* **1964,** 47, 152. See also Nangia; Chandrasekaran *J. Chem. Res., (S)* **1984,** 100.

[713]Weiss; Havelka; Nefedov *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1978,** 27, 193.

[714]Meerwein; Hederich; Wunderlich *Arch. Pharm.* **1958,** 291/63, 541. For a review, see Perst, Ref. 84, pp. 22-39.
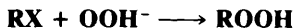
Alkyl halides can be converted to symmetrical ethers by treatment with oxide ion generated in situ by a reaction between an organotin oxide and fluoride ion in the presence of a quaternary ammonium iodide or a crown ether.[715]

$$R_3'Sn-O-SnR_3' + 2F^- \longrightarrow 2R_3'SnF + O^{2-}$$

The procedure was used for R = primary alkyl and benzylic. Some unsymmetrical ethers ROR″ were also made, by using R″OSnR$_3'$ instead of R$_3'$SnOSnR$_3'$.
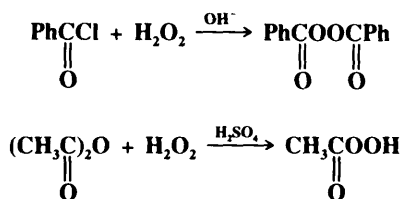
0-31 Preparation of Peroxides and Hydroperoxides
Hydroperoxy-de-halogenation
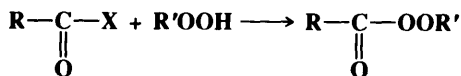
$$RX + OOH^- \longrightarrow ROOH$$

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^-.[716] Sodium peroxide is similarly used to prepare dialkyl peroxides ($2RX + Na_2O_2 \rightarrow ROOR$). 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.[717] Peroxides can also be prepared[718] by treatment of alkyl bromides or tosylates with potassium superoxide KO_2 in the presence of crown ethers (though alcohols may be side products[719]) and by the reaction between alkyl triflates and germanium or tin peroxide.[720]

Diacyl peroxides and acyl hydroperoxides can similarly be prepared[721] from acyl halides or anhydrides

$$\underset{O}{PhCCl} + H_2O_2 \xrightarrow{OH^-} \underset{O \quad O}{PhCOOCPh}$$

$$\underset{O}{(CH_3C)_2O} + H_2O_2 \xrightarrow{H_2SO_4} \underset{O}{CH_3COOH}$$

and from carboxylic acids.[722] Diacyl peroxides can also be prepared by the treatment of carboxylic acids with hydrogen peroxide in the presence of dicyclohexylcarbodiimide,[723] H_2SO_4, methanesulfonic acid, or some other dehydrating agent. Mixed alkyl–acyl peroxides (peresters) can be made from acyl halides and hydroperoxides.

$$\underset{O}{R-C-X} + R'OOH \longrightarrow \underset{O}{R-C-OOR'}$$

OS **III**, 619, 649; **V**, 805, 904; **VI**, 276.

[715]Harpp; Gingras *J. Am. Chem. Soc.* **1988**, *110*, 7737.

[716]For a review, see Hiatt, in Swern *Organic Peroxides*, vol. 2, Wiley: New York, 1971, pp. 1-151. For a review of hydrogen peroxide, see Pandiarajan, in Pizey, Ref. 593, vol. 6, 1985, pp. 60-155.

[717]Cookson; Davies; Roberts *J. Chem. Soc., Chem. Commun.* **1976**, 1022. For another preparation of unsymmetrical peroxides, see Bourgeois; Montaudon; Maillard *Synthesis* **1989**, 700.

[718]Johnson; Nidy; Merritt *J. Am. Chem. Soc.* **1978**, *100*, 7960.

[719]Alcohols have also been reported to be the main products: San Filippo; Chern; Valentine *J. Org. Chem.* **1975**, *40*, 1678; Corey; Nicolaou; Shibasaki; Machida; Shiner *Tetrahedron Lett.* **1975**, 3183.

[720]Salomon; Salomon *J. Am. Chem. Soc.* **1979**, *101*, 4290.

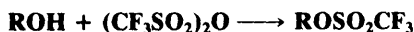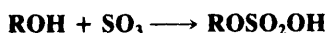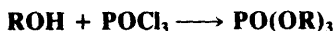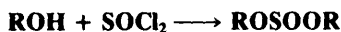[721]For a review of the synthesis and reactions of acyl peroxides and peresters, see Bouillon; Lick; Schank, in Patai, *The Chemistry of Peroxides*; Wiley: New York, 1983, pp. 279-309. For a review of the synthesis of acyl peroxides, see Hiatt, Ref. 716, vol. 2, pp. 799-929.

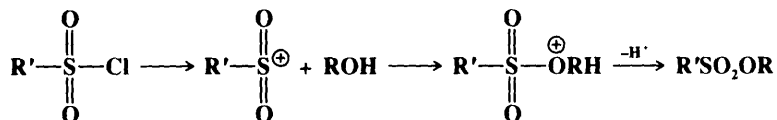[722]See Silbert; Siegel; Swern *J. Org. Chem.* **1962**, *27*, 1336.

[723]Greene; Kazan *J. Org. Chem.* **1963**, *28*, 2168.

0-32   Preparation of Inorganic Esters
Nitrosooxy-de-hydroxylation, etc.

$$ROH + HONO \xrightarrow{H^+} RONO$$

$$ROH + HONO_2 \xrightarrow{H^+} RONO_2$$

$$ROH + SOCl_2 \longrightarrow ROSOOR$$

$$ROH + POCl_3 \longrightarrow PO(OR)_3$$

$$ROH + SO_3 \longrightarrow ROSO_2OH$$

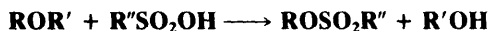$$ROH + (CF_3SO_2)_2O \longrightarrow ROSO_2CF_3$$

The above transformations show a few of the many inorganic esters that can be prepared by attack of an inorganic acid or, better, its acid halide or anhydride, on an alcohol.[724] Although for convenience all these similar reactions are grouped together, these are not all nucleophilic substitutions at R. The other possible pathway is nucleophilic substitution at the inorganic central atom:[725]

$$R'-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-Cl \longrightarrow R'-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}{}^{\oplus} + ROH \longrightarrow R'-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-\overset{\oplus}{O}RH \xrightarrow{-H^+} R'SO_2OR$$

or a corresponding SN2 type (see p. 496). 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, Cl-SO_2OH, or SO_3 complexes.[726] Alcohols are often converted to silyl ethers, for protection and other synthetic purposes: $ROH + Me_3CSiCl \rightarrow ROSiMe_3$.[727] Alkyl nitrites[728] can be conveniently prepared by an exchange reaction $ROH + R'ONO \rightarrow RONO + R'OH$, where R = t-Bu.[729] 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.[730]

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 **0-60**).[731] Dialkyl or aryl alkyl ethers can be cleaved with anhydrous sulfonic acids.[732]

$$ROR' + R''SO_2OH \longrightarrow ROSO_2R'' + R'OH$$

[724]For a review, see Ref. 575, pp. 481-497.

[725]For an example involving nitrite formation, see Aldred; Williams; Garley *J. Chem. Soc., Perkin Trans. 2* **1982,** 777.

[726]For a review, see Sandler; Karo, *Organic Functional Group Preparations,* 2d ed., vol. 3; Academic Press: New York, 1989, pp. 129-151.

[727]For a review, see Lalonde; Chan *Synthesis* **1985,** 817-845.

[728]For a review of alkyl nitrites, see Williams *Nitrosation*; Cambridge University Press: Cambridge, 1988, pp. 150-172.

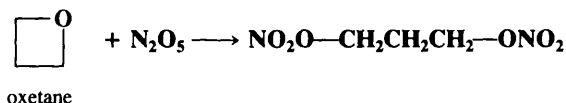[729]Doyle; Terpstra; Pickering; LePoire *J. Org. Chem.* **1983,** *48,* 3379. For a review of the nitrosation of alcohols, see Ref. 728, pp. 150-156.

[730]Barton; Narang *J. Chem. Soc., Perkin Trans.1* **1977,** 1114.

[731]For a review of formation of nitrates from alkyl halides, see Boguslavskaya; Chuvatkin; Kartashov *Russ. Chem. Rev.* **1988,** *57,* 760-775.

[732]Klamann; Weyerstahl *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 **0-16**), which in turn is further cleaved to R'OSO$_2$R″ 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[733] (prepared as in **0-33**). β-Hydroxyalkyl perchlorates[734] and sulfonates can be obtained from epoxides.[735] Epoxides and oxetanes give dinitrates when treated with N$_2$O$_5$,[736] e.g.,

$$\overset{\displaystyle \rlap{\raisebox{1ex}{}O}{}}{\boxed{}} \quad + \; N_2O_5 \longrightarrow NO_2O\text{—}CH_2CH_2CH_2\text{—}ONO_2$$

oxetane

Aziridines and azetidines react similarly, giving nitramine nitrates; e.g., N-butylazetidine gave NO$_2$OCH$_2$CH$_2$CH$_2$N(Bu)NO$_2$.[736]

OS **II**, 106, 108, 109, 112, 204, 412; **III**, 148, 471; **IV**, 955; **V**, 839; **66**, 211; **67**, 1, 13. Also see OS **II**, 111.

0-33 Preparation of Mixed Organic–Inorganic Anhydrides
       Nitrooxy-de-acyloxy-substitution

$$(RCO)_2O \; + \; HONO_2 \longrightarrow RCOONO_2$$

Mixed organic–inorganic anhydrides are seldom isolated, though they are often intermediates when acylation is carried out with acid derivatives catalyzed by inorganic acids. Sulfuric, perchloric, phosphoric, and other acids form similar anhydrides, most of which are unstable or not easily obtained because the equilibrium lies in the wrong direction. These intermediates are formed from amides, carboxylic acids, and esters, as well as anhydrides. Organic anhydrides of phosphoric acid are more stable than most others and, for example, RCOOPO(OH)$_2$ can be prepared in the form of its salts.[737] Mixed anhydrides of carboxylic and sulfonic acids (RCOOSO$_2$R') are obtained in high yields by treatment of sulfonic acids with acyl halides or (less preferred) anhydrides.[738]

OS **I**, 495; **VI**, 207; **VII**, 81.

0-34 Alkylation of Oximes

$$RX \; + \; \underset{\underset{\textstyle N\text{—}OH}{\|}}{R'\text{—}\overset{}{C}\text{—}R''} \longrightarrow \underset{\underset{\textstyle N\text{—}OR}{\|}}{R'\text{—}\overset{}{C}\text{—}R''} \; + \; \underset{\underset{\textstyle R''\;\;O_\ominus}{|\quad\;|}}{R'\text{—}C{=}\overset{\oplus}{N}\text{—}R}$$

A nitrone

Oximes can be alkylated by alkyl halides or sulfates. N-Alkylation is a side reaction, yielding a nitrone.[739] The relative yield of oxime ether and nitrone depends on the nature of the

[733]Karger; Mazur *J. Org. Chem.* **1971**, *36*, 532, 540.
[734]For a review of the synthesis and reactions of organic perchlorates, see Zefirov; Zhdankin; Koz'min *Russ. Chem. Rev.* **1988**, *57*, 1041-1053.
[735]Zefirov; Kirin; Yur'eva; Zhdankin; Kozmin *J. Org. Chem. USSR* **1987**, *23*, 1264.
[736]Golding; Millar; Paul; Richards *Tetrahedron Lett.* **1988**, *29*, 2731, 2735.
[737]Avison *J. Chem. Soc.* **1955**, 732.
[738]Karger; Mazur *J. Org. Chem.* **1971**, *36*, 528.
[739]For a review of nitrones, see Torssell *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*; VCH: New York, 1988, pp. 75-93.

reagents, including the configuration of the oxime, and on the reaction conditions.[740] For example, *anti*-benzaldoximes give nitrones, while the syn isomers give oxime ethers.[741]

OS **III**, 172; **V**, 1031. Also see OS **V**, 269; **VI**, 199.
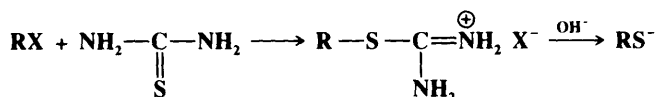
Sulfur Nucleophiles

Sulfur compounds[742] are better nucleophiles than their oxygen analogs (p. 349), 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.[743]

0-35 Attack by SH at an Alkyl Carbon. Formation of Thiols[744]
      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. 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.[745] The conversion can also be accomplished under neutral conditions by treatment of a primary halide with F^- and a tin sulfide such as $Ph_3SnSSnPh_3$.[746] An indirect method for the conversion of an alkyl halide to a thiol consists of treatment with thiourea to give an isothiuronium salt, which with alkali or a high-molecular-weight amine is cleaved to the thiol:

$$RX + NH_2\!-\!\underset{\underset{S}{\|}}{C}\!-\!NH_2 \longrightarrow R\!-\!S\!-\!\underset{\underset{NH_2}{|}}{\overset{\oplus}{C}}\!\!=\!\!NH_2 \;\; X^- \xrightarrow{\;OH^-\;} RS^-$$

Another indirect method is hydrolysis of Bunte salts (see **0-39**).

Thiols have also been prepared from alcohols. One method involves treatment with H_2S and a catalyst such as Al_2O_3,[747] but this is limited to primary alcohols. Another method involves treatment with Lawesson's reagent (see **6-11**).[748] Still another method, involving the use of a fluoropyridinium salt and sodium N,N-dimethylthiocarbamate, can be applied

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[740]For a review, see Reutov; Beletskaya; Kurts, Ref. 422, pp. 262-272.

[741]Buehler *J. Org. Chem.* **1967**, *32*, 261.

[742]For monographs on sulfur compounds, see Bernardi; Csizmadia; Mangini *Organic Sulfur Chemistry*; Elsevier: New York, 1985; Oae *Organic Chemistry of Sulfur*; Plenum: New York, 1977. For monographs on selenium compounds, see Krief; Hevesi *Organoselenium Chemistry I*; Springer: New York, 1988; Liotta *Organoselenium Chemistry*; Wiley: New York, 1987.

[743]See Ashby; Park; Goel; Su *J. Org. Chem.* **1985**, *50*, 5184.

[744]For a review, see Wardell, in Patai *The Chemistry of the Thiol Group*, pt. 1; Wiley: New York, 1974, pp. 179-211.
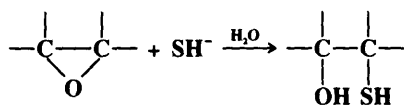
[745]For a method of avoiding thioether formation, see Vasil'tsov; Trofimov; Amosova *J. Org. Chem. USSR* **1983**, *19*, 1197.

[746]Gingras; Harpp *Tetrahedron Lett.* **1990**, *31*, 1397.

[747]Lucien; Barrault; Guisnet; Maurel *Nouv. J. Chim.* **1979**, *3*, 15.
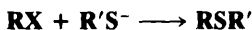
[748]Nishio *J. Chem. Soc., Chem. Commun.* **1989**, 205.

to primary, secondary, allylic, and benzylic alcohols.[749] When epoxides are substrates, the products are β-hydroxy thiols:[750]

$$-\overset{|}{\underset{\diagdown\!\!O\!\!\diagup}{C}}-\overset{|}{\underset{}{C}}- \ + \ SH^- \ \xrightarrow{\text{H}_2\text{O}} \ -\overset{|}{\underset{OH}{C}}-\overset{|}{\underset{SH}{C}}-$$

Tertiary nitro compounds give thiols ($RNO_2 \rightarrow RSH$) when treated with sulfur and sodium sulfide, followed by amalgamated aluminum.[751]

OS **III**, 363, 440; **IV**, 401, 491; **V**, 1046; **65**, 50. Also see OS **II**, 345, 411, 573; **IV**, 232; **V**, 223; **VI**, 620.

0-36   Attack by S at an Alkyl Carbon. Formation of Thioethers
Alkylthio-de-halogenation

$$RX \ + \ R'S^- \ \longrightarrow \ RSR'$$

Thioethers (sulfides) can be prepared by treatment of alkyl halides with salts of thiols (thiolate ions).[752] R' may be alkyl or aryl. As in **0-35**, RX cannot be a tertiary halide, and sulfuric and sulfonic esters can be used instead of halides. As in the Williamson reaction (**0-12**), yields are improved by phase-transfer catalysis.[753] Instead of RS^- ions, thiols themselves can be used, if the reaction is run in benzene in the presence of DBU (p. 1023).[754] 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.[755] This probably takes place by an S$_{RN}$1 mechanism (see p. 648). Vinylic sulfides can be prepared by treating vinylic bromides with PhS^- in the presence of a nickel complex,[756] and with R_3SnPh in the presence of $Pd(PPh_3)_4$.[757]

R can be tertiary if an alcohol is the substrate, e.g.,[758]

$$R_3COH \ + \ R_3'CSH \ \xrightarrow{\text{H}_2\text{SO}_4} \ R_3CSCR_3'$$

This reaction is analogous to **0-16**. Primary and secondary alcohols can be converted to alkyl aryl sulfides ($ROH \rightarrow RSAr$) in high yields by treatment with Bu_3P and an N-(aryl-thio)succinimide in benzene.[759] 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.[760]

Thiolate ions are also useful for the demethylation of certain ethers,[761] esters, amines, and quaternary ammonium salts. Aryl methyl ethers[762] can be cleaved by heating with EtS^-

[749]Hojo; Yoshino; Mukaiyama *Chem. Lett* **1977**, 133, 437. For another method, see Alper; Sibtain *J. Org. Chem.* **1988**, *53*, 3306.
[750]For a review, see Ref. 744, pp. 246-251.
[751]Kornblum; Widmer *J. Am. Chem. Soc.* **1978**, *100*, 7086.
[752]For a review, see Peach, in Patai, Ref. 744, pt. 2, pp. 721-735.
[753]For a review of the use of phase transfer catalysis to prepare sulfur-containing compounds, see Weber; Gokel *Phase Transfer Catalysis in Organic Synthesis*, Ref. 404, pp. 221-233.
[754]Ono; Miyake; Saito; Kaji *Synthesis* **1980**, 952. See also Ferreira; Comasseto; Braga *Synth. Commun.* **1982**, *12*, 595; Ando; Furuhata; Tsumaki; Sekiguchi *Synth. Commun.* **1982**, *12*, 627.
[755]Pierini; Peñéñory; Rossi *J. Org. Chem.* **1985**, *50*, 2739.
[756]Cristau; Chabaud; Labaudiniere; Christol *J. Org. Chem.* **1986**, *51*, 875.
[757]Carpita; Rossi; Scamuzzi *Tetrahedron Lett.* **1989**, *30*, 2699. For another method, see Ogawa; Hayami; Suzuki *Chem. Lett.* **1989**, 769.
[758]Fehnel; Carmack *J. Am. Chem. Soc.* **1949**, *71*, 84; Cain; Evans; Lee *J. Chem. Soc.* **1962**, 1694.
[759]Walker *Tetrahedron Lett.* **1977**, 4475. See the references in this paper for other methods of converting alcohols to sulfides. See also Cleary *Synth. Commun.* **1989**, *19*, 737.
[760]Fujisaki; Fujiwara; Norisue; Kajigaeshi *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2429.
[761]For a review, see Evers *Chem. Scr.* **1986**, *26*, 585-597.
[762]Certain other sulfur-containing reagents also cleave methyl and other ethers: see Hanessian; Guindon *Tetrahedron Lett.* **1980**, *21*, 2305; Williard; Fryhle *Tetrahedron Lett.* **1980**, *21*, 3731; Node; Nishide; Fuji; Fujita *J. Org. Chem.* **1980**, *45*, 4275. For cleavage with selenium-containing reagents, see Evers; Christiaens *Tetrahedron Lett.* **1983**, *24*, 377. For a review of the cleavage of aryl alkyl ethers, see Tiecco *Synthesis* **1988**, 749-759.

in the dipolar aprotic solvent DMF: $ROAr + EtS^- \rightarrow ArO^- + EtSR$.[763] Carboxylic esters and lactones are cleaved (the lactones give ω-alkylthio carboxylic acids) with a thiol and $AlCl_3$ or $AlBr_3$.[764] Esters and lactones are similarly cleaved in high yield by phenyl selenide ion $PhSe^-$.[765] Allylic sulfides have been prepared by treating allylic carbonates ROCOOMe (R = an allylic group) with a thiol and a Pd(0) catalyst.[766] A good method for the demethylation of quaternary ammonium salts consists of refluxing them with PhS^- in butanone:[767]

$$R_3\overset{\oplus}{N}Me + PhS^- \xrightarrow{\text{MeCOEt}} R_3N + PhSMe$$
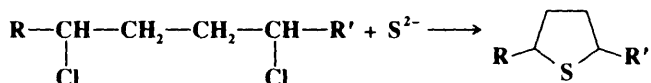
A methyl group is cleaved more readily than other simple alkyl groups (such as ethyl), though loss of these groups competes, but benzylic and allylic groups cleave even more easily, and this is a useful procedure for the cleavage of benzylic and allylic groups from quaternary ammonium salts, even if methyl groups are also present.[768]

Symmetrical thioethers can also be prepared by treatment of an alkyl halide with sodium sulfide,[769] in a reaction similar to **0-30.**

$$2RX + Na_2S \longrightarrow RSR$$

This reaction can be carried out internally, by treatment of sulfide ions with 1,4- or 1,5-dihalides, to prepare five- and six-membered sulfur-containing heterocyclic rings.

Certain larger rings have also been closed in this way.[770]

gem-Dihalides can be converted to thioacetals $RCH(SR')_2$,[771] and acetals have been converted to monothioacetals $R_2C(OR')(SR'')$,[772] and to thioacetals.[773]

Selenides and tellurides can be prepared similarly.[774] When epoxides are substrates, β-hydroxy sulfides are obtained in a manner analogous to that mentioned in **0-35.** Epoxides can also be directly converted to episulfides,[775] by treatment with a phosphine sulfide such as Ph_3PS[776] or with thiourea and titanium tetraisopropoxide.[777]

[763]Feutrill; Mirrington *Tetrahedron Lett.* **1970**, 1327, *Aust. J. Chem.* **1972**, *25*, 1719, 1731.
[764]Node; Nishide; Ochiai; Fuji; Fujita *J. Org. Chem.* **1981**, *46*, 5163.
[765]Scarborough; Smith *Tetrahedron Lett.* **1977**, 4361; Liotta; Santiesteban *Tetrahedron Lett.* **1977**, 4369; Liotta; Sunay; Santiesteban; Markiewicz *J. Org. Chem.* **1981**, *46*, 2605; Kong; Chen; Zhou *Synth. Commun.* **1988**, *18*, 801.
[766]Trost; Scanlan *Tetrahedron Lett.* **1986**, *27*, 4141.
[767]Shamma; Deno; Remar *Tetrahedron Lett.* **1966**, 1375. For alternative procedures, see Hutchins; Dux *J. Org. Chem.* **1973**, *38*, 1961; Posner; Ting *Synth. Commun.* **1974**, *4*, 355.
[768]Kametani; Kigasawa; Hiiragi; Wagatsuma; Wakisaka *Tetrahedron Lett.* **1969**, 635.
[769]For another reagent, see Harpp; Gingras; Aida; Chan *Synthesis* **1987**, 1122.
[770]See Hammerschmidt; Bieber; Vögtle *Chem. Ber.* **1978**, *111*, 2445; Singh; Mehrotra; Regen *Synth. Commun.* **1981**, *11*, 409.
[771]See, for example Wähälä; Ojanperä; Häyri; Hase *Synth. Commun.* **1987**, *17*, 137.
[772]Masaki; Serizawa; Kaji *Chem. Lett.* **1985**, 1933; Sato; Kobayashi; Gojo; Yoshida; Otera; Nozaki *Chem. Lett.* **1987**, 1661.
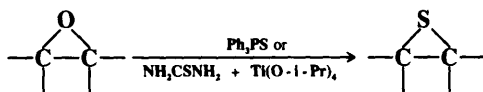[773]Park; Kim *Chem. Lett.* **1989**, 629.
[774]Brandsma; Wijers *Recl. Trav. Chim. Pays-Bas* **1963**, *82*, 68; Clarembeau; Krief *Tetrahedron Lett.* **1984**, *25*, 3625. For a review of nucleophilic selenium, see Monahan; Brown; Waykole; Liotta, in Liotta, Ref. 742, pp. 207-241.
[775]For a review of episulfide information, see Fokin; Kolomiets *Russ. Chem. Rev.* **1975**, *44*, 138-153.
[776]Chan; Finkenbine *J. Am. Chem. Soc.* **1972**, *94*, 2880.
[777]Gao; Sharpless *J. Org. Chem.* **1988**, *53*, 4114. For other methods, see Calò; Lopez; Marchese; Pesce *J. Chem. Soc., Chem. Commun.* **1975**, 621; Takido; Kobayashi; Itabashi *Synthesis* **1986**, 779; Bouda; Borredon; Delmas; Gaset *Synth. Commun.* **1987**, *17*, 943, **1989**, *19*, 491.
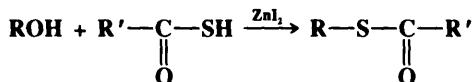
$$\text{—}\overset{O}{\overset{|}{\underset{|}{C}}}\text{—}\overset{}{\underset{|}{C}}\text{—} \quad \xrightarrow[\text{NH}_2\text{CSNH}_2 \ + \ \text{Tl(O-1-Pr)}_4]{\text{Ph}_3\text{PS or}} \quad \text{—}\overset{S}{\overset{|}{\underset{|}{C}}}\text{—}\overset{}{\underset{|}{C}}\text{—}$$

Alkyl halides, treated with thioethers, give sulfonium salts.[778]

$$RI + R_2'S \longrightarrow R_2'SR^+ \ I^-$$

Other leaving groups have also been used for this purpose.[779]

Alcohols, when treated with a thiol acid and zinc iodide, give thiol esters:[780]

$$ROH + R'\text{—}\overset{}{\underset{\overset{||}{O}}{C}}\text{—SH} \xrightarrow{\text{ZnI}_2} R\text{—S—}\overset{}{\underset{\overset{||}{O}}{C}}\text{—R'}$$

This method is an alternative to **0-37** as a way to prepare thiol esters.

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; **65,** 150. See also OS **VI**, 776.

0-37   Attack by SH or SR at an Acyl Carbon[781]

$$RCOCl + H_2S \longrightarrow R\text{—}\overset{}{\underset{\overset{||}{O}}{C}}\text{—SH} \qquad \textbf{Mercapto-de-halogenation}$$

$$RCOCl + R'SH \longrightarrow R\text{—}\overset{}{\underset{\overset{||}{O}}{C}}\text{—SR'} \qquad \textbf{Alkylthio-de-halogenation}$$

Thiol acids and thiol esters[782] can be prepared in this manner, which is analogous to **0-8** and **0-23**. Anhydrides[783] and aryl esters (RCOOAr)[784] are also used as substrates, but the reagents in these cases are usually SH$^-$ and SR$^-$. Thiol esters can also be prepared by treatment of carboxylic acids with trisalkylthioboranes B(SR)$_3$,[785] with P$_4$S$_{10}$-Ph$_3$SbO,[786] or with a thiol RSH and either polyphosphate ester or phenyl dichlorophosphate PhOPOCl$_2$.[787] Esters RCOOR' can be converted to thiol esters RCOSR'' by treatment with trimethylsilyl sulfides Me$_3$SiSR'' and AlCl$_3$.[788]

OS **III**, 116, 599; **IV**, 924, 928; **VII**, 81; **66,** 108.

[778]For a review of the synthesis of sulfonium salts, see Lowe, in Stirling, Ref. 363, pp. 267-312.

[779]See Badet; Jacob; Julia *Tetrahedron* **1981**, *37*, 887; Badet; Julia *Tetrahedron Lett.* **1979**, 1101, and references cited in the latter paper.

[780]Gauthier; Bourdon; Young *Tetrahedron Lett.* **1986**, *27*, 15.

[781]For a review, see Satchell *Q. Rev., Chem. Soc.* **1963**, *17*, 160-203, pp. 182-184.

[782]For a review of these compounds, see Scheithauer; Mayer *Top. Sulfur Chem.* **1979**, *4*, 1-373.

[783]Ahmad; Iqbal *Tetrahedron Lett.* **1986**, *27*, 3791.
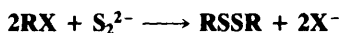
[784]Hirabayashi; Mizuta; Mazume *Bull. Chem. Soc. Jpn.* **1965**, *38*, 320.

[785]Pelter; Levitt; Smith; Jones *J. Chem. Soc., Perkin Trans. 1* **1977**, 1672.

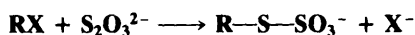[786]Nomura; Miyazaki; Nakano; Matsuda *Chem. Ber.* **1990**, *123*, 2081.

[787]Imamoto; Kodera; Yokoyama *Synthesis* **1982**, 134; Liu; Sabesan *Can. J. Chem.* **1980**, *58*, 2645. For other methods of converting carboxylic acids to thiol esters, see the references given in these papers. See also Dellaria; Nordeen; Swett *Synth. Commun.* **1986**, *16*, 1043.

[788]Mukaiyama; Takeda; Atsumi *Chem. Lett.* **1974**, 187. See also Hatch; Weinreb *J. Org. Chem.* **1977**, *42*, 3960; Cohen; Gapinski *Tetrahedron.* **1978**, 4319.
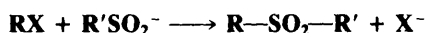
0-38   Formation of Disulfides
Dithio-de-dihalo-*aggre*-substitution

$$2RX + S_2{}^{2-} \longrightarrow RSSR + 2X^-$$

Disulfides can be prepared by treatment of alkyl halides with disulfide ions and also indirectly by the reaction of Bunte salts (see **0-39**) with acid solutions of iodide, thiocyanate ion, or thiourea,[789] or by pyrolysis or treatment with hydrogen peroxide. Alkyl halides also give disulfides when refluxed with sulfur and NaOH,[790] and with piperidinium tetrathiotungstate or piperidinium tetrathiomolybdate.[791]

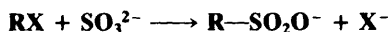There are no OS references, but a similar preparation of a polysulfide may be found in OS **IV**, 295.

0-39   Formation of Bunte Salts
Sulfonatothio-de-halogenation

$$RX + S_2O_3{}^{2-} \longrightarrow R\!-\!S\!-\!SO_3{}^- + X^-$$

Primary and secondary but not tertiary alkyl halides are easily converted to Bunte salts $(RSSO_3{}^-)$ by treatment with thiosulfate ion.[792] Bunte salts can be hydrolyzed with acids to give the corresponding thiols[793] or converted to disulfides, tetrasulfides, or pentasulfides.[794]

OS **VI**, 235.

0-40   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.[795] Alkyl sulfinates R'SO—OR may be side products.[796] Sulfonic acids themselves can be used, if DBU (p. 1023) is present.[797] Sulfones have also been prepared by treatment of alkyl halides with tosylhydrazide.[798]

OS **IV**, 674. See also OS **VI**, 1016.

0-41   Attack by Sulfite Ion
Sulfonato-de-halogenation

$$RX + SO_3{}^{2-} \longrightarrow R\!-\!SO_2O^- + X^-$$

Salts of sulfonic acids can be prepared by treatment of primary or secondary alkyl halides with sulfite ion.[799] Even tertiary halides have been used, though the yields are low. Epoxides treated with bisulfite give β-hydroxy sulfonic acids.[800]

[789]Milligan; Swan *J. Chem. Soc.* **1962**, 2712.
[790]Chorbadjiev; Roumian; Markov *J. Prakt. Chem.* **1977**, *319*, 1036.
[791]Dhar; Chandrasekaran *J. Org. Chem.* **1989**, *54*, 2998.
[792]For a review of Bunte salts, see Distler *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 544-553 [*Angew. Chem. 79*, 520-529].
[793]Kice *J. Org. Chem.* **1963**, *28*, 957.
[794]Milligan; Saville; Swan *J. Chem. Soc.* **1963**, 3608.
[795]For a review, see Schank, in Patai; Rappoport; Stirling *The Chemistry of Sulphones and Sulphoxides*; Wiley: New York, 1988, pp. 165-231. pp. 177-188.
[796]See, for example Meek; Fowler *J. Org. Chem.* **1968**, *33*, 3422; Kiełbasiński; Żurawiński; Drabowicz; Mikołajczyk *Tetrahedron* **1988**, *44*, 6687.
[797]Biswas; Mal *J. Chem. Res. (S)* **1988**, 308.
[798]Ballini; Marcantoni; Petrini *Tetrahedron* **1989**, *45*, 6791.
[799]For a review, see Gilbert *Sulfonation and Related Reactions*; Wiley: New York, 1965, pp. 136-148, 161-163.
[800]For a discussion, see Yoneda; Griffin; Carlyle *J. Org. Chem.* **1975**, *40*, 375.

$$-\underset{\underset{O}{\diagdown\diagup}}{C}-\underset{}{C}- \ + \ HSO_3^- \ \xrightarrow{H_2O} \ -\underset{\underset{OH}{|}}{C}-\underset{\underset{SO_2O^-}{|}}{C}-$$
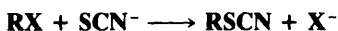
OS **II**, 558, 564; **IV**, 529.

0-42 Formation of Alkyl Thiocyanates
Thiocyanato-de-halogenation

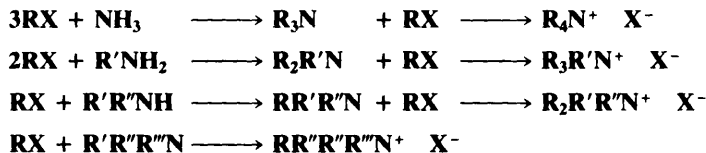$$RX + SCN^- \longrightarrow RSCN + X^-$$

Alkyl halides or sulfuric or sulfonic esters can be heated with sodium or potassium thiocyanate to give alkyl thiocyanates,[801] though the attack by the analogous cyanate ion **(0-62)** gives exclusive N-alkylation. Primary amines can be converted to thiocyanates by the Katritzky pyrylium–pyridinium method (p. 354).[802]
    OS **II**, 366.

Nitrogen Nucleophiles

A. Attack by NH_2, NHR, or NR_2 at an Alkyl Carbon

0-43 Alkylation of Amines
Amino-de-halogenation

$$3RX + NH_3 \longrightarrow R_3N \quad + RX \longrightarrow R_4N^+ \ \ X^-$$

$$2RX + R'NH_2 \longrightarrow R_2R'N \quad + RX \longrightarrow R_3R'N^+ \ \ X^-$$

$$RX + R'R''NH \longrightarrow RR'R''N + RX \longrightarrow R_2R'R''N^+ \ \ X^-$$

$$RX + R'R''R'''N \longrightarrow RR'R''R'''N^+ \ \ X^-$$

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[803] and quaternary ammonium salts. If ammonia is the nucleophile,[804] 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*.[805] 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. However, the limitations of this approach can be seen in the reaction of a saturated solution of ammonia in 90% ethanol with ethyl bromide

[801]For a review of thiocyanates, see Guy, in Patai *The Chemistry of Cyanates and Their Thio Derivatives*, pt. 2; pp. 819-886, Wiley: New York, 1977, pp. 819-886.
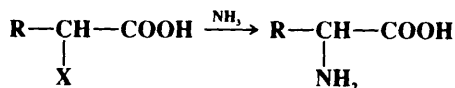   [802]Katritzky; Gruntz; Mongelli; Rezende *J. Chem. Soc., Perkin Trans. 1* **1979**, 1953. For the conversion of primary alcohols to thiocyanates see Tamura; Kawasaki; Adachi; Tanio; Kita *Tetrahedron Lett.* **1977**, 4417.
    [803]For reviews of this reaction, see Gibson, in Patai, Ref. 355, pp. 45-55; Spialter; Pappalardo *The Acyclic Aliphatic Tertiary Amines*; Macmillan: New York, 1965, pp. 14-29.
    [804]For a review of ammonia as a synthetic reagent, see Jeyaraman, in Pizey, Ref. 593, vol. 5, 1983, pp. 9-83.
    [805]For a review of stereoselectivity in this reaction, especially where the tertiary nitrogen is included in a ring, see Bottini, *Sel. Org. Transform.* **1970**, *1*, 89-142. For a review of quaternization of heteroaromatic rings, see Zoltewicz; Deady *Adv. Heterocycl. Chem.* **1978**, *22*, 71-121.

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%).[806] 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.

$$R-\underset{\underset{X}{|}}{CH}-COOH \xrightarrow{NH_3} R-\underset{\underset{NH_2}{|}}{CH}-COOH$$
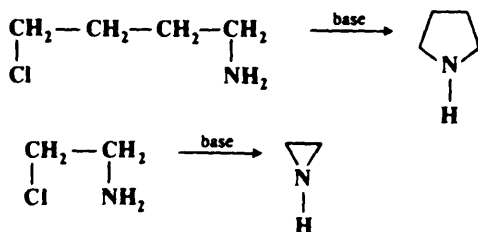
Primary amines can be prepared from alkyl halides by **0-44**, by **0-63**, by **0-61** followed by reduction of the azide (**9-53**), or by the Gabriel synthesis (**0-58**).

The immediate product in any particular step is the protonated amine, which, however, rapidly loses a proton to another molecule of ammonia or amine in an equilibrium process, e.g.,

$$RX + R_2NH \longrightarrow R_3\overset{\oplus}{N}H + R_2NH \rightleftharpoons R_3N + R_2\overset{\oplus}{N}H_2$$
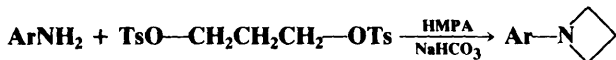
When it is desired to convert a primary or secondary amine directly to the quaternary salt (*exhaustive alkylation*), the rate can be increased by the addition of a nonnucleophilic strong base that serves to remove the proton from $RR'NH_2^+$ or $RR'R''NH^+$ and thus liberates the amine to attack another molecule of RX.[807]

The conjugate bases of ammonia and of primary and secondary amines (NH_2^-, RNH^-, R_2N^-) are sometimes used as nucleophiles,[808] but in most cases offer no advantage over ammonia or amines, since the latter are basic enough. This is in contrast to the analogous methods **0-1**, **0-12**, **0-35**, and **0-36**. Primary arylamines are easily alkylated, but diaryl- and triarylamines are very poor nucleophiles. However, the reaction has been carried out with diarylamines.[809] 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[810] (analogous to **0-13**):

$$\underset{\underset{Cl}{|}}{CH_2}-CH_2-CH_2-\underset{\underset{NH_2}{|}}{CH_2} \xrightarrow{base} \underset{\underset{H}{|}}{\overset{}{N}}$$

$$\underset{\underset{Cl}{|}}{CH_2}-\underset{\underset{NH_2}{|}}{CH_2} \xrightarrow{base} \underset{\underset{H}{|}}{\overset{}{N}}$$

Four-membered cyclic amines (azetidines) have been prepared in a different way:[811]

$$ArNH_2 + TsO-CH_2CH_2CH_2-OTs \xrightarrow[NaHCO_3]{HMPA} Ar-N$$

This reaction was also used to close five-, six-, and seven-membered rings.

[806]Werner *J. Chem. Soc.* **1918**, *113*, 899.
[807]Sommer; Jackson *J. Org. Chem.* **1970**, *35*, 1558; Sommer; Lipp; Jackson *J. Org. Chem.* **1971**, *36*, 824.
[808]For a discussion of the mechanism of the reaction between a primary halide and Ph_2NLi, see DePue; Collum *J. Am. Chem. Soc.* **1988**, *110*, 5524.
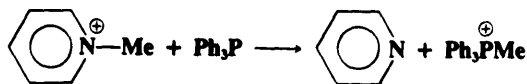[809]Patai; Weiss *J. Chem. Soc.* **1959**, 1035.
[810]For a review of aziridine formation by this method, see Dermer; Ham, Ref. 437, pp. 1-59.
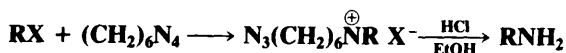[811]Juaristi; Madrigal *Tetrahedron* **1989**, *45*, 629.

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 $AlCl_3$[812] in a reaction related to **0-50**.

Phosphines behave similarly, and compounds of the type R_3P and R_4P^+ X^- can be so prepared. The reaction between triphenylphosphine and quaternary salts of nitrogen heterocycles in an aprotic solvent is probably the best way of dealkylating the heterocycles, e.g.,[813]

$$\langle \bigcirc \rangle \overset{\oplus}{N}-Me + Ph_3P \longrightarrow \langle \bigcirc \rangle N + Ph_3\overset{\oplus}{P}Me$$

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; **67**, 105, 133; **68**, 188, 227. Also see OS **II**, 395; **IV**, 950.
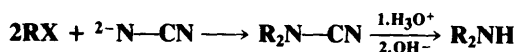
0-44 Conversion of Alkyl Halides to Primary Amines with Hexamethylenetetramine
  Amino-de-halogenation (overall transformation)

$$RX + (CH_2)_6N_4 \longrightarrow N_3(CH_2)_6\overset{\oplus}{N}R \ X^- \xrightarrow[EtOH]{HCl} RNH_2$$

Primary amines can be prepared from alkyl halides by the use of hexamethylenetetramine[814] 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 iodides.

OS **V**, 121.

0-45 Conversion of Alkyl Halides to Secondary Amines with Cyanamide
  Imino-de-dihalo-*aggre*-substitution (overall transformation)

$$2RX + {}^{2-}N-CN \longrightarrow R_2N-CN \xrightarrow[2.OH^-]{1.H_3O^+} R_2NH$$

A convenient way of obtaining secondary amines without contamination by primary or tertiary amines involves treatment of alkyl halides with the sodium or 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.[815] R may be primary, secondary, allylic, or benzylic. 1,ω-Dihalides give cyclic secondary amines.

OS **I**, 203.

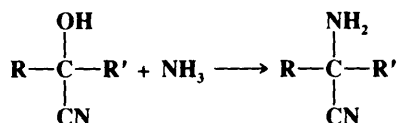[812]Kovacic; Lowery *J. Org. Chem.* **1969**, *34*, 911; Strand; Kovacic *J. Am. Chem. Soc.* **1973**, *95*, 2977.
[813]For example, see Deady; Finlayson; Korytsky *Aust. J. Chem.* **1979**, *32*, 1735.
[814]For a review of the reactions of this reagent, see Blažević; Kolbah; Belin; Šunjić; Kajfež *Synthesis* **1979**, 161-176.
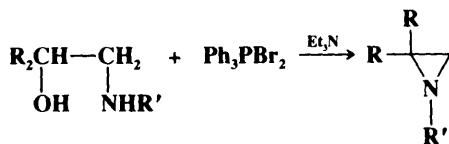[815]Jończyk; Ochal; Mąkosza *Synthesis* **1978**, 882.

0-46 Replacement of a Hydroxy by an Amino Group
Amino-de-hydroxylation

$$
R\!-\!\underset{\underset{CN}{|}}{\overset{\overset{OH}{|}}{C}}\!-\!R' + NH_3 \longrightarrow R\!-\!\underset{\underset{CN}{|}}{\overset{\overset{NH_2}{|}}{C}}\!-\!R'
$$

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 **6-50**). α-Hydroxy ketones (acyloins and benzoins) behave similarly.[816] 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$_3$P in THF, followed by water or aqueous acid.[817] This is a type of Mitsunobu reaction (see **0-22**). Other alcohol-to-amine Mitsunobu reactions have also been reported.[818] Primary and secondary alcohols ROH (but not methanol) can be converted to tertiary amines[819] R$_2'$NR by treatment with the secondary amine R$_2'$NH and (t-BuO)$_3$Al in the presence of Raney nickel.[820] The use of aniline gives secondary amines PhNHR. Allylic alcohols ROH react with primary (R'NH$_2$) or secondary (R$_2'$NH) amines in the presence of platinum or palladium complexes, to give secondary (RNHR') or tertiary (RNR$_2'$) allylic amines.[821]

β-Amino alcohols give aziridines when treated with triphenylphosphine dibromide in the presence of triethylamine:[822]

$$
\underset{\underset{OH}{|}\quad\underset{NHR'}{|}}{R_2CH\!-\!CH_2} + Ph_3PBr_2 \xrightarrow{Et_3N} R\!-\!\underset{\underset{R'}{|}}{\overset{\overset{R}{|}}{N}}\!\triangleleft
$$

The fact that inversion takes place at the OH carbon indicates that an S$_N$2 mechanism is involved, with OPPh$_3$ as the leaving group.

Alcohols can be converted to amines in an indirect manner.[823] The alcohols are converted to alkyloxyphosphonium perchlorates which in DMF successfully *monoalkylate* not only secondary but also primary amines.[824]

$$
ROH \xrightarrow[\text{2.NH}_4\text{ClO}_4]{\text{1.CCl}_4\text{–P(NMe}_2)_3} RO\overset{\oplus}{P}(NMe_2)_3 \quad CClO_4^- \xrightarrow[\text{R'R"NH}]{\text{DMF}} RR'R"N + OP(NMe_2)_3
$$

[816]For example, see Klemmensen; Schroll; Lawesson *Ark. Kemi* **1968**, *28*, 405.

[817]Fabiano; Golding; Sadeghi *Synthesis* **1987**, 190.

[818]See, for example, Henry; Marcin; McIntosh; Scola; Harris; Weinreb *Tetrahedron Lett.* **1989**, *30*, 5709; Edwards; Stemerick; McCarthy *Tetrahedron Lett.* **1990**, *31*, 3417.

[819]For other methods of converting certain alcohols to secondary and tertiary amines, see Murahashi; Kondo; Hakata *Tetrahedron Lett.* **1982**, *23*, 229; Baiker; Richarz *Tetrahedron Lett.* **1977**, 1937, *Helv. Chim. Acta* **1978**, *61*, 1169, *Synth. Commun.* **1978**, *8*, 27; Grigg; Mitchell; Sutthivaiyakit; Tongpenyai *J. Chem. Soc., Chem. Commun* **1981**, 611; Arcelli; Bui-The-Khai; Porzi *J. Organomet. Chem.* **1982**, *235*, 93; Kelly; Eskew; Evans *J. Org. Chem.* **1986**, *51*, 95; Huh; Tsuji; Kobayashi; Okuda; Watanabe *Chem. Lett.* **1988**, 449.

[820]Botta; De Angelis; Nicoletti *Synthesis* **1977**, 722.

[821]Atkins; Walker; Manyik *Tetrahedron Lett.* **1970**, 3821; Tsuji; Takeuchi; Ogawa; Watanabe *Chem. Lett.* **1986**, 293.

[822]Okada; Ichimura; Sudo *Bull. Chem. Soc. Jpn.* **1970**, *43*, 1185. See also Pfister *Synthesis* **1984**, 969; Suzuki; Tani *Chem. Lett.* **1984**, 2129; Marsella *J. Org. Chem.* **1987**, *52*, 467.

[823]For some other indirect methods, see White; Ellinger *J. Am. Chem. Soc.* **1965**, *87*, 5261; Burgess; Penton; Taylor *J. Am. Chem. Soc.* **1970**, *92*, 5224; Hendrickson; Joffee *J. Am. Chem. Soc.* **1973**, *95*, 4083; Trost; Keinan *J. Org. Chem.* **1979**, *44*, 3451; Ref 619 in Chapter 19.

[824]Castro; Selve *Bull. Soc. Chim. Fr.* **1971**, 4368. For a similar method, see Tanigawa; Murahashi; Moritani *Tetrahedron Lett.* **1975**, 471.
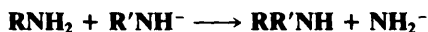
Thus by this means secondary as well as tertiary amines can be prepared in good yields.

A solution of the sodium salt of N-methylaniline in HMPA can be used to cleave the methyl group from aryl methyl ethers:[825] $ArOMe + PhNMe^- \rightarrow ArO^- + PhNMe_2$. This reagent also cleaves benzylic groups. In a similar reaction, methyl groups of aryl methyl ethers can be cleaved with lithium diphenylphosphide Ph_2PLi.[826] This reaction is specific for methyl ethers and can be carried out in the presence of ethyl ethers with high selectivity.
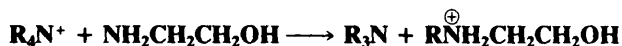
OS **II**, 29, 231; **IV**, 91, 283; **VI**, 567, 788; **VII**, 501. Also see OS **I**, 473; **III**, 272, 471.

0-47   Transamination
Alkylamino-de-amination

$$RNH_2 + R'NH^- \longrightarrow RR'NH + NH_2^-$$

Where the nucleophile is the conjugate base of a primary amine, NH_2 can be a leaving group. The method has been used to prepare secondary amines.[827] In another process, primary amines are converted to secondary amines in which both R groups are the same $(2RNH_2 \rightarrow R_2NH + NH_3)$[828] by refluxing in xylene in the presence of Raney nickel.[829] Quaternary salts can be dealkylated with ethanolamine.[830]

$$R_4N^+ + NH_2CH_2CH_2OH \longrightarrow R_3N + \overset{\oplus}{R}NH_2CH_2CH_2OH$$

In this reaction, methyl groups are cleaved in preference to other saturated alkyl groups. A similar reaction takes place between a Mannich base (see **6-16**) and a secondary amine, where the mechanism is elimination–addition (see p. 338). See also **9-5**.

OS **V**, 1018.

0-48   Alkylation of Amines with Diazo Compounds
Hydro,dialkylamino-de-diazo-bisubstitution

$$CR_2N_2 + R_2'NH \overset{BF_3}{\longrightarrow} CHR_2NR_2'$$

The reaction of diazo compounds with amines is similar to **0-15**.[831] 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.[832] The most common substrate is diazomethane,[593] 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 **0-43**, 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.

[825]Loubinoux; Coudert; Guillaumet *Synthesis* **1980**, 638.
[826]Ireland; Walba *Org. Synth.* *VI*, 567.
[827]Baltzly; Blackman *J. Org. Chem.* **1963**, *28*, 1158.
[828]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 *Russ. Chem. Rev.* **1978**, *47*, 297-306.
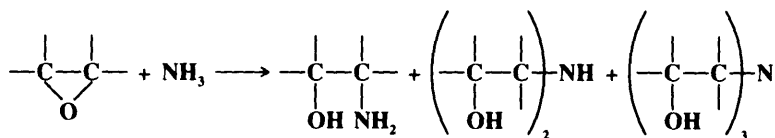[829]De Angelis; Grgurina; Nicoletti *Synthesis* **1979**, 70; See also Ballantine; Purnell; Rayanakorn; Thomas; Williams *J. Chem. Soc., Chem. Commun.* **1981**, 9; Arcelli; Bui-The-Khai; Porzi *J. Organomet. Chem.* **1982**, *231*, C31; Jung; Fellmann; Garrou *Organometallics* **1983**, *2*, 1042; Tsuji; Shida; Takeuchi; Watanabe *Chem. Lett.* **1984**, 889; Bank; Jewett *Tetrahedron Lett.* **1991**, *32*, 303.
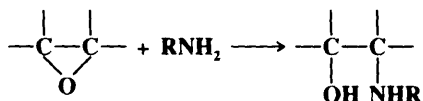[830]Hünig; Baron *Chem. Ber.* **1957**, *90*, 395, 403.
[831]Müller; Huber-Emden; Rundel *Liebigs. Ann. Chem.* **1959**, *623*, 34.
[832]Saegusa; Ito; Kobayashi; Hirota; Shimizu *Tetrahedron Lett.* **1966**, 6131.

0-49   Amination of Epoxides
(3)OC-seco-Amino-de-alkoxylation

$$-\overset{|}{\underset{\underset{O}{}}{C}}\overset{|}{-}\overset{|}{C}- + NH_3 \longrightarrow -\overset{|}{\underset{\underset{OH}{}}{C}}-\overset{|}{\underset{\underset{NH_2}{}}{C}}- + \left(-\overset{|}{\underset{\underset{OH}{}}{C}}-\overset{|}{C}-\right)_2 NH + \left(-\overset{|}{\underset{\underset{OH}{}}{C}}-\overset{|}{C}-\right)_3 N$$

The reaction between epoxides and ammonia is a general and useful method for the preparation of β-hydroxyamines.[833] Ammonia gives largely the primary amine, but also some secondary and tertiary amines. The useful solvents, the ethanolamines, are prepared by this reaction. For another way of accomplishing this conversion, see **0-51**. Primary and secondary amines give, respectively, secondary and tertiary amines,[834] e.g.,
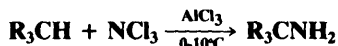
$$-\overset{|}{\underset{\underset{O}{}}{C}}\overset{|}{-}\overset{|}{C}- + RNH_2 \longrightarrow -\overset{|}{\underset{\underset{OH}{}}{C}}-\overset{|}{\underset{\underset{NHR}{}}{C}}-$$

Episulfides, which can be generated in situ in various ways, react similarly to give β-amino thiols,[835] and aziridines give 1,2-diamines.[836] Triphenylphosphine similarly reacts with epoxides to give an intermediate that undergoes elimination to give olefins (see the Wittig reaction, **6-47**).
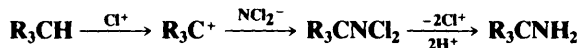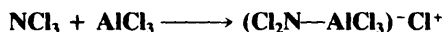
There are no OS references, but see OS **VI**, 652 for a related reaction.

0-50   Amination of Alkanes
Amino-de-hydrogenation or **Amination**

$$R_3CH + NCl_3 \xrightarrow[\text{0-10°C}]{\text{AlCl}_3} R_3CNH_2$$

Alkanes, arylalkanes, and cycloalkanes can be aminated, at tertiary positions only, by treatment with trichloroamine and aluminum chloride at 0 to 10°C.[837] For example, p-MeC$_6$H$_4$CHMe$_2$ gives p-MeC$_6$H$_4$CMe$_2$NH$_2$, 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 t-alkyl amines. The mechanism has been rationalized as an S$_N$1 process with H⁻ as the leaving group:[837]

$$NCl_3 + AlCl_3 \longrightarrow (Cl_2N\text{—}AlCl_3)^- Cl^+$$

$$R_3CH \xrightarrow{Cl^+} R_3C^+ \xrightarrow{NCl_2^-} R_3CNCl_2 \xrightarrow[2H^+]{-2Cl^+} R_3CNH_2$$
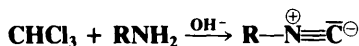
See also **2-11**.
OS **V**, 35.

[833]For an example, see McManus; Larson; Hearn *Synth. Commun.* **1973**, *3*, 177.
[834]For improved methods, see Carre; Houmounou; Caubere *Tetrahedron Lett.* **1985**, *26*, 3107; Fujiwara; Imada; Baba; Matsuda *Tetrahedron Lett.* **1989**, *30*, 739; Yamada; Yumoto; Yamamoto *Tetrahedron Lett.* **1989**, *30*, 4255; Chini; Crotti; Macchia *Tetrahedron Lett.* **1990**, *31*, 4661.
[835]Reynolds; Massad; Fields; Johnson *J. Org. Chem.* **1961**, *26*, 5109; Reynolds, Fields; Johnson *J. Org. Chem.* **1961**, *26*, 5111, 5116, 5119, 5125; Wineman; Gollis; James; Pomponi *J. Org. Chem.* **1962**, *27*, 4222.
[836]For a review, see Dermer; Ham, Ref. 437, pp. 262-268.
[837]Kovacic; Chaudhary *Tetrahedron* **1967**, *23*, 3563; Strand; Kovacic, Ref. 812; Wnuk; Chaudhary; Kovacic *J. Am. Chem. Soc.* **1976**, *98*, 5678, and references cited in these papers.

0-51   Formation of Isocyanides
Haloform–isocyanide transformation
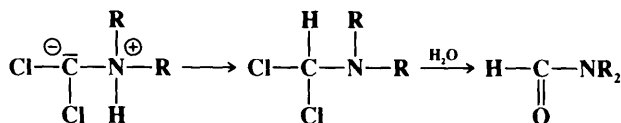
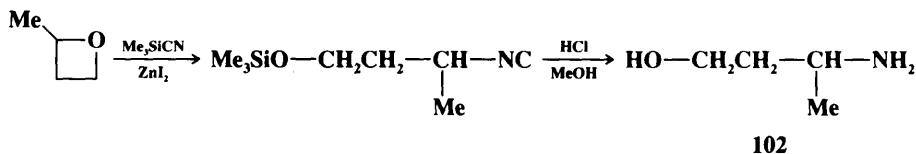$$CHCl_3 + RNH_2 \xrightarrow{OH^-} R{-}\overset{\oplus}{N}{\equiv}\overset{\ominus}{C}$$

Reaction with chloroform under basic conditions is a common test for primary amines, both aliphatic and aromatic, since isocyanides have very strong bad odors. The reaction probably proceeds by an S_N1cB mechanism with dichlorocarbene as an intermediate:

$$CHCl_3 + OH^- \xrightarrow[-Cl^-]{-H^+} CCl_2 \xrightarrow{R\bar{N}H_2} Cl{-}\overset{\overset{H}{\underset{\oplus}{|}}}{\underset{\underset{Cl}{\underset{|}{|}}}{\overset{\ominus}{C}}}{-}\overset{\underset{H}{|}}{N}{-}R \xrightarrow{-2HCl} \overset{\ominus}{C}{\equiv}\overset{\oplus}{N}{-}R$$

The reaction can also be used synthetically for the preparation of isocyanides, though yields are generally not high.[838] An improved procedure has been reported.[839] When secondary amines are involved, the adduct cannot lose two moles of HCl. Instead it is hydrolyzed to an N,N-disubstituted formamide:[840]

$$Cl{-}\overset{\overset{R}{\underset{\oplus}{|}}}{\underset{\underset{H}{\underset{||}{|}}}{\overset{\ominus}{C}}}{-}\overset{\underset{}{|}}{N}{-}R \longrightarrow Cl{-}\overset{\overset{H}{|}}{\underset{\underset{Cl}{|}}{C}}{-}\overset{\overset{R}{|}}{N}{-}R \xrightarrow{H_2O} H{-}\overset{\overset{}{\underset{\underset{O}{||}}{}}}{C}{-}NR_2$$
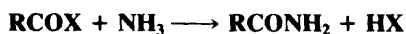
A completely different way of preparing isocyanides involves the reaction of epoxides or oxetanes with trimethylsilyl cyanide and zinc iodide, e.g.,[841]

$$\text{Me}\overset{O}{\square} \xrightarrow[\text{ZnI}_2]{\text{Me}_3\text{SiCN}} Me_3SiO{-}CH_2CH_2{-}\overset{\underset{Me}{|}}{CH}{-}NC \xrightarrow[\text{MeOH}]{\text{HCl}} HO{-}CH_2CH_2{-}\overset{\underset{Me}{|}}{CH}{-}NH_2$$

102

The products can be hydrolyzed to hydroxyamines, e.g., **102**.
OS **VI**, 232.

B.   Attack by NH$_2$, NHR, or NR$_2$ at an Acyl Carbon[842]

0-52   Acylation of Amines by Acyl Halides
Amino-de-halogenation

$$RCOX + NH_3 \longrightarrow RCONH_2 + HX$$

The treatment of acyl halides with ammonia or amines is a very general reaction for the preparation of amides.[843] The reaction is highly exothermic and must be carefully controlled,

[838]For a review of isocyanides, see Periasamy; Walborsky *Org. Prep. Proceed. Int.* **1979**, *11*, 293-311.
[839]Weber; Gokel *Tetrahedron Lett.* **1972**, 1637; Weber; Gokel; Ugi *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 530 [*Angew. Chem. 84*, 587].
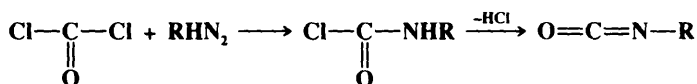[840]Saunders; Murray *Tetrahedron* **1959**, *6*, 88; Frankel; Feuer; Bank *Tetrahedron Lett.* **1959**, no. 7, 5.
[841]Gassman; Haberman *Tetrahedron Lett.* **1985**, *26*, 4971, and references cited therein.
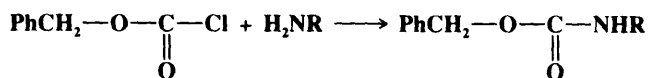[842]For a review, see Challis; Butler, in Patai, Ref. 355, pp. 279-290.
[843]For a review, see Beckwith, in Zabicky, Ref. 555, pp. 73-185.

usually by cooling or dilution. Ammonia gives unsubstituted amides, primary amines give N-substituted amides, and secondary amines give N,N-disubstituted amides. Arylamines can be similarly acylated. In some cases aqueous alkali is added to combine with the liberated HCl. This is called the *Schotten–Baumann procedure*, as in **0-20**.
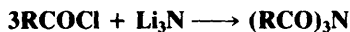
Hydrazine and hydroxylamine also react with acyl halides to give, respectively, hydrazides $RCONHNH_2$[844] and hydroxamic acids $RCONHOH$,[845] and these compounds are often made in this way. When phosgene is the acyl halide, both aliphatic and aromatic primary amines give chloroformamides $ClCONHR$ that lose HCl to give isocyanates $RNCO$.[846] This is one of the most common methods for the preparation of isocyanates.[847] Thiophosgene,[847a] sim-

$$\text{Cl—C—Cl} + RHN_2 \longrightarrow \text{Cl—C—NHR} \xrightarrow{\ -HCl\ } O{=}C{=}N{-}R$$
$$\quad\ \ \overset{\|}{O} \qquad\qquad\qquad\ \ \overset{\|}{O}$$

ilarly treated, gives isothiocyanates. A safer substitute for phosgene in this reaction is trichloromethyl chloroformate CCl_3OCOCl.[848] When chloroformates $ROCOCl$ are treated with primary amines, carbamates $ROCONHR'$ are obtained.[849] An example of this reaction is the use of benzyl chloroformate to protect the amino group of amino acids and peptides:

$$\text{PhCH}_2\text{—O—C—Cl} + H_2NR \longrightarrow \text{PhCH}_2\text{—O—C—NHR}$$
$$\qquad\qquad \overset{\|}{O} \qquad\qquad\qquad\qquad\ \ \overset{\|}{O}$$

The $PhCH_2OCO$ group is called the carbobenzoxy group, and is often abbreviated Cbz or Z. Another important group similarly used is the *t*-butoxycarbonyl group Me_3COCO, abbreviated as Boc. In this case, the chloride $Me_3COCOCl$ is unstable, so the anhydride $(Me_3COCO)_2O$ is used instead, in an example of **0-53**. Amino groups in general are often protected by conversion to amides. The treatment of acyl halides with lithium nitride gives N,N-diacyl amides (triacylamines):[850]
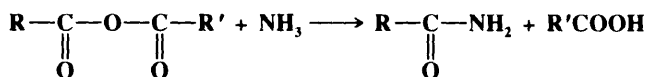
$$\textbf{3RCOCl} + \textbf{Li}_3\textbf{N} \longrightarrow \textbf{(RCO)}_3\textbf{N}$$

The reactions proceed by the tetrahedral mechanism.[851]

OS **I**, 99, 165; **II**, 76, 208, 278, 328, 453; **III**, 167, 375, 415, 488, 490, 613; **IV**, 339, 411, 521, 620, 780; **V**, 201, 336; **VI**, 382, 715; **VII**, 56, 287, 307; **67**, 187; **68**, 83. See also OS **VII**, 302.

0-53 Acylation of Amines by Anhydrides
    Amino-de-acyloxy-substitution

$$\text{R—C—O—C—R'} + NH_3 \longrightarrow \text{R—C—NH}_2 + R'\text{COOH}$$
$$\quad\ \overset{\|}{O} \quad\ \ \overset{\|}{O} \qquad\qquad\qquad\ \ \overset{\|}{O}$$

[844]For a review of hydrazides, see Paulsen; Stoye, in Zabicky, Ref. 555, pp. 515-600.
[845]For an improved method, see Ando; Tsumaki *Synth. Commun.* **1983**, *13*, 1053.
[846]For reviews of the preparation and reactions of isocyanates and isothiocyanates, see, respectively, the articles by Richter; Ulrich, pp. 619-818, and Drobnica; Kristián; Augustín pp. 1003-1221, in Patai *The Chemistry of Cyanates and Their Thio Derivatives*, pt. 2; Wiley: New York, 1977.
[847]For examples, see Ozaki *Chem. Rev.* **1972**, *72*, 457-496, pp. 457-460. For a review of the industrial preparation of isocyanates by this reaction, see Twitchett *Chem. Soc. Rev.* **1974**, *3*, 209-230.
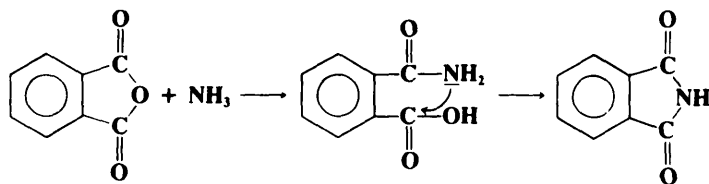[847a]For a review of thiophosgene, see Sharma *Sulfur Rep.* **1986**, *5*, 1-100.
[848]Kurita; Iwakura *Org. Synth. VI*, 715.
[849]For an improved procedure, see Raucher; Jones *Synth. Commun.* **1985**, *15*, 1025.
[850]Baldwin; Blanchard; Koening *J. Org. Chem.* **1965**, *30*, 671.
[851]Kivinen, Ref. 502; Bender; Jones *J. Org. Chem.* **1962**, *27*, 3771. See also Song; Jencks *J. Am. Chem. Soc.* **1989**, *111*, 8479.

This reaction, similar in scope and mechanism[852] to **0-52**, can be carried out with ammonia or primary or secondary amines.[853] However, ammonia and primary amines can also give imides, in which two acyl groups are attached to the nitrogen. This is especially easy with cyclic anhydrides, which produce cyclic imides.[854]

The second step in this case, which is much slower than the first, is the attack of the amide nitrogen on the carboxylic carbon. Unsubstituted and N-substituted amides have been used instead of ammonia. Since the other product of this reaction is RCOOH, this is a way of "hydrolyzing" such amides in the absence of water.[855]

Even though formic anhydride is not a stable compound (see p. 542), amines can be formylated with the mixed anhydride of acetic and formic acids HCOOCOMe[856] or with a mixture of formic acid and acetic anhydride. Acetamides are not formed with these reagents. Secondary amines can be acylated in the presence of a primary amine by conversion to their salts and addition of 18-crown-6.[857] The crown ether complexes the primary ammonium salt, preventing its acylation, while the secondary ammonium salts, which do not fit easily into the cavity, are free to be acylated.
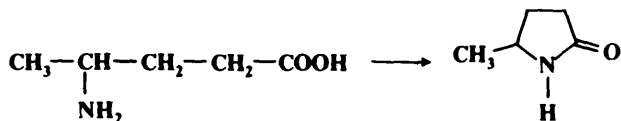
OS **I**, 457; **II**, 11; **III**, 151, 456, 661, 813; **IV**, 5, 42, 106, 657; **V**, 27, 373, 650, 944, 973; **VI**, 1; **VII**, 4, 70; **66**, 132.

0-54   Acylation of Amines by Carboxylic Acids
         Amino-de-hydroxylation

$$\textbf{RCOOH} + \textbf{NH}_3 \longrightarrow \textbf{RCOO}^- \textbf{NH}_4{}^+ \xrightarrow{\text{pyrolysis}} \textbf{RCONH}_2$$

When carboxylic acids are treated with ammonia or amines, salts are obtained. The salts of ammonia or primary or secondary amines can be pyrolyzed to give amides,[858] but the method is less convenient than **0-52**, **0-53**, and **0-55** and is seldom of preparative value.[859] Lactams are produced fairly easily from γ- or δ-amino acids,[860] e.g.,

Although treatment of carboxylic acids with amines does not directly give amides, the reaction can be made to proceed in good yield at room temperature or slightly above by

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[852]For a discussion of the mechanism, see Kluger; Hunt *J. Am. Chem. Soc.* **1989**, *111*, 3325.
[853]For a review, see Beckwith, in Zabicky, Ref. 555, pp. 86-96.
[854]For reviews of imides, see Wheeler; Rosado, in Zabicky, Ref. 555, pp. 335-381; Hargreaves; Pritchard; Dave *Chem. Rev.* **1970**, *70*, 439-469 (cyclic imides).
[855]Eaton; Rounds; Urbanowicz; Gribble *Tetrahedron Lett.* **1988**, *29*, 6553.
[856]For the formylation of amines with the mixed anhydride of formic and trimethylacetic acid, see Vlietstra; Zwikker; Nolte; Drenth *Recl. Trav. Chim. Pays-Bas* **1982**, *101*, 460.
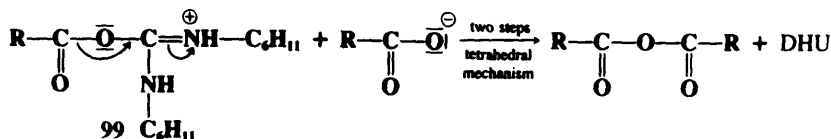[857]Barrett; Lana *J. Chem. Soc., Chem. Commun.* **1978**, 471.
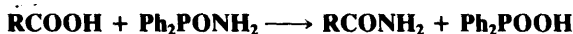[858]For example, see Mitchell; Reid *J. Am. Chem. Soc.* **1931**, *53*, 1879.
[859]For a review of amide formation from carboxylic acids, see Beckwith, in Zabicky, Ref. 555, pp. 105-109.
[860]See, for example, Bladé-Font *Tetrahedron Lett.* **1980**, *21*, 2443.

the use of coupling agents,[861] the most important of which is dicyclohexylcarbodiimide. This is very convenient and is used[862] a great deal in peptide synthesis.[863] The mechanism is probably the same as in **0-22** up to the formation of **99**. This intermediate is then attacked by another molecule of $RCOO^-$ to give the anhydride $(RCO)_2O$, which is the actual species that reacts with the amine:

$$R-\overset{\overset{\oplus}{|}}{\underset{\underset{O}{||}}{C}}-\overset{}{\underset{\underset{NH}{|}}{O}}-C=NH-C_6H_{11} + R-\overset{}{\underset{\underset{O}{||}}{C}}-\overset{\ominus}{O} \xrightarrow[\text{mechanism}]{\substack{\text{two steps} \\ \text{tetrahedral}}} R-\overset{}{\underset{\underset{O}{||}}{C}}-O-\overset{}{\underset{\underset{O}{||}}{C}}-R + DHU$$

$$\textbf{99}\;\; C_6H_{11}$$

The anhydride has been isolated from the reaction mixture and then used to acylate an amine.[864] Other promoting agents[865] are N,N'-carbonyldiimidazole (**100**, p. 396),[664] which behaves as in reaction **0-22**, $POCl_3$,[866] $TiCl_4$,[867] sulfuryl chloride fluoride SO_2ClF,[868] benzotriazol-1-yl diethyl phosphate,[869] $Ti(OBu)_4$,[870] molecular sieves,[871] N,N,N',N'-tetramethyl(succinimido)uronium tetrafluoroborate,[872] CBMIT[656] (p. 396), Lawesson's reagent (p. 893),[873] chlorosulfonyl isocyanate,[660] P_2I_4,[874] pyridinium salts– Bu_3N,[875] and a mixture of Bu_3P and $PhCNO$.[876] Certain dicarboxylic acids form amides simply on treatment with primary aromatic amines. In these cases the cyclic anhydride is an intermediate and is the species actually attacked by the amine.[877] Carboxylic acids can also be converted to amides by heating with amides of carboxylic acids (exchange),[878] sulfonic acids, or phosphoric acids, e.g.,[879]

$$\text{RCOOH} + \text{Ph}_2\text{PONH}_2 \longrightarrow \text{RCONH}_2 + \text{Ph}_2\text{POOH}$$

or by treatment with trisalkylaminoboranes $[B(NHR')_3]$, with trisdialkylaminoboranes $[B(NR_2')_3]$,[880]

$$\text{RCOOH} + \text{B(NR}_2')_3 \longrightarrow \text{RCONR}_2'$$

or with bis(diorganoamino)magnesium reagents $(R_2N)_2Mg$.[881]

[861]For a review of peptide synthesis with dicyclohexylcarbodiimide and other coupling agents, see Klausner; Bodansky *Synthesis* **1972**, 453-463.

[862]It was first used this way by Sheehan; Hess *J. Am. Chem. Soc.* **1955**, 77, 1067.

[863]For a treatise on peptide synthesis, see Gross; Meienhofer *The Peptides*, 3 vols.; Academic Press: New York, 1979-1981. For a monograph, see Bodanszky; Bodanszky *The Practice of Peptide Synthesis*; Springer: New York, 1984.

[864]Schüssler; Zahn *Chem. Ber.* **1962**, 95, 1076; Rebek; Feitler *J. Am. Chem. Soc.* **1974**, 96, 1606. There is evidence that some of the **99** is converted to products by another mechanism. See Rebek; Feitler *J. Am. Chem. Soc.* **1973**, 95, 4052.

[865]For a list of reagents, with references, see Ref. 508, pp. 972-976.

[866]Klosa *J. Prakt. Chem.* **1963**, [4] 19, 45.

[867]Wilson; Weingarten *Can. J. Chem.* **1970**, 48, 983.

[868]Olah; Narang; Garcia-Luna *Synthesis* **1980**, 661.

[869]Kim; Chang; Ko *Tetrahedron Lett.* **1985**, 26, 1341.

[870]Shteinberg; Kondratov; Shein *J. Org. Chem. USSR* **1988**, 24, 1774.

[871]Cossy; Pale-Grosdemange *Tetrahedron Lett.* **1989**, 30, 2771.

[872]Bannwarth; Knorr *Tetrahedron Lett.* **1991**, 32, 1157.

[873]Thorsen; Andersen; Pedersen; Yde; Lawesson *Tetrahedron* **1985**, 41, 5633.

[874]Suzuki; Tsuji; Hiroi; Sato; Osuka *Chem. Lett.* **1983**, 449.

[875]Bald; Saigo; Mukaiyama *Chem. Lett.* **1975**, 1163. See also Mukaiyama; Aikawa; Kobayashi *Chem. Lett.* **1976**, 57.

[876]Grieco; Clark; Withers *J. Org. Chem.* **1979**, 44, 2945.

[877]Higuchi; Miki; Shah; Herd *J. Am. Chem. Soc.* **1963**, 85, 3655.

[878]For example, see Schindbauer *Monatsh. Chem.* **1968**, 99, 1799.

[879]Zhmurova; Voitsekhovskaya; Kirsanov *J. Gen. Chem. USSR* **1959**, 29, 2052. See also Kopecký; Šmejkal *Chem. Ind. (London)* **1966**, 1529; Liu; Chan; Lee *Synth. Commun.* **1979**, 9, 31.

[880]Pelter; Levitt; Nelson *Tetrahedron* **1970**, 26, 1539; Pelter; Levitt *Tetrahedron* **1970**, 26, 1545, 1899.

[881]Sanchez; Vest; Despres *Synth. Commun.* **1989**, 19, 2909.

An important technique, discovered by R. B. Merrifield in 1963[882] and since used for the synthesis of many peptides,[883] is called *solid phase synthesis* or *polymer-supported synthesis*.[884] The reactions used are the same as in ordinary synthesis, but one of the reactants is anchored onto a solid polymer. For example, if it is desired to couple two amino acids (to form a dipeptide), the polymer selected might be polystyrene with CH_2Cl side chains (Fig. 10.2, **103**). One of the amino acids, protected by a *t*-butoxycarbonyl group (Boc), would then be coupled to the side chains (step A). It is not necessary that all the side chains be converted, but a random selection will be. The Boc group is then removed by hydrolysis with trifluoroacetic acid in CH_2Cl_2 (step B) and the second amino acid is coupled to the first, using DCC or some other coupling agent (step C). The second Boc group is removed (step D), resulting in a dipeptide that is still anchored to the polymer. If this dipeptide is the desired product, it can be cleaved from the polymer by various methods,[885] one of which is treatment with HF (step E). If a longer peptide is wanted, additional amino acids can be added by repeating steps C and D.
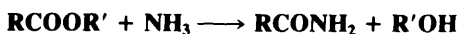
The basic advantage of the polymer support techniques is that the polymer (including all chains attached to it) is easily separated from all other reagents, because it is insoluble in the solvents used. Excess reagents, other reaction products (such as DHU), side products, and the solvents themselves are quickly washed away. Purification of the polymeric species (such as **104**, **105**, and **106**) is rapid and complete. The process can even be automated,[886] to the extent that six or more amino acids can be added to a peptide chain in one day. Commercial automated peptide synthesizers are now available.[887]

Although the solid phase technique was first developed for the synthesis of peptide chains and has seen considerable use for this purpose, it has also been used to synthesize chains of polysaccharides and polynucleotides; in the latter case, solid phase synthesis has almost completely replaced synthesis in solution.[888] The technique has been applied less often to reactions in which only two molecules are brought together (nonrepetitive syntheses), but many examples have been reported.[889]

OS **I**, 3, 82, 111, 172, 327; **II**, 65, 562; **III**, 95, 328, 475, 590, 646, 656, 768; **IV**, 6, 62, 513; **V**, 670, 1070; **69**, 55. Also see OS **III**, 360; **VI**, 263; **67**, 69.

0-55 Acylation of Amines by Carboxylic Esters
Amino-de-alkoxylation

$$RCOOR' + NH_3 \longrightarrow RCONH_2 + R'OH$$

[882]Merrifield *J. Am. Chem. Soc.* **1963**, *85*, 2149.
[883]For a monograph on solid state peptide synthesis, see Birr *Aspects of the Merrifield Peptide Synthesis*; Springer: New York, 1978. For reviews, see Bayer *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 113-129 [*Angew. Chem. 103*, 117-133]; Kaiser *Acc. Chem. Res.* **1989**, *22*, 47-54; Jacquier *Bull. Soc. Chim. Fr.* **1989**, 220-236; Barany; Kneib-Cordonier; Mullen *Int. J. Pept. Protein Res.* **1987**, *30*, 705-739; Andreev; Samoilova; Davidovich; Rogozhin *Russ. Chem. Rev.* **1987**, *56*, 366-381; in vol. 2 of Ref. 863, the articles by Barany; Merrifield, pp. 1-184, Fridkin, pp. 333-363; Erickson; Merrifield, in Neurath; Hill; Boeder *The Proteins*, 3rd ed., vol. 2; Academic Press: New York, 1976, pp. 255-527. For R. B. Merrifield's Nobel Prize lecture, see Merrifield *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 799-810 [*Angew. Chem. 97*, 801-812], *Chem. Scr.* **1985**, *25*, 121-131.
[884]For monographs on solid phase synthesis in general, see Laszlo *Preparative Organic Chemistry Using Supported Reagents*; Academic Press: New York, 1987; Mathur; Narang; Williams *Polymers as Aids in Organic Chemistry*; Academic Press: New York 1980; Hodge; Sherrington *Polymer-supported Reactions in Organic Synthesis*; Wiley: New York, 1980. For reviews, see Sheppard, *Chem. Br.* **1983**, 402-414; Pillai; Mutter *Top. Curr. Chem.* **1982**, *106*, 119-175; Akelah; Sherrington *Chem. Rev.* **1981**, *81*, 557-587; Akelah *Synthesis* **1981**, 413-438; Rebek *Tetrahedron* **1979**, *35*, 723-731; McKillop; Young *Synthesis* **1979**, 401-422, 481-500; Neckers, *CHEMTECH* **1978** (Feb.), 108-116; Crowley; Rapoport *Acc. Chem. Res.* **1976**, *9*, 135-144; Patchornik; Kraus *Pure Appl. Chem.* **1975**, *43*, 503-526.
[885]For some of these methods, see Whitney; Tam; Merrifield *Tetrahedron* **1984**, *40*, 4237.
[886]This was first reported by Merrifield; Stewart; Jernberg *Anal. Chem.* **1966**, *38*, 1905.
[887]For a discussion of automated organic synthesis, see Frisbee; Nantz; Kramer; Fuchs *J. Am. Chem. Soc.* **1984**, *106*, 7143. For an improved method, see Schnorrenberg; Gerhardt *Tetrahedron* **1989**, *45*, 7759.
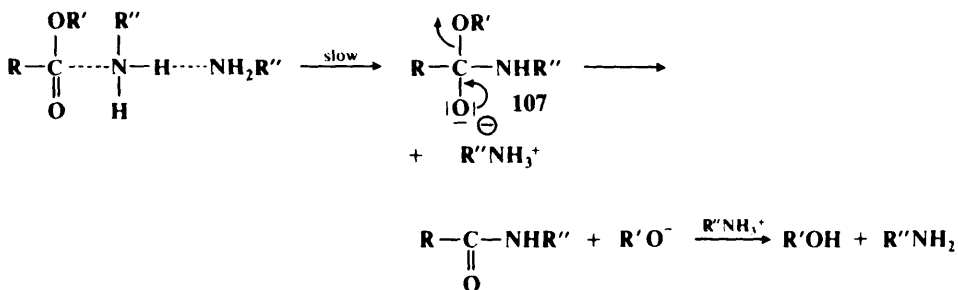[888]For a review, see Bannwarth *Chimia* **1987**, *41*, 302-317.
[889]For reviews, see Fréchet *Tetrahedron* **1981**, *37*, 663-683; Fréchet, in Hodge; Sherrington, Ref. 884, pp. 293-342, Leznoff, *Acc. Chem. Res.* **1978**, *11*, 327-333, *Chem. Soc. Rev.* **1974**, *3*, 64-85.

FIGURE 10.2 An outline of dipeptide synthesis by the solid phase technique.

The conversion of carboxylic esters to amides is a useful reaction, and unsubstituted, N-substituted, and N,N-disubstituted amides can be prepared this way from the appropriate amine.[890] Both R and R' can be alkyl or aryl. An especially good leaving group is *p*-nitrophenyl. Many simple esters (R = Me, Et, etc.) are not very reactive, and strongly basic catalysis has been used,[891] as well as catalysis by cyanide ion,[892] and high pressure.[893] β-Keto esters undergo the reaction especially easily.[894] In another procedure, esters are treated with dimethylaluminum amides Me_2AlNRR' to give good yields of amides under mild conditions.[895] The reagents are easily prepared from Me_3Al and NH_3 or a primary or secondary amine or their salts. The ester-to-amide conversion has also been accomplished electrochemically, by passing electric current in the cathodic compartment.[896]

As in **0-52** hydrazides and hydroxamic acids can be prepared from carboxylic esters, with hydrazine and hydroxylamine, respectively. Both hydrazine and hydroxylamine react more rapidly than ammonia or primary amines (the alpha effect, p. 351). Imidates $RC(=NH)OR'$ give amidines $RC(=NH)NH_2$. Lactones, when treated with ammonia or primary amines, give lactams. Lactams are also produced from γ- and δ-amino esters in an internal example of this reaction. Isopropenyl formate is a useful compound for the formylation of primary and secondary amines.[897]

$$R_2NH + HCOOCMe{=}CH_2 \longrightarrow R_2NCHO + CH_2{=}CMeOH \rightleftharpoons MeCOMe$$

Although more studies have been devoted to the mechanism of the acylation of amines with carboxylic esters than with other reagents, the mechanistic details are not yet entirely clear.[898] In its broad outlines, the mechanism appears to be essentially $B_{AC}2$.[899] Under the normal basic conditions, the reaction is general base-catalyzed,[900] indicating that a proton is being transferred in the rate-determining step and that two molecules of amine are involved.[901]

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[890]For a review, see Ref. 843, pp. 96-105. For a list of reagents, with references, see Ref. 508, pp. 987-988.

[891]For references, see Ref. 893.

[892]Högberg; Ström; Ebner; Rämsby *J. Org. Chem.* **1987**, *52*, 2033.

[893]Matsumoto; Hashimoto; Uchida; Okamoto; Otani *Chem. Ber.* **1989**, *122*, 1357.

[894]Labelle; Gravel *J. Chem. Soc., Chem. Commun.* **1985**, 105.

[895]Basha; Lipton; Weinreb *Tetrahedron Lett.* **1977**, 4171, *Org. Synth.* VI, 492; Levin; Turos; Weinreb *Synth. Commun.* **1982**, *12*, 989; Barrett; Dhanak *Tetrahedron Lett.* **1987**, *28*, 3327. For the extension of this method to the formation of hydrazides, see Benderly; Stavchansky *Tetrahedron Lett.* **1988**, *29*, 739.

[896]Arai; Shaw; Nozawa; Kawai; Nakajima *Tetrahedron Lett.* **1987**, *28*, 441.

[897]van Melick; Wolters *Synth. Commun.* **1972**, *2*, 83.
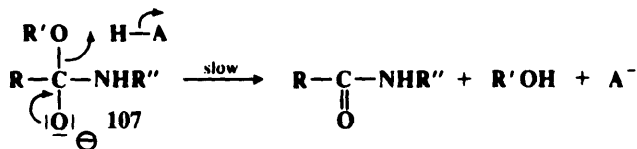
[898]For a discussion of the mechanism, see Satchell; Satchell, Ref. 197, pp. 410-431.

[899]Bunnett; Davis *J. Am. Chem. Soc.* **1960**, *82*, 665; Bruice; Donzel; Huffman; Butler *J. Am. Chem. Soc.* **1967**, *89*, 2106.

[900]Bunnett; Davis, Ref. 899, Jencks; Carriuolo *J. Am. Chem. Soc.* **1960**, *82*, 675; Bruice; Mayahi *J. Am. Chem. Soc.* **1960**, *82*, 3067.
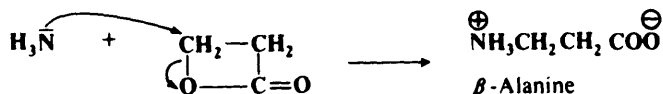
[901]Blackburn; Jencks *J. Am. Chem. Soc.* **1968**, *90*, 2638; Bruice; Felton *J. Am. Chem. Soc.* **1969**, *91*, 2799; Felton; Bruice *J. Am. Chem. Soc.* **1969**, *91*, 6721; Nagy; Reuliaux; Bertrand; Van Der Mensbrugghe; Leseul; Nagy *Bull. Soc. Chim. Belg.* **1985**, *94*, 1055.

Alternatively, another base, such as H_2O or OH^-, can substitute for the second molecule of amine. With some substrates and under some conditions, especially at low pH, the breakdown of **107** can become rate-determining.[902] The reaction also takes place under acidic conditions and is general acid-catalyzed, so that breakdown of **107** is rate-determining and proceeds as follows:[903]

$$R-\underset{\underset{\ominus}{\overset{|}{\underset{|}{C}}}{\overset{R'O}{\underset{}{|}}}-NHR'' \xrightarrow{\text{slow}} R-\underset{\overset{\|}{O}}{\overset{|}{C}}-NHR'' + R'OH + A^-$$

$$\mathbf{107}$$

HA may be $R''NH_3^+$ or another acid. **107** may or may not be further protonated on the nitrogen. Even under basic conditions, a proton donor may be necessary to assist leaving-group removal. Evidence for this is that the rate is lower with NR_2^- in liquid ammonia than with NHR_2 in water, apparently owing to the lack of acids to protonate the leaving oxygen.[904]
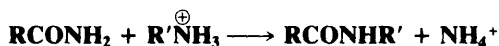
In the special case of β-lactones, where small-angle strain is an important factor, alkyl-oxygen cleavage is observed (BAL2 mechanism, as in the similar case of hydrolysis of β-lactones, **0-10**), and the product is not an amide but a β-amino acid:

$$H_3\overset{\frown}{N} + \overset{CH_2-CH_2}{\underset{O\underline{}C=O}{\overset{||}{}}} \longrightarrow \overset{\oplus}{N}H_3CH_2CH_2\overset{\ominus}{COO}$$

$$ \beta\text{-Alanine}$$

A similar result has been found for certain sterically hindered esters.[905] This reaction is similar to **0-43**, with OCOR as the leaving group.

OS **I**, 153, 179; **II**, 67, 85; **III**, 10, 96, 108, 404, 440, 516, 536, 751, 765; **IV**, 80, 357, 441, 486, 532, 566, 819; **V**, 168, 301, 645; **VI**, 203, 492, 620, 936; **VII**, 4, 30, 41, 411; **65**, 173; **67**, 52; **68**, 77. Also see OS **I**, 5; **V**, 582; **VII**, 75.

0-56 Acylation of Amines by Amides
Alkylamino-de-amination

$$RCONH_2 + R'\overset{\oplus}{N}H_3 \longrightarrow RCONHR' + NH_4^+$$

This is an exchange reaction and is usually carried out with the salt of the amine.[906] The leaving group is usually NH_2 rather than NHR or NR_2 and primary amines (in the form of their salts) are the most common reagents. BF_3 can be added to complex with the leaving ammonia. The reaction is often used to convert urea to substituted ureas: $NH_2CONH_2 +$ $RNH_3^+ \rightarrow NH_2CONHR + NH_4^+$.[907] N-R-Substituted amides are converted to N-R'-substituted amides by treatment with N_2O_4 to give an N-nitroso compound, followed by treat-

[902]Hansen *Acta Chem. Scand.* **1963**, *17*, 1307; Satterthwait; Jencks *J. Am. Chem. Soc.* **1974**, *96*, 7018, 7031; Blackburn; Jencks, Ref. 901; Gresser; Jencks *J. Am. Chem. Soc.* **1977**, *99*, 6963, 6970. See also Yang; Jencks *J. Am. Chem. Soc.* **1988**, *110*, 2972.
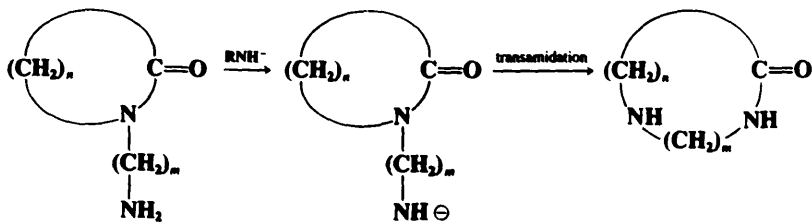[903]Blackburn; Jencks, Ref. 901.
[904]Bunnett; Davis, Ref. 899.
[905]Zaugg; Helgren; Schaefer *J. Org. Chem.* **1963**, *28*, 2617. See also Weintraub; Terrell *J. Org. Chem.* **1965**, *30*, 2470; Harada; Kinoshita *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2706.
[906]For a list of procedures, with references, see Ref. 508, pp. 990-991.
[907]For a discussion of the mechanism, see Chimishkyan; Snagovskii; Gulyaev; Leonova; Kusakin *J. Org. Chem. USSR* **1985**, *21*, 1955.

ment of this with a primary amine $R'NH_2$.[908] Lactams can be converted to ring-expanded lactams if a side chain containing an amino group is present on the nitrogen. A strong base

is used to convert the NH_2 to NH^-, which then acts as a nucleophile, expanding the ring by means of a transamidation.[909] The discoverers call it the Zip reaction, by analogy with the action of zippers.[910]

OS I, 302 (but see V, 589), 450, 453; II, 461; III, 151, 404; IV, 52, 361. See also OS 67, 60.

0-57 Acylation of Amines by Other Acid Derivatives

Acid derivatives that can be converted to amides include thiol acids RCOSH, thiol esters RCOSR',[911] acyloxyboranes $RCOB(OR')_2$,[912] silicic esters $(RCOO)_4Si$, 1,1,1-trihalo ketones $RCOCX_3$,[913] α-keto nitriles, acyl azides, and nonenolizable ketones (see the Haller–Bauer reaction 2-33).

OS III, 394; IV, 6, 569; V, 160, 166; VI, 1004.

C. Attack by NHCOR

0-58 N-Alkylation of Amides and Imides
Acylamino-de-halogenation

$$RX + {}^{\ominus}NHCOR' \longrightarrow RNHCOR'$$

Amides are very weak bases, 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.[914] Esters of sulfuric or sulfonic acids can also be substrates. Tertiary substrates give elimination. O-Alkylation is at times a side reaction.[915] Both amides and sulfonamides have been alkylated under phase transfer conditions.[916]

[908]Garcia; Vilarrasa Tetrahedron Lett. 1982, 23, 1127.

[909]Kramer; Guggisberg; Hesse; Schmid Angew. Chem. Int. Ed. Engl. 1977, 16, 861 [Angew. Chem. 89, 899], Helv. Chim. Acta 1978, 61, 1342; Askitoğlu; Guggisberg; Hesse Helv. Chim. Acta 1985, 68, 750. For a carbon analog, see Nakashita; Hesse Helv. Chim. Acta 1983, 66, 845; Süsse; Hájiček; Hesse Helv. Chim. Acta 1985, 68, 1986.

[910]For a review of this reaction, and of other ring expansions to form macrocyclic rings, see Stach; Hesse Tetrahedron 1988, 44, 1573-1590.

[911]For a discussion of the mechanism, see Douglas Acc. Chem. Res. 1986, 19, 186-192.

[912]The best results are obtained when the acyloxyboranes are made from a carboxylic acid and catecholborane (p. 615); Collum; Chen; Ganem J. Org. Chem. 1978, 43, 4393.

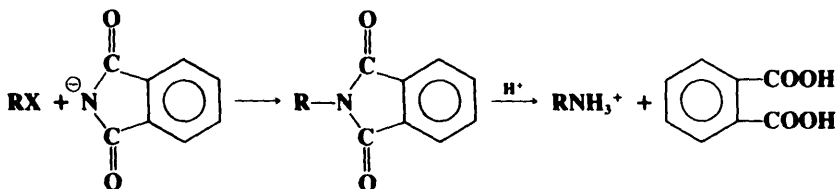[913]See, for example Salim; Nome; Rezende Synth. Commun. 1989, 19, 1181; Druzian; Zucco; Rezende; Nome J. Org. Chem. 1989, 54, 4767.

[914]For procedures, see Luh; Fung Synth. Commun. 1979, 9, 757; Koziara; Zawadzki; Zwierzak Synthesis 1979, 527; Gajda; Koziara; Zawadzki; Zwierzak Synthesis 1979, 549; Yamawaki; Ando; Hanafusa Chem. Lett. 1981, 1143; Sukata Bull. Chem. Soc. Jpn. 1985, 58, 838.
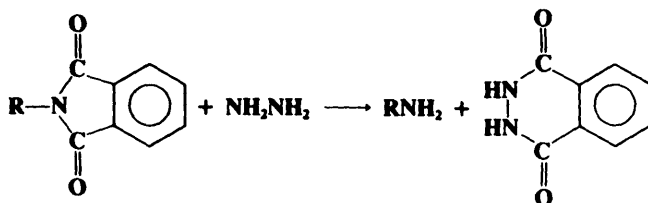
[915]For a review of alkylation of amides, see Challis; Challis, Ref. 555, pp. 734-754.

[916]Gajda; Zwierzak Synthesis 1981, 1005; Burke; Spillane Synthesis 1985, 935.

The *Gabriel synthesis*[917] for converting halides to primary amines is based on this reaction. The halide is treated with potassium phthalimide and the product hydrolyzed (**0-11**):

It is obvious that the primary amines formed in this reaction will be uncontaminated by secondary or tertiary amines (unlike **0-43**). The reaction is usually rather slow but can be conveniently speeded by the use of a dipolar aprotic solvent such as DMF[918] or with a crown ether.[919] 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,[920] in which the phthalimide is heated

with hydrazine in an exchange reaction, but other methods have been introduced, using Na_2S in aqueous THF or acetone,[921] $NaBH_4$–2-propanol followed by acetic acid;[922] 40% aqueous methylamine,[923] and *n*-pentylamine.[924]

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, see p. 396).[925]

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.[926] In another alternative,[927] the sodium salt of diphenyl-

[917]For a review, see Gibson; Bradshaw *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 919-930 [*Angew. Chem. 80*, 986-996].

[918]For example, see Sheehan; Bolhofer *J. Am. Chem. Soc.* **1950**, *72*, 2786. See also Landini; Rolla *Synthesis* **1976**, 389.

[919]Soai; Ookawa; Kato *Bull. Chem. Soc. Jpn.* **1982**, *55*, 1671.

[920]Ing; Manske *J. Chem. Soc.* **1926**, 2348.

[921]Kukolja; Lammert *J. Am. Chem. Soc.* **1975**, *97*, 5582.

[922]Osby; Martin; Ganem *Tetrahedron Lett.* **1984**, *25*, 2093.

[923]Wolfe; Hasan *Can. J. Chem.* **1970**, *48*, 3572.

[924]Kasztreiner; Szilágyi; Kosáry; Huszti *Acta. Chim. Acad. Sci. Hung.* **1975**, *84*, 167 [*Chem. Abstr. 83*, 113084].

[925]Mitsunobu; Wada; Sano *J. Am. Chem. Soc.* **1972**, *94*, 679; Grunewald; Paradkar; Pazhenchevsky; Pleiss; Sall; Seibel; Reitz *J. Org. Chem.* **1983**, *48*, 2321; Slusarska; Zwierzak *Liebigs Ann. Chem.* **1986**, 402; Kolasa; Miller *J. Org. Chem.* **1987**, *52*, 4978; Sammes; Thetford *J. Chem. Soc., Perkin Trans. 1* **1989**, 655.
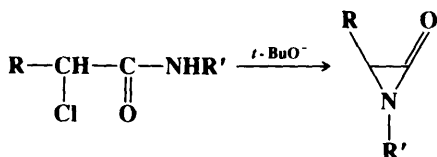
[926]Hebrard; Olomucki *Bull. Soc. Chim. Fr.* **1970**, 1938.

[927]For other methods, see Mukaiyama; Taguchi; Nishi *Bull. Chem. Soc. Jpn.* **1971**, *44*, 2797; Hendrickson; Bergeron; Sternbach *Tetrahedron* **1975**, *31*, 2517; Hendrickson; Bergeron; Giga; Sternbach *J. Am. Chem. Soc.* **1973**, *95*, 3412; Clarke; Elliott; Jones *J. Chem. Soc., Perkin Trans 1* **1978**, 1088; Mukaiyama; Tsuji; Watanabe *Chem. Lett.* **1978**, 1057; Zwierzak; Pilichowska *Synthesis* **1982**, 922; Calverley *Synth. Commun.* **1983**, *13*, 601; Harland; Hodge; Maughan; Wildsmith *Synthesis* **1984**, 941; Grehn; Ragnarsson *Synthesis* **1987**, 275; Dalla Croce; La Rosa; Ritieni *J. Chem. Res. (S)* **1988**, 346; Yinglin; Hongwen *Synthesis* **1990**, 122.

phosphinamide Ph_2PONH_2 is alkylated with primary[928] or secondary[929] alkyl halides or with alcohols in the presence of $MeSO_2Cl$,[930] which converts ROH to $ROSO_2Me$. Hydrolysis of Ph_2PONHR with HCl gives the amine.

Amides can also be alkylated with diazo compounds, as in **0-48**. 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 $F_3CCONRR'$.[931]

Internal N-alkylation has been used to prepare the highly strained compounds α-lactams.[932]

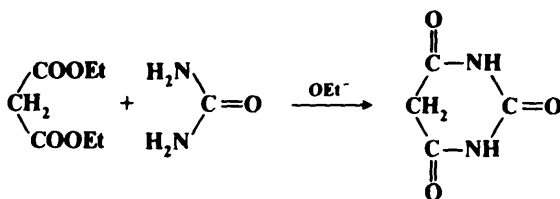$$R-\underset{\underset{Cl}{|}}{CH}-\underset{\underset{O}{\|}}{C}-NHR' \xrightarrow{\;t\text{-}BuO^-\;} \text{(α-lactam structure with R, O, N-R')}$$

OS **I**, 119, 203, 271; **II**, 25, 83, 208; **III**, 151; **IV**, 810; **V**, 1064; **VI**, 951; **VII**, 501.

0-59   N-Acylation of Amides and Imides
Acylamino-de-halogenation

$$RCOCl + H_2NCOR' \longrightarrow RCONHCOR'$$

Imides can be prepared by the attack of amides or their salts on acyl halides, anhydrides, and carboxylic acids or esters.[933] The best synthetic method for the preparation of acyclic imides is the reaction between an amide and an anhydride at 100°C catalyzed by H_2SO_4.[934] When acyl chlorides are treated with amides in a 2:1 molar ratio at low temperatures in the presence of pyridine, the products are N,N-diacylamides $(RCO)_3N$.[935]

This reaction is often used to prepare urea derivatives, an important example being the preparation of barbituric acid:[936]

$$\underset{\displaystyle \overset{COOEt}{\underset{COOEt}{CH_2}}}{} + \underset{\displaystyle \overset{H_2N}{\underset{H_2N}{C=O}}}{} \xrightarrow{\;OEt^-\;} \text{(barbituric acid ring structure)}$$

[928]Zwierzak; Podstawczyńska Angew. Chem. Int. Ed. Engl. **1977**, 16, 702 [Angew. Chem. **89**, 737].

[929]Ślusarska; Zwierzak Synthesis **1980**, 717.

[930]Ślusarska; Zwierzak Synthesis **1981**, 155.

[931]Nordlander; Catalane; Eberlein; Farkas; Howe; Stevens; Tripoulas Tetrahedron Lett. **1978**, 4987. For other methods, see Zwierzak; Brylikowska-Piotrowicz Angew. Chem. Int. Ed. Engl. **1977**, 16, 107 [Angew. Chem. **89**, 109]; Briggs; Brown; Jiricny; Meidine Synthesis **1980**, 295; Ref. 928.

[932]Baumgarten; Fuerholzer; Clark; Thompson J. Am. Chem. Soc. **1963**, 85, 3303; Quast; Leybach Chem. Ber. **1991**, 124, 849. For a review of α-lactams, see Lengyel; Sheehan Angew. Chem. Int. Ed. Engl. **1968**, 7, 25-36 [Angew. Chem. **80**, 27-37].

[933]For a review, see Challis; Challis, Ref. 555, pp. 759-773.

[934]Baburao; Costello; Petterson; Sander J. Chem. Soc. C **1968**, 2779; Davidson; Skovronek J. Am. Chem. Soc. **1958**, 80, 376.

[935]For example, see LaLonde; Davis J. Org. Chem. **1970**, 35, 771.

[936]For a review of barbituric acid, see Bojarski; Mokrosz; Bartoń; Paluchowska Adv. Heterocycl. Chem. **1985**, 38, 229-297.
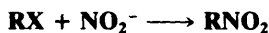
When the substrate is oxalyl chloride (ClCOCOCl) and the reagent an unsubstituted amide, an acyl isocyanate (RCONCO) is formed. The "normal" product (RCONHCOCOCl) does not form, or if it does, it rapidly loses CO and HCl.[937]

OS **II**, 60, 79, 422; **III**, 763; **IV**, 245, 247, 496, 566, 638, 662, 744; **V**, 204, 944.

D. Other Nitrogen Nucleophiles

0-60 Formation of Nitro Compounds[938]
Nitro-de-halogenation

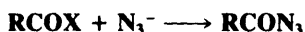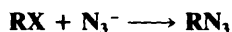$$RX + NO_2^- \longrightarrow RNO_2$$

Sodium nitrite can be used to form nitro compounds with primary or secondary alkyl bromides or iodides, though the method is of limited scope. Silver nitrite gives nitro compounds only when RX is a primary bromide or iodide. Nitrite esters are an important side product in all these cases **(0-32)** and become the major product (by an SN1 mechanism) when secondary or tertiary halides are treated with silver nitrite.
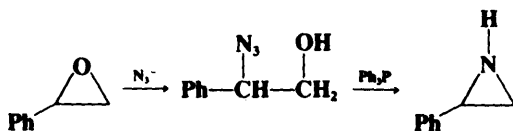
OS **I**, 410; **IV**, 368, 454, 724.

0-61 Formation of Azides
Azido-de-halogenation

$$RX + N_3^- \longrightarrow RN_3$$

$$RCOX + N_3^- \longrightarrow RCON_3$$

Alkyl azides can be prepared by treatment of the appropriate halide with azide ion.[939] Phase transfer catalysis[940] and ultrasound[941] have been used. Other leaving groups have also been used,[942] for example, OH,[943] OMs, OTs,[944] and OAc.[945] Epoxides react with NaN$_3$, with HN$_3$ in DMF,[946] or with HN$_3$–Et$_3$Al[947] to give β-azido alcohols; these are easily converted to aziridines,[948] e.g.,

[937]Speziale; Smith *J. Org. Chem.* **1962, 27,** 3742; Speziale; Smith; Fedder *J. Org. Chem.* **1965,** *30,* 4306.

[938]For reviews, see Larson, in Feuer *The Chemistry of the Nitro and Nitroso Groups,* pt. 1; Wiley: New York, 1969, pp. 325-339; Kornblum *Org. React.* **1962,** *12,* 101-156.

[939]For reviews, see Scriven; Turnbull *Chem. Rev.* **1988,** *88,* 297-368; Biffin; Miller; Paul, in Patai *The Chemistry of the Azido Group;* Wiley: New York, 1971, pp. 57-119.

[940]See Reeves; Bahr *Synthesis* **1979,** 823; Nakajima; Oda; Inouye *Tetrahedron Lett.* **1978,** 3107; Marti; Rico; Ader; de Savignac; Lattes *Tetrahedron Lett.* **1989,** *30,* 1245.

[941]Priebe *Acta Chem. Scand., Ser. B* **1984,** *38,* 895.

[942]See, for example, Svetlakov; Mikheev; Fedotov *J. Org. Chem. USSR* **1971,** 7, 2304; Hojo; Kobayashi; Soai; Ikeda; Mukaiyama *Chem. Lett.* **1977,** 635; Murahashi; Tanigawa; Imada; Taniguchi *Tetrahedron Lett.* **1986,** 27, 227.

[943]See, for example, Viaud; Rollin *Synthesis* **1990,** 130.

[944]Scriven; Turnbull, Ref. 939, p. 306.

[945]Murahashi; Taniguchi; Imada; Tanigawa *J. Org. Chem.* **1989,** *54,* 3292.

[946]Saito; Bunya; Inaba; Moriwake; Torii *Tetrahedron Lett.* **1985,** *26,* 5309.

[947]Mereyala; Frei *Helv. Chim. Acta* **1986,** *69,* 415.

[948]See, for example, Ittah; Sasson; Shahak; Tsaroom; Blum *J. Org. Chem.* **1978,** *43,* 4271. For the mechanism of the conversion to aziridines, see Pöchlauer; Müller; Peringer *Helv. Chim. Acta* **1984,** *67,* 1238.

This conversion has been used as a key step in the preparation of optically active aziridines from optically active 1,2-diols (prepared by **5-35**).[949] 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. 1163).[950]
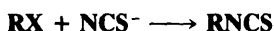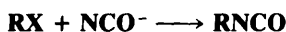
Tertiary alkyl azides can be prepared by stirring tertiary alkyl chlorides with NaN_3 and $ZnCl_2$ in CS_2[951] or by treating tertiary alcohols with NaN_3 and CF_3COOH[952] or with HN_3 and $TiCl_4$[953] or BF_3.[954] Acyl azides, which can be used in the Curtius reaction (**8-15**), can be similarly prepared from acyl halides or anhydrides.[955]

OS **III**, 846; **IV**, 715; **V**, 273, 586; **VI**, 95, 207, 210, 910; **VII**, 433; **69**, 205. See also OS **VII**, 206.

0-62 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 (**0-42**), but the cyanate ion practically always gives exclusive N-alkylation.[422] Primary alkyl halides have been converted to isocyanates by treatment with sodium nitrocyanamide $NaNCNNO_2$ and m-chloroperbenzoic acid, followed by heating of the initially produced $RN(NO_2)CN$.[956] When alkyl halides are treated with NCO^- in the presence of ethanol, carbamates can be prepared directly (see **6-8**).[957] Acyl halides give the corresponding acyl isocyanates and isothiocyanates.[958] For the formation of isocyanides, see **0-101**.
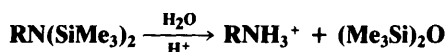
OS **III**, 735.

0-63 Formation of Bis(trimethylsilyl)amines
Bis(trimethylsilyl)amino-de-halogenation

$$RX + (Me_3Si)_2N^- Na^+ \longrightarrow RN(SiMe_3)_2$$

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.[959]

$$RN(SiMe_3)_2 \xrightarrow[\text{H}^+]{\text{H}_2\text{O}} RNH_3^+ + (Me_3Si)_2O$$

This is therefore an indirect way of converting halides to primary amines.

[949]Lohray; Gao; Sharpless *Tetrahedron Lett.* **1989**, *30*, 2623.
[950]Guy; Lemor; Doussot; Lemaire *Synthesis* **1988**, 900.
[951]Miller *Tetrahedron Lett.* **1975**, 2959. See also Koziara; Zwierzak *Tetrahedron Lett.* **1987**, *28*, 6513.
[952]Balderman; Kalir *Synthesis* **1978**, 24.
[953]Hassner; Fibiger; Andisik *J. Org. Chem.* **1984**, *49*, 4237.
[954]See, for example, Adam; Andrieux; Plat *Tetrahedron* **1985**, *41*, 399.
[955]For a review of acyl azides, see Lwowski, in Patai, Ref. 939, pp. 503-554.
[956]Manimaran; Wolford; Boyer *J. Chem. Res. (S)* **1989**, 331.
[957]Argabright; Rider; Sieck *J. Org. Chem.* **1965**, *30*, 3317; Effenberger; Drauz; Förster; Müller *Chem. Ber.* **1981**, *114*, 173.
[958]For reviews of acyl isocyanates, see Tsuge, in Patai, Ref. 585, pt. 1, pp. 445-506; Nuridzhanyan *Russ. Chem. Rev.* **1970**, *39*, 130-139; Lozinskii; Pel'kis *Russ. Chem. Rev.* **1968**, *37*, 363-375.
[959]Bestmann; Wölfel *Chem. Ber.* **1984**, *117*, 1250.

0-64   Formation of Azoxy Compounds
Alkyl-*NNO*-azoxy-de-halogenation

$$RX + R'N{=}N{-}O^- \longrightarrow R{-}\overset{\oplus}{\underset{\underset{O_{\ominus}}{|}}{N}}{=}N{-}R'$$

$$108$$

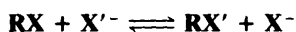The reaction between alkyl halides and alkanediazotates (**108**) gives azoxyalkanes.[960] R and R' may be the same or different, but neither may be aryl or tertiary alkyl. The reaction is regioselective; only the isomer shown is obtained.

Halogen Nucleophiles[961]

A.   Attack at an Alkyl Carbon

0-65   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.[962] 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.[963] Vinylic bromides give vinylic iodides with retention of configuration when treated with KI and a nickel bromide-zinc catalyst,[964] or with KI and CuI in hot HMPA.[965]

Fluorides[966] are prepared by treatment of other alkyl halides with any of a number of fluorinating agents, among them anhydrous HF (which is useful only for reactive substrates such as benzylic or allylic), AgF, KF, HgF_2, Bu_4N^+ HF_2^-,[967] BrF_3,[968] $Et_3N{\cdot}2HF$,[969] and, for polyhalo compounds (such as chloroform), HF plus SbF_3.[970] The equilibria in these cases

[960]For reviews, see Yandovskii; Gidaspov; Tselinskii *Russ. Chem. Rev.* **1980**, *49*, 237-248; Moss *Acc. Chem. Res.* **1974**, *7*, 421-427.

[961]For a review of the formation of carbon–halogen bonds, see Hudlicky; Hudlicky, in Patai; Rappoport, Ref. 88, pt. 2, pp. 1021-1172.

[962]For a list of reagents for alkyl halide interconversion, see Ref. 508, pp. 337-339.

[963]Miller; Nunn *J. Chem. Soc., Perkin Trans 1* **1976**, 416.

[964]Takagi; Hayama; Inokawa *Chem. Lett.* **1978**, 1435.

[965]Suzuki; Aihara; Yamamoto; Takamoto; Ogawa *Synthesis* **1988**, 236.

[966]For reviews of the introduction of fluorine into organic compounds, see Mann *Chem. Soc. Rev.* **1987**, *16*, 381-436; Rozen; Filler *Tetrahedron* **1985**, *41*, 1111-1153; Hudlický, Ref. 448, pp. 24-169; Sheppard; Sharts, Ref. 448, pp. 52-184, 409-430.

[967]Bosch; Camps; Chamorro; Gasol; Guerrero *Tetrahedron Lett.* **1987**, *28*, 4733. See also Cox; Terpinski; Lawrynowicz *J. Org. Chem.* **1984**, *49*, 3216.

[968]Kartashov; Chuvatkin; Kurskii; Boguslavskaya *J. Org. Chem. USSR* **1988**, *24*, 2279.

[969]Giudicelli; Picq; Veyron *Tetrahedron Lett.* **1990**, *31*, 6527.

[970]For reviews of the use of halogen exchange to prepare alkyl fluorides, see Sharts; Sheppard *Org. React.* **1974**, *21*, 125-406; Hudlický, Ref. 448, pp. 91-136.
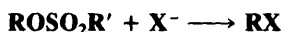
are shifted because the alkyl fluoride once formed has little tendency to react, owing to the extremely poor leaving-group ability of fluorine. Phase transfer catalysis of the exchange reaction is a particularly effective way of preparing both fluorides and iodides.[971]

Primary alkyl chlorides can be converted to bromides with ethyl bromide, N-methyl-2-pyrrolidinone and a catalytic amount of NaBr,[972] with LiBr under phase-transfer conditions,[973] and with $Bu_4N^+ Br^-$.[974] 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[975] (this procedure is also successful for chroride-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.[976] Primary iodides give the chlorides when treated with PCl_5 in $POCl_3$.[977] 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.[978]

OS **II**, 476; **IV**, 84, 525; **66**, 87.

0-66   Formation of Alkyl Halides from Esters of Sulfuric and Sulfonic Acids
Halo-de-sulfonyloxy-substitution, etc.

$$ROSO_2R' + X^- \longrightarrow RX$$

Alkyl sulfates, tosylates, and other esters of sulfuric and sulfonic acids can be converted to alkyl halides with any of the four halide ions.[979] Neopentyl tosylate reacts with Cl^-, Br^-, or I^- without rearrangement in HMPA.[980] Similarly, allylic tosylates can be converted to chlorides without allylic rearrangement by reaction with LiCl in the same solvent.[981] Inorganic esters are intermediates in the conversion of alcohols to alkyl halides with $SOCl_2$, PCl_5, PCl_3, etc. (**0-67**), but are seldom isolated.

OS **I**, 25; **II**, 111, 404; **IV**, 597, 753; **V**, 545.

0-67   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,[982] the most common of which are halogen acids HX and inorganic acid halides such as $SOCl_2$,[983] PCl_5, PCl_3, $POCl_3$, etc.[984] HBr is usually used for alkyl bromides and HI for alkyl iodides. These reagents are

[971]For reviews, see Starks; Liotta, Ref. 404, pp. 112-125; Weber; Gokel *Phase Transfer Catalysis in Organic Synthesis.* Ref. 404, pp. 117-124. See also Clark; Macquarrie *Tetrahedron Lett.* **1987**, *28*, 111; Bram; Loupy; Pigeon *Synth. Commun.* **1988**, *18*, 1661.
[972]Willy; McKean; Garcia *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1989. See also Babler; Spina *Synth. Commun.* **1984**, *14*, 1313.
[973]Sasson; Weiss; Loupy; Bram; Pardo *J. Chem. Soc., Chem. Commun.* **1986**, 1250; Loupy; Pardo *Synth. Commun.* **1988**, *18*, 1275.
[974]Bidd; Whiting *Tetrahedron Lett.* **1984**, *25*, 5949.
[975]Yoon; Kochi *J. Org. Chem.* **1989**, *54*, 3028.
[976]Svetlakov; Moisak; Averko-Antonovich *J. Org. Chem. USSR* **1969**, *5*, 971.
[977]Bartley; Carman; Russell-Maynard *Aust. J. Chem.* **1985**, *38*, 1879.
[978]Namavari; Satyamurthy; Phelps; Barrio *Tetrahedron Lett.* **1990**, *31*, 4973.
[979]For a list of reagents, with references, see Ref. 508, pp. 360-362.
[980]Stephenson; Solladié; Mosher, Ref. 248.
[981]Stork; Grieco; Gregson *Tetrahedron Lett.* **1969**, 1393.
[982]For a list of reagents, with references, see Ref. 508, pp. 353-360.
[983]For a review of thionyl chloride $SOCl_2$, see Pizey, Ref. 593, vol. 1, 1974, pp. 321-357.
[984]For a review, see Brown, in Patai, Ref. 575, pt. 1, pp.595-622.

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 (0-76) and, if the substrate is unsaturated, can also reduce the double bond.[985] 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. 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.[986] Primary alcohols give good yields of chlorides upon treatment with HCl in HMPA.[987] The inorganic acid chlorides $SOCl_2$, PCl_3, etc., give primary, secondary, or tertiary alkyl chlorides with much less rearrangement than is observed with HCl.

Analogous bromides and iodides, especially PBr_3, have also been used, but they are more expensive and used less often than HBr or HI, though some of them may also be generated in situ (e.g., PBr_3 from phosphorous and bromine). 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 0-66,[988] or by the use of phase transfer catalysis.[989] HF does not generally convert alcohols to alkyl fluorides.[990] The most important reagent for this purpose is the commercially available diethylaminosulfur trifluoride Et_2NSF_3 (DAST),[991] which converts primary, secondary, tertiary, allylic, and benzylic alcohols to fluorides in high yields under mild conditions.[992] Fluorides have also been prepared from alcohols by treatment with SF_4,[993] SeF_4,[994] TsF,[995] and indirectly, by conversion to a sulfate or tosylate, etc. (0-66).

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.[996] 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.[997]

Other reagents[998] have also been used, for example, $(RO)_3PRX$[999] and R_3PX_2[1000] (made from R_3P and X_2), which give good yields for primary (including neopentyl), secondary,

[985]Jones; Pattison *J. Chem. Soc. C* **1969**, 1046.
[986]Phase-transfer catalysts have been used instead of $ZnCl_2$; Landini; Montanari; Rolla *Synthesis* **1974**, 37.
[987]Fuchs; Cole *Can. J. Chem.* **1975**, *53*, 3620.
[988]Cason; Correia *J. Org. Chem.* **1961**, *26*, 3645.
[989]Dakka; Sasson *Tetrahedron Lett.* **1987**, *28*, 1223.
[990]For an exception, see Hanack; Eggensperger; Hähnle *Liebigs Ann. Chem.* **1962**, *652*, 96; See also Politanskii; Ivanyk; Sarancha; Shevchuk *J. Org. Chem. USSR* **1974**, *10*, 697.
[991]For a review of this reagent, see Hudlický *Org. React.* **1988**, *35*, 513-637.
[992]Middleton *J. Org. Chem.* **1975**, *40*, 574.
[993]For reviews, see Wang *Org. React.* **1985**, *34*, 319-400; Kollonitsch *Isr. J. Chem.* **1978**, *17*, 53-59; Boswell; Ripka; Scribner; Tullock *Org. React.* **1974**, *21*, 1-124.
[994]Olah; Nojima; Kerekes *J. Am. Chem. Soc.* **1974**, *96*, 925.
[995]Shimizu; Nakahara; Yoshioka *Tetrahedron Lett.* **1985**, *26*, 4207. For another method, see Olah; Li *Synlett* **1990**, 267.
[996]Olah; Welch *Synthesis* **1974**, 653; Olah; Welch; Vankar; Nojima; Kerekes; Olah *J. Org. Chem.* **1979**, *44*, 3872; Alvernhe; Lacombe; Laurent; Rousset *J. Chem. Res., (S)* **1983**, 246.
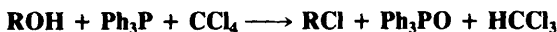[997]Matveeva; Yalovskaya; Cherepanov; Kurts; Bundel' *J. Org. Chem. USSR* **1989**, *25*, 587.
[998]For some other reagents, not listed here, see Echigo; Mukaiyama *Chem. Lett.* **1978**, 465; Barton; Stick; Subramanian *J. Chem. Soc., Perkin Trans. 1* **1976**, 2112; Savel'yanov; Nazarov; Savel'yanova; Suchkov *J. Org. Chem. USSR* **1977**, *13*, 604; Jung; Hatfield *Tetrahedron Lett.* **1978**, 4483; Sevrin; Krief *J. Chem. Soc., Chem. Commun.* **1980**, 656; Olah; Gupta; Malhotra; Narang *J. Org. Chem.* **1980**, *45*, 1638; Hanessian; Leblanc; Lavallée *Tetrahedron Lett.* **1982**, *23*, 4411; Cristol; Seapy *J. Org. Chem.* **1982**, *47*, 132; Richter; Tucker *J. Org. Chem.* **1983**, *48*, 2625; Imamoto; Matsumoto; Kusumoto; Yokoyama *Synthesis* **1983**, 460; Ref. 515; Toto; Doi *J. Org. Chem.* **1987**, *52*, 4999; Camps; Gasol; Guerrero *Synthesis* **1987**, 511; Schmidt; Brooks *Tetrahedron Lett.* **1987**, *28*, 767; Collingwood; Davies; Golding *Tetrahedron Lett.* **1987**, *28*, 4445; Kozikowski; Lee *Tetrahedron Lett.* **1988**, *29*, 3053; Classon; Liu; Samuelsson *J. Org. Chem.* **1988**, *53*, 6126; Munyemana; Frisque-Hesbain; Devos; Ghosez *Tetrahedron Lett.* **1989**, *30*, 3077; Ernst; Winkler *Tetrahedron Lett.* **1989**, *30*, 3081.
[999]Rydon *Org. Synth. VI*, 830.
[1000]Wiley; Hershkowitz; Rein; Chung *J. Am. Chem. Soc.* **1964**, *86*, 964; Wiley; Rein; Hershkowitz *Tetrahedron Lett.* **1964**, 2509; Schaefer; Weinberg *J. Org. Chem.* **1965**, *30*, 2635; Kaplan *J. Org. Chem.* **1966**, *31*, 3454; Weiss; Snyder *J. Org. Chem.* **1971**, *36*, 403; Garegg; Johansson; Samuelsson *Synthesis* **1984**, 168.

and tertiary halides without rearrangements,[1001] Me_2SBr_2[1002] (prepared from Me_2S and Br_2), Me_3SiCl–SeO_2,[1003] and a mixture of PPh_3 and CCl_4[1004] (or CBr_4[1005]).

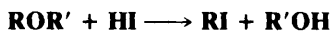$$ROH + Ph_3P + CCl_4 \longrightarrow RCl + Ph_3PO + HCCl_3$$

The last method converts allylic alcohols[1006] to the corresponding halides without allylic rearrangements.[1007] 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.[1008] 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. Allylic and benzylic alcohols can also be converted to bromides or iodides with NaX–BF_3 etherate,[1009] and to iodides with AlI_3.[1010]

When the reagent is HX, the mechanism is SN1cA or SN2cA; i.e., the leaving group is not OH^-, but OH_2 (p. 352). The leaving group is not OH^- with the other reagents either, since in these cases the alcohol is first converted to an inorganic ester, e.g., ROSOCl with $SOCl_2$ (**0-32**). The leaving group is therefore $OSOCl^-$ or a similar group (**0-66**). These may react by the SN1 or SN2 mechanism and, in the case of ROSOCl, by the SNi mechanism (p. 326).

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; **65**, 119, 211. Also see OS **III**, 818; **IV**, 278, 383, 597.

0-68   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.[1011] HCl is seldom successful.[1012] HBr reacts more slowly than HI, but it is often a superior reagent, since it causes fewer side reactions. Phase transfer catalysis has also been used.[1013] Dialkyl ethers and alkyl aryl ethers can be cleaved. In the latter case the alkyl–oxygen bond is the one broken. As in **0-67** 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 moles of alkyl halide. This

[1001]For reviews of reactions with these reagents, see Castro *Org. React.* **1983**, *29*, 1-162; Mackie, in Cadogan *Organophosphorus Reagents in Organic Synthesis*; Academic Press: New York, 1979; pp. 433-466.
[1002]Furukawa; Inoue; Aida; Oae *J. Chem. Soc., Chem. Commun.* **1973**, 212.
[1003]Lee; Kang *J. Org. Chem.* **1988**, *53*, 3634.
[1004]For a review, see Appel, *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 801-811 [*Angew. Chem.* **87**, 863-874]. For a general review of this and related reagents, see Appel; Halstenberg, in Cadogan, Ref. 1001, pp. 387-431. For a discussion of the mechanism, see Slagle, Huang, Franzus *J. Org. Chem.* **1981**, *46*, 3526.
[1005]Katritzky; Nowak-Wydra; Marson *Chem. Scr.* **1987**, *27*, 477; Wagner; Heitz; Mioskowski *Tetrahedron Lett.* **1989**, *30*, 557.
[1006]For a review of the conversion of allylic alcohols to allylic halides, see Magid *Tetrahedron* **1980**, *36*, 1901-1930, pp. 1924-1926.
[1007]Snyder *J. Org. Chem.* **1972**, *37*, 1466; Axelrod; Milne; van Tamelen *J. Am. Chem. Soc.* **1973**, *92*, 2139.
[1008]Corey; Kim; Takeda *Tetrahedron Lett.* **1972**, 4339.
[1009]Vankar; Rao *Tetrahedron Lett.* **1985**, *26*, 2717; Mandal; Mahajan *Tetrahedron Lett.* **1985**, *26*, 3863.
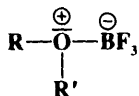[1010]Sarmah; Barua *Tetrahedron* **1989**, *45*, 3569.
[1011]For reviews of ether cleavage in general, see Bhatt; Kulkarni *Synthesis* **1983**, 249-282; Ref. 333. For a review of cleavage of aryl alkyl ethers, see Tiecco, Ref. 762.
[1012]Cleavage with HCl has been accomplished in the presence of surfactants: Juršić *J. Chem. Res. (S)* **1989**, 284.
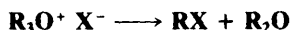[1013]Landini; Montanari; Rolla *Synthesis* **1978**, 771.

procedure is often carried out so that a mixture of only two products is obtained instead of four. Cyclic ethers (usually tetrahydrofuran derivatives) can be similarly cleaved (see **0-69** for epoxides). Ethers have also been cleaved with Lewis acids such as BF_3, BCl_3, Me_2BBr,[1014] BBr_3,[1015] or $AlCl_3$.[1016] In such cases, the departure of the OR is assisted by complex formation with the Lewis acid:

$$R-\overset{\oplus}{\underset{\underset{R'}{|}}{O}}-\overset{\ominus}{BF_3}$$

Lewis acids are also used in conjunction with acyl halides. The reagent $NaI-BF_3$ etherate selectively cleaves ethers in the order benzylic ethers > alkyl methyl ethers > aryl methyl ethers.[1017]

Dialkyl and alkyl aryl ethers can be cleaved with iodotrimethylsilane:[1017a] ROR' + Me_3SiI → RI + Me_3SiOR.[1018] A more convenient and less expensive alternative, which gives the same products, is a mixture of chlorotrimethylsilane and NaI.[1019] A mixture of $SiCl_4$ and NaI has also been used,[1020] as has diiodosilane SiH_2I_2.[1021] Alkyl aryl ethers can also be cleaved with LiI to give alkyl iodides and salts of phenols[1022] in a reaction similar to **0-70**. Triphenyldibromophosphorane (Ph_3PBr_2) cleaves dialkyl ethers to give 2 moles of alkyl bromide.[1023]

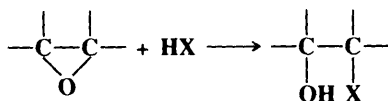A closely related reaction is cleavage of oxonium salts.

$$R_3O^+ \ X^- \longrightarrow RX + R_2O$$

For these substrates, HX is not required, and X can be any of the four halide ions.

t-Butyldimethylsilyl ethers $ROSiMe_2CMe_3$ can be converted to bromides RBr by treatment with Ph_3PBr_2,[1024] Ph_3P-CBr_4,[1025] or BBr_3.[1026] Alcohols are often protected by conversion to this kind of silyl ether.[1027]

OS **I**, 150; **II**, 571; **III**, 187, 432, 586, 692, 753, 774, 813; **IV**, 266, 321; **V**, 412; **VI**, 353. See also OS **65**, 68; **67**, 210.

0-69 Formation of Halohydrins from Epoxides
(3)OC-seco-Halo-de-alkoxylation

[1014]Guindon; Yoakim; Morton *Tetrahedron Lett.* **1983**, *24*, 2969; Guindon; Bernstein; Anderson *Tetrahedron Lett.* **1987**, *28*, 2225; Guindon; Therien; Girard; Yoakim *J. Org. Chem.* **1987**, *52*, 1680.

[1015]Manson; Musgrave *J. Chem. Soc.* **1963**, 1011; McOmie; Watts; West *Tetrahedron* **1968**, *24*, 2289; Egly; Pousse; Brini *Bull. Soc. Chim. Fr.* **1972**, 1357; Press *Synth. Commun.* **1979**, *9*, 407; Niwa; Hida; Yamada *Tetrahedron Lett.* **1981**, *22*, 4239.

[1016]For a review, see Johnson, in Olah *Friedel-Crafts and Related Reactions*, vol. 4; Wiley: New York, 1965, pp. 1-109.

[1017]Vankar; Rao *J. Chem. Res. (S)* **1985**, 232. See also Mandal; Soni; Ratnam *Synthesis* **1985**, 274.

[1017a]For a review of this reagent, see Olah; Prakash; Krishnamurti *Adv. Silicon Chem.* **1991**, *1*, 1-64.

[1018]Jung; Lyster *J. Org. Chem.* **1977**, *42*, 3761; *Org. Synth. VI*, 353.

[1019]Morita; Okamoto; Sakurai *J. Chem. Soc., Chem. Commun.* **1978**, 874; Olah; Narang; Gupta; Malhotra *J. Org. Chem.* **1979**, *44*, 1247; Amouroux; Jatczak; Chastrette *Bull. Soc. Chim. Fr.* **1987**, 505.

[1020]Bhatt; El-Morey *Synthesis* **1982**, 1048.

[1021]Keinan; Perez *J. Org. Chem.* **1987**, *52*, 4846.

[1022]Harrison *Chem. Commun.* **1969**, 616.

[1023]Anderson; Freenor *J. Org. Chem.* **1972**, *37*, 626.

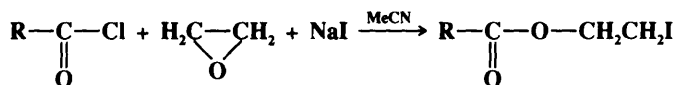[1024]Aizpurua; Cossío; Palomo *J. Org. Chem.* **1986**, *51*, 4941.

[1025]Mattes; Benezra *Tetrahedron Lett.* **1987**, *28*, 1697.

[1026]Kim; Park *J. Org. Chem.* **1988**, *53*, 3111.

[1027]See Corey; Venkateswarlu *J. Am. Chem. Soc.* **1972**, *94*, 6190.

This is a special case of **0-68** 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, though with HF[1028] the reaction is unsuccessful with simple aliphatic and cycloalkyl epoxides.[1029] HF does react with more rigid epoxides, such as those in steroid systems. The reaction can applied to simple epoxides[1030] if polyhydrogen fluoride–pyridine is the reagent. The epoxide-to-fluorohydrin conversion has also been carried out with SiF_4 and a tertiary amine.[1031] Chloro-, bromo-, and iodohydrins can also be prepared[1032] by treating epoxides with Ph_3P and X_2.[1033] Epoxides can be converted directly to 1,2-dichloro compounds by treatment with $SOCl_2$ and pyridine,[1034] with Ph_3P and CCl_4,[1035] or with Ph_3PCl_2.[1036] These are two-step reactions: a halohydrin is formed first and is then converted by the reagents to the dihalide (**0-67**). As expected, inversion is found at both carbons. Meso epoxides were cleaved enantioselectively with the chiral reagents B-halodiisopino-campheylboranes (see **5-12**), where the halogen was Cl, Br, or I.[1037]
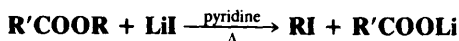
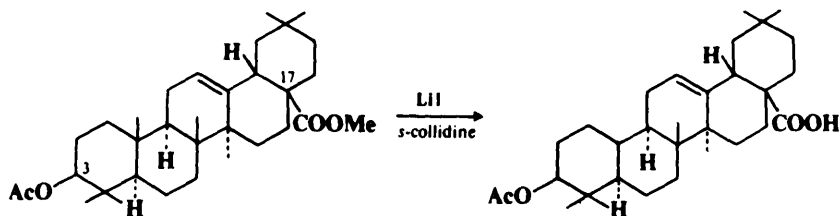Acyl chlorides react with ethylene oxide in the presence of NaI to give 2-iodoethyl esters.[1038]

$$ R-\underset{\underset{O}{\|}}{C}-Cl + H_2C-CH_2 + NaI \xrightarrow{MeCN} R-\underset{\underset{O}{\|}}{C}-O-CH_2CH_2I $$

OS **I**, 117; **VI**, 424.

0-70 Cleavage of Carboxylic Esters with Lithium Iodide
Iodo-de-acyloxy-substitution

$$ R'COOR + LiI \xrightarrow[\Delta]{pyridine} RI + R'COOLi $$

Carboxylic esters where R is methyl or ethyl can be cleaved by heating with lithium iodide in refluxing pyridine or a higher-boiling amine.[1039] The reaction is useful where a molecule is sensitive to acid and base (so that **0-10** 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

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[1028]For a review of reactions HF with epoxides, see Sharts; Sheppard, Ref. 966. For a related review, see Yoneda *Tetrahedron* **1991**, *47*, 5329-5365.

[1029]Shahak; Manor; Bergmann *J. Chem. Soc. C* **1968**, 2129.

[1030]Olah; Meidar *Isr. J. Chem.* **1978**, *17*, 148.

[1031]Shimizu; Yoshioka *Tetrahedron Lett.* **1988**, *29*, 4101. For other methods, see Muehlbacher; Poulter *J. Org. Chem.* **1988**, *53*, 1026; Ichihara; Hanafusa *J. Chem. Soc., Chem. Commun.* **1989**, 1848.

[1032]Einhorn; Luche *J. Chem. Soc., Chem. Commun.* **1986**, 1368; Ciaccio; Addess; Bell *Tetrahedron Lett.* **1986**, *27*, 3697; Spawn; Drtina; Wiemer *Synthesis* **1986**, 315.

[1033]Palumbo; Ferreri; Caputo *Tetrahedron Lett.* **1983**, *24*, 1307.

[1034]Campbell; Jones; Wolfe *Can. J. Chem.* **1966**, *44*, 2339.

[1035]Isaccs; Kirkpatrick *Tetrahedron Lett.* **1972**, 3869.

[1036]Sonnet; Oliver *J. Org. Chem.* **1976**, *41*, 3279; *Org. Synth. VI*, 424. This method also applies to Ph_3PBr_2. For another method, see Echigo; Watanabe; Mukaiyama *Chem. Lett.* **1977**, 1013.

[1037]Srebnik; Joshi; Brown *Isr. J. Chem.* **1989**, *29*, 229.

[1038]Belsner; Hoffmann *Synthesis* **1982**, 239. See also Roloff *Chimia* **1985**, *39*, 392; Iqbal; Khan; Srivastava *Tetrahedron Lett.* **1988**, *29*, 4985.

[1039]Taschner; Liberek *Rocz. Chem.* **1956**, *30*, 323 [*Chem. Abstr.* **1957**, *51*, 1039]. For a review, see Ref. 364.

group, not the 3-acetyl group.[1040] Esters RCOOR' and lactones can also be cleaved with a mixture of Me₃SiCl and NaI to give R'I and RCOOH.[1041]

0-71 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 (**0-82**). α-Fluoro ketones can be prepared by addition of the diazo ketone to polyhydrogen fluoride–pyridine.[1042] This method is also successful for diazoalkanes.
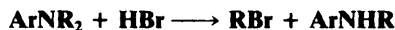
Diazotization of α-amino acids in the above solvent at room temperature gives α-fluoro carboxylic acids.[1043] If this reaction is run in the presence of excess KCl or KBr, the corresponding α-chloro or α-bromo acid is obtained instead.[1044]

OS **III**, 119.

0-72 Conversion of Amines to Halides
Halo-de-amination

$$RNH_2 \longrightarrow RNTs_2 \xrightarrow[DMF]{I^-} RI$$

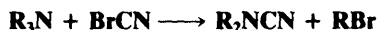Primary alkyl amines RNH₂ can be converted[1045] to alkyl halides by (1) conversion to RNTs₂ (p. 354) and treatment of this with I⁻ or Br⁻ in DMF,[347] (2) diazotization with *t*-butyl nitrite and a metal halide such as TiCl₄ in DMF,[1046] or (3) the Katritzky pyrylium–pyridinium method (p. 354).[1047] Alkyl groups can be cleaved from secondary and tertiary aromatic amines by concentrated HBr in a reaction similar to **0-68**, e.g.,[1048]

$$ArNR_2 + HBr \longrightarrow RBr + ArNHR$$

Tertiary aliphatic amines are also cleaved by HI, but useful products are seldom obtained. Tertiary amines can be cleaved by reaction with phenyl chloroformate:[1049] R₃N + ClCOOPh → RCl + R₂NCOOPh. α-Chloroethyl chloroformate behaves similarly.[1050] Alkyl halides may be formed when quaternary ammonium salts are heated: R₄N⁺ X⁻ → R₃N + RX.[1051]

OS **66**, 151. See also OS **I**, 428.

0-73 Conversion of Tertiary Amines to Cyanamides. The von Braun Reaction
Bromo-de-dialkylamino-substitution

$$R_3N + BrCN \longrightarrow R_2NCN + RBr$$

[1040]Elsinger; Schreiber; Eschenmoser *Helv. Chim. Acta* **1960**, *43*, 113.
[1041]Olah; Narang; Gupta; Malhotra, Ref. 1019. See also Kolb; Barth *Synth. Commun.* **1981**, *11*, 763.
[1042]Olah; Welch *Synthesis* **1974**, 896; Olah; Welch; Vankar; Nojima; Kerekes; Olah, Ref. 996.
[1043]Olah; Prakash; Chao *Helv. Chim. Acta* **1981**, *64*, 2528; Faustini; De Munary; Panzeri; Villa; Gandolfi *Tetrahedron Lett.* **1981**, *22*, 4533; Barber; Keck; Rétey *Tetrahedron Lett.* **1982**, *23*, 1549.
[1044]Olah; Shih; Prakash *Helv. Chim. Acta* **1983**, *66*, 1028.
[1045]For another method, see Lorenzo; Molina; Vilaplana *Synthesis* **1980**, 853.
[1046]Doyle; Bosch; Seites *J. Org. Chem.* **1978**, *43*, 4120.
[1047]Katritzky; Horvath; Plau *Synthesis* **1979**, 437; Katritzky; Chermprapai; Patel *J. Chem. Soc., Perkin Trans. 1* **1980**, 2901.
[1048]Chambers; Pearson *J. Org. Chem.* **1963**, *28*, 3144.
[1049]Hobson; McCluskey *J. Chem. Soc. C* **1967**, 2015. For a review, see Cooley; Evain *Synthesis* **1989**, 1-7.
[1050]Olofson; Martz; Senet; Piteau; Malfroot *J. Org. Chem.* **1984**, *49*, 2081; Olofson; Abbott *J. Org. Chem.* **1984**, *49*, 2795. See also Campbell; Pilipauskas; Khanna; Rhodes *Tetrahedron Lett.* **1987**, *28*, 2331.
[1051]For examples, see Ko; Leffek *Can. J. Chem.* **1970**, *48*, 1865, **1971**, *49*, 129; Deady; Korytsky *Tetrahedron Lett.* **1979**, 451.

The *von Braun reaction*, which involves the cleavage of tertiary amines by cyanogen bromide to give an alkyl bromide and a disubstituted cyanamide, has been applied to many tertiary amines.[1052] Usually, the R group that cleaves is the one that gives the most reactive halide (for example, benzyl or allyl). For simple alkyl groups, the smallest 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.[1053]

The mechanism consists of two successive nucleophilic substitutions, with the tertiary amine as the first nucleophile and the liberated bromide ion as the second:

Step 1 $NC\!-\!Br + R_3\bar{N} \longrightarrow NC\!-\!\overset{\oplus}{N}R_3 + Br^-$

Step 2 $R\!-\!\overset{\oplus}{N}R_2CN + Br^- \longrightarrow RBr + R_2NCN$

The intermediate N-cyanoammonium bromide has been trapped, and its structure confirmed by chemical, analytical, and spectral data.[1054] 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.[1055]
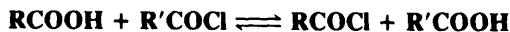
OS III, 608.

B. Attack at an Acyl Carbon

0-74   Formation of Acyl Halides from Carboxylic Acids
Halo-de-hydroxylation

$$RCOOH + SOCl_2 \longrightarrow RCOCl$$

The same inorganic acid halides that convert alcohols to alkyl halides (**0-67**) also convert carboxylic acids to acyl halides.[1056] The reaction is the best and the most common method for the preparation of acyl chlorides. Bromides and iodides[1057] are also made in this manner, but much less often. Thionyl chloride[983] is the best reagent, since the by-products are gases and the acyl halide is easily isolated, but PX_3 and PX_5 (X = Cl or Br) are also commonly used.[1058] Hydrogen halides do not give the reaction. A particularly mild procedure, similar to one mentioned in **0-67**, involves reaction of the acid with Ph_3P in CCl_4, whereupon acyl chlorides are produced without obtaining any acidic compound as a by-product.[1059] Acyl fluorides can be prepared by treatment of carboxylic acids with cyanuric fluoride.[1060] Acid salts are also sometimes used as substrates. Acyl halides are also used as reagents in an exchange reaction:

$$RCOOH + R'COCl \rightleftharpoons RCOCl + R'COOH$$

[1052]For a review, see Cooley; Evain, Ref. 1049.
[1053]For a detailed discussion of the scope of the reaction and of the ease of cleavage of different groups, see Hageman *Org. React.* **1953**, pp. 205-225.
[1054]Fodor; Abidi *Tetrahedron Lett.* **1971**, 1369; Fodor; Abidi; Carpenter *J. Org. Chem.* **1974**, *39*, 1507. See also Paukstelis; Kim *J. Org. Chem.* **1974**, *39*, 1494.
[1055]For a review of counterattack reagents, see Hwu; Gilbert *Tetrahedron* **1989**, *45*, 1233-1261.
[1056]For a review, see Ansell, in Patai, Ref. 502, pp. 35-68.
[1057]Carboxylic acids and some of their derivatives react with diiodosilane SiH_2I_2 to give good yields of acyl iodides: Keinan; Sahai *J. Org. Chem.* **1990**, *55*, 3922.
[1058]For a list of reagents, with references, see Ref. 508, pp. 963-964.
[1059]Lee *J. Am. Chem. Soc.* **1966**, *88*, 3440. For other methods of preparing acyl chlorides, see Venkataraman; Wagle *Tetrahedron Lett.* **1979**, 3037; Devos; Remion; Frisque-Hesbain; Colens; Ghosez *J. Chem. Soc., Chem. Commun.* **1979**, 1180.
[1060]Olah; Nojima; Kerekes *Synthesis* **1973**, 487. For other methods of preparing acyl fluorides, see Mukaiyama; Tanaka *Chem. Lett.* **1976**, 303; Ishikawa; Sasaki *Chem. Lett.* **1976**, 1407.

which probably involves an anhydride intermediate. This is an equilibrium reaction that must be driven to the desired side. Oxalyl chloride and bromide are frequently used as the acyl halide reagent, since oxalic acid decomposes to CO and CO_2, and the equilibrium is thus driven to the side of the other acyl halide.

OS **I**, 12, 147, 394; **II**, 74, 156, 169, 569; **III**, 169, 490, 547, 555, 613, 623, 712, 714; **IV**, 34, 88, 154, 263, 339, 348, 554, 608, 616, 620, 715, 739, 900; **V**, 171, 258, 887; **VI**, 95, 190, 549, 715; **VII**, 467; **66**, 87, 116, 121.

0-75   Formation of Acyl Halides from Acid Derivatives
   Halo-de-acyloxy-substitution
   Halo-de-halogenation

$$(RCO)_2O + HF \longrightarrow RCOF$$

$$RCOCl + HF \longrightarrow RCOF$$

These reactions are most important for the preparation of acyl fluorides.[1061] Acyl chlorides and anhydrides can be converted to acyl fluorides by treatment with polyhydrogen fluoride–pyridine solution[996] or with liquid HF at $-10°C$.[1062] Formyl fluoride, which is a stable compound, was prepared by the latter procedure from the mixed anhydride of formic and acetic acids.[1063] Acyl fluorides can also be obtained by reaction of acyl chlorides with KF in acetic acid[1064] or with diethylaminosulfur trifluoride (DAST).[1065] Carboxylic esters and anhydrides can be converted to acyl halides other than fluorides by the inorganic acid halides mentioned in **074**, as well as with Ph_3PX_2 (X = Cl or Br),[1066] but this is seldom done. Halide exchange can be carried out in a similar manner. When halide exchange is done, it is always acyl bromides and iodides that are made from chlorides, since chlorides are by far the most readily available.[1067]

OS **II**, 528; **III**, 422; **V**, 66, 1103. See also OS **IV**, 307.

Hydrogen as Nucleophile

The reactions in this section (**0-76** to **0-85**) are reductions and could have been considered in Chapter 19. They are treated here because they involve replacement of a leaving group by hydrogen, which frequently attacks as the nucleophile hydride ion. However, not all the reactions in this section are true nucleophilic substitutions and for some of them more than one kind of mechanism may be involved, depending on the reagents and on the conditions. When cleavage of a carbon-hetero atom bond is accomplished by catalytic hydrogenation, the reaction is called *hydrogenolysis*.

A.   Attack at an Alkyl Carbon

0-76   Reduction of Alkyl Halides
   Hydro-de-halogenation or **Dehalogenation**

$$RX + LiAlH_4 \longrightarrow RH$$

[1061]For lists of reagents converting acid derivatives to acyl halides, see Ref. 508, pp. 977, 980, 985.
[1062]Olah; Kuhn *J. Org. Chem.* **1961**, *26*, 237.
[1063]Olah; Kuhn *J. Am. Chem. Soc.* **1960**, *82*, 2380.
[1064]Emsley; Gold; Hibbert; Szeto *J. Chem. Soc., Perkin Trans. 2* **1988**, 923.
[1065]Markovski; Pashinnik *Synthesis* **1975**, 801.
[1066]Burton; Koppes *J. Chem. Soc., Chem. Commun.* **1973**, 425, *J. Org. Chem.* **1975**, *40*, 3026; Anderson; Kono *Tetrahedron Lett.* **1973**, 5121.
[1067]For methods of converting acyl chlorides to bromides or iodides, see Schmidt; Russ; Grosse *Synthesis* **1981**, 216; Hoffmann; Haase *Synthesis* **1981**, 715.

This type of reduction can be accomplished with many reducing agents,[1068] the most common being lithium aluminum hydride.[1069] This reagent reduces almost all types of alkyl halide, including vinylic, bridgehead, and cyclopropyl halides.[1070] Reduction with lithium aluminum deuteride serves to introduce deuterium into organic compounds. An even more powerful reducing agent, reportedly the strongest S_N2 nucleophile known, is lithium triethylboro-hydride $LiEt_3BH$. This reagent rapidly reduces primary, secondary, allylic, benzylic, and neopentyl halides, but not tertiary (these give elimination) or aryl halides.[1071] Another powerful reagent, which reduces primary, secondary, tertiary, allylic, vinylic, aryl, and neopentyl halides, is a complex formed from lithium trimethoxyaluminum hydride $LiAlH(OMe)_3$ and CuI.[1072] A milder reducing agent is $NaBH_4$ in a dipolar aprotic solvent such as Me_2SO, DMF, or sulfolane,[1073] which at room temperature or above reduces primary, secondary, and some tertiary[1074] halides in good yield without affecting other functional groups that would be reduced by $LiAlH_4$, for example, COOH, COOR, CN.[1075] Other reducing agents[1076] are zinc (with acid or base), $SnCl_2$, chromium(II) ion,[1077] either in the form of simple chromous salts (for active substrates or *gem*-dihalides[1078]) or complexed with ethylenediamine or ethanolamine (for ordinary alkyl halides[1079]), tris(trimethylsilyl)silane $(Me_3Si)_3SiH$–$NaBH_4$,[1080] SmI_2–THF–HMPA,[1081] and Et_3SiH in the presence of $AlCl_3$.[1082] The last two methods are good for primary, secondary, and tertiary halides. Sodium arsenite and base, diethyl phosphonate–Et_3N,[1083] phosphorus tris(dimethylamide) $(Me_2N)_3P$,[1084] a metal carbonyl such as $Fe(CO)_5$ and a hydrogen donor,[1085] or organotin hydrides R_nSnH_{4-n}[1086] (chiefly Bu_3SnH).[1087] can be used to reduce just one halogen of a *gem*-dihalide or a 1,1,1-trihalide.[1088] The organotin hydride $(MeOCH_2CH_2OCH_2CH_2CH_2)_3SnH$ reduces

[1068]For reviews, see Hudlický *Reductions in Organic Chemistry*; Ellis Horwood: Chichester, 1984, pp. 62-67, 181; Pinder *Synthesis* **1980**, 425-452. For a list of reagents, see Ref. 508, pp. 18-24.

[1069]For a review of $LiAlH_4$, see Pizey, Ref. 593, vol. 1, 1974, pp. 101-294. For monographs on complex metal hydrides, see Seyden-Penne *Reductions by the Alumino- and Borohydrides*; VCH: New York, 1991; Hajós *Complex Hydrides*; Elsevier: New York, 1979.

[1070]Jefford; Kirkpatrick; Delay *J. Am. Chem. Soc.* **1972**, *94*, 8905; Krishnamurthy; Brown *J. Org. Chem.* **1982**, *47*, 276.

[1071]Brown; Kim; Krishnamurthy *J. Org. Chem.* **1980**, *45*, 1; Krishnamurthy; Brown *J. Org. Chem.* **1980**, *45*, 849, **1983**, *48*, 3085.

[1072]Masamune; Rossy; Bates *J. Am. Chem. Soc.* **1973**, *95*, 6452; Masamune; Bates; Georghiou *J. Am. Chem. Soc.* **1974**, *96*, 3686.

[1073]Bell; Vanderslice; Spehar *J. Org. Chem.* **1969**, *34*, 3923; Hutchins; Hoke; Keogh; Koharski *Tetrahedron Lett.* **1969**, 3495; Vol'pin; Dvolaitzky; Levitin *Bull. Soc. Chim. Fr.* **1970**, 1526; Hutchins; Kandasamy; Dux; Maryanoff; Rotstein; Goldsmith; Burgoyne; Cistone; Dalessandro; Puglis *J. Org. Chem.* **1978**, *43*, 2259.

[1074]Hutchins; Bertsch; Hoke *J. Org. Chem.* **1971**, *36*, 1568.

[1075]For the use of $NaBH_4$ under phase transfer conditions, see Bergbreiter; Blanton *J. Org. Chem.* **1987**, *52*, 472.

[1076]For some other reducing agents, not mentioned here, see Akiba; Shimizu; Ohnari; and Ohkata *Tetrahedron Lett.* **1985**, *26*, 3211; Kim; Yi *Bull. Chem. Soc. Jpn.* **1985**, *58*, 789; Cole; Kirwan; Roberts; Willis *J. Chem. Soc., Perkin Trans. 1* **1991**, 103; and Ref. 1068.

[1077]For reviews, see Hanson *Synthesis* **1974**, 1-8, pp. 2-5; Hanson; Premuzic *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 247-252 [*Angew. Chem. 80*, 271-276]. For a review of the mechanisms of reduction of alkyl halides by metal complexes, see Kochi *Organometallic Mechanisms and Catalysis*; Academic Press: New York, 1978, pp. 138-177.

[1078]Castro; Kray *J. Am. Chem. Soc.* **1966**, *88*, 4447.

[1079]Kochi; Mocadlo *J. Am. Chem. Soc.* **1966**, *88*, 4094; Kochi; Powers *J. Am. Chem. Soc.* **1970**, *92*, 137.

[1080]Lesage; Chatgilialoglu; Griller *Tetrahedron Lett.* **1989**, *30*, 2733. See also Ballestri; Chatgilialoglu; Clark; Griller; Giese; Kopping *J. Org. Chem.* **1991**, *56*, 678.

[1081]Inanaga; Ishikawa; Yamaguchi *Chem. Lett.* **1987**, 1485. See also Molander; Hahn *J. Org. Chem.* **1986**, *51*, 1135. For reviews of SmI_2, see Soderquist *Aldrichimica Acta* **1991**, *24*, 15-23; Kagan *New J. Chem.* **1990**, *14*, 453-460.

[1082]Doyle; McOsker; West *J. Org. Chem.* **1976**, *41*, 1393; Parnes; Romanova; Vol'pin *J. Org. Chem. USSR* **1988**, *24*, 254.

[1083]Hirao; Kohno; Ohshiro; Agawa *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1881.

[1084]Downie; Lee *Tetrahedron Lett.* **1968**, 4951.

[1085]For reviews, see Freidlina; Gasanov; Kuz'mina *Russ. Chem. Rev.* **1985**, *54*, 662-675; Chukov-skaya; Freidlina; Kuz'mina *Synthesis* **1983**, 773-784.

[1086]Seyferth; Yamazaki; Alleston *J. Org. Chem.* **1963**, *28*, 703.

[1087]For reviews of organotin hydrides, see Neumann *Synthesis* **1987**, 665-683; Kuivila *Synthesis* **1970**, 499-509, *Acc. Chem. Res.* **1968**, *1*, 299-305.

[1088]See, for example Chukovskaya; Freidlina; Kuz'mina, Ref. 1085.

alkyl halides and is water soluble, unlike Bu_3SnH.[1089] Reduction, especially of bromides and iodides, can also be effected by catalytic hydrogenation,[1090] and electrochemically.[1091] A good reducing agent for the removal of all halogen atoms in a polyhalo compound (including vinylic, allylic, geminal, and even bridgehead halogens) is lithium[1092] or sodium[1093] and *t*-BuOH in THF. Propargylic halides can often be reduced with allylic rearrangement to give allenes.[1094]

$$R_2C\!-\!C\!\equiv\!CH \xrightarrow{\text{LiAlH}_4} R_2C\!=\!C\!=\!CH_2$$
$$\underset{\displaystyle X}{|}$$

The choice of a reducing agent usually depends on what other functional groups are present. Each reducing agent reduces certain groups and not others. This type of selectivity is called *chemoselectivity*. A chemoselective reagent is one that reacts with one functional group (e.g., halide) but not another (e.g., C=O). For example, there are several reagents that reduce only the halogen of α-halo ketones, leaving the carbonyl group intact.[1095] Among them are i-Pr_2NLi,[1096] CH_3SNa,[1097] aqueous $TiCl_3$,[1098] NaI in aqueous acid–THF,[1099] PI_3 or P_2I_4,[1100] nickel boride,[1101] sodium formaldehyde sulfoxylate,[1102] i-Bu_2AlH–$SnCl_2$,[1103] NaHS–$SnCl_2$,[1104] $AlCl_3$–EtSH,[1105] $MeSiCl_3$–NaI,[515] and sodium hydrosulfite $Na_2S_2O_4$.[1106] Both $NaBH_3CN$–$SnCl_2$[1107] and the *n*-butyllithium ate complex (p. 260) of B-*n*-butyl-9-BBN[1108] (see p. 785) reduce tertiary alkyl, benzylic, and allylic halides, but do not react with primary or secondary alkyl or aryl halides. Another highly selective reagent, in this case for primary and secondary iodo and bromo groups, is sodium cyanoborohydride $NaBH_3CN$ in HMPA.[1109] Most of the reducing agents mentioned reduce chlorides, bromides, and iodides, but organotin hydrides also reduce fluorides.[1110] See page 1206 for a discussion of selectivity in reduction reactions.

[1089]Light; Breslow *Tetrahedron Lett.* **1990**, *31*, 2957.

[1090]For a discussion, see Rylander *Hydrogenation Methods*; Academic Press: New York, 1985.

[1091]For reviews, see Fry *Synthetic Organic Electrochemistry*, 2nd ed.; Wiley: New York, 1989, pp. 136-151; Feoktistov, in Baizer; Lund *Organic Electrochemistry*; Marcel Dekker: New York, 1983, pp. 259-284.

[1092]For example, see Bruck; Thompson; Winstein *Chem. Ind.(London)* **1960**, 405; Gassman; Pape *J. Org. Chem.* **1964**, *29*, 160; Fieser; Sachs *J. Org. Chem.* **1964**, *29*, 1113; Nazer *J. Org. Chem.* **1965**, *30*, 1737; Berkowitz *Synthesis* **1990**, 649.

[1093]For example, see Gassman; Aue; Patton *J. Am. Chem. Soc.* **1968**, *90*, 7271; Gassman; Marshall *Org. Synth.* V, 424.

[1094]For examples, see Crandall; Keyton; Kohne *J. Org. Chem.* **1968**, *33*, 3655; Claesson; Olsson *J. Am. Chem. Soc.*, **1979**, *101*, 7302.

[1095]For a review of reductive dehalogenation of polyhalo ketones, see Noyori; Hayakawa *Org. React.* **1983**, *29*, 163-344.

[1096]Dubois; Lion; Dugast *Tetrahedron Lett.* **1983**, *24*, 4207.

[1097]Oki; Funakoshi; Nakamura *Bull. Chem. Soc. Jpn.* **1971**, *44*, 828. See also Inoue; Hata; Imoto *Chem. Lett.* **1975**, 1241.

[1098]Ho; Wong *Synth. Commun.* **1973**, *3*, 237; McMurry *Acc. Chem. Res.* **1974**, *7*, 281-286, pp. 284-285; Pradhan; Patil *Tetrahedron Lett.* **1989**, *30*, 2999. See also Clerici; Porta *Tetrahedron Lett.* **1987**, *28*, 1541.

[1099]Gemal; Luche *Tetrahedron Lett.* **1980**, *21*, 3195. See also Olah; Arvanaghi; Vankar *J. Org. Chem.* **1980**, *45*, 3531; Ho *Synth. Commun.* **1981**, *11*, 101; Ono; Kamimura; Suzuki *Synthesis* **1987**, 406.

[1100]Denis; Krief *Tetrahedron Lett.* **1981**, *22*, 1431.

[1101]Sarma; Borbaruah; Sharma *Tetrahedron Lett.* **1985**, *26*, 4657.

[1102]Harris *Synth. Commun.* **1987**, *17*, 1587.

[1103]Oriyama; Mukaiyama *Chem. Lett.* **1984**, 2069.

[1104]Ono; Maruyama; Kamimura *Synthesis* **1987**, 1093.

[1105]Fuji; Node; Kawabata; Fujimoto *J. Chem. Soc., Perkin Trans. 1* **1987**, 1043.

[1106]Chung; Hu *Synth. Commun.* **1982**, *12*, 261.

[1107]Kim; Ko *Synth. Commun.* **1985**, *15*, 603.

[1108]Toi; Yamamoto; Sonoda; Murahashi *Tetrahedron* **1981**, *37*, 2261.

[1109]Hutchins; Kandasamy; Maryanoff; Masilamani; Maryanoff *J. Org. Chem.* **1977**, *42*, 82.

[1110]Fluorides can also be reduced by a solution of K and dicyclohexano-18-crown-6 in toluene or diglyme: Ohsawa; Takagaki; Haneda; Oishi *Tetrahedron Lett.* **1981**, *22*, 2583. See also Brandänge; Dahlman; Ölund *Acta Chem. Scand., Ser. B* **1983**, *37*, 141.

With lithium aluminum hydride and most other metallic hydrides, the mechanism usually consists of simple nucleophilic substitution with attack by hydride ion that may or may not be completely free. The mechanism is SN2 rather than SN1, since primary halides react better than secondary or tertiary (tertiary generally give alkenes or do not react at all) and since Walden inversion has been demonstrated. However, rearrangements found in the reduction of bicyclic tosylates with LiAlH$_4$ indicate that the SN1 mechanism can take place.[1111] There is evidence that LiAlH$_4$ and other metal hydrides can also reduce halides by an SET mechanism,[1112] especially those, such as vinylic,[1113] cyclopropyl,[1114] or bridgehead halides, that are resistant to nucleophilic substitution. Reduction of halides by NaBH$_4$ in 80% aqueous diglyme[1115] and by BH$_3$ in nitromethane[1116] takes place by an SN1 mechanism. NaBH$_4$ in sulfolane reduces tertiary halides possessing a β hydrogen by an elimination–addition mechanism.[1117]

With other reducing agents the mechanism is not always nucleophilic substitution. For example, reductions with organotin hydrides generally[1118] take place by free-radical mechanisms,[1119] as do those with Fe(CO)$_5$[1120] and (Me$_3$Si)$_3$SiH–NaBH$_4$.[1080] Alkyl halides, including fluorides and polyhalides, can be reduced with magnesium and a secondary or tertiary alcohol (most often 2-propanol).[1121] This is actually an example of the occurrence in one step of the sequence:

$$\text{RX} \longrightarrow \text{RMgX} \xrightarrow{\text{H}^+} \text{RH}$$

More often the process is carried out in two separate steps (**2-38** and **2-23**).

OS **I**, 357, 358, 548; **II**, 320, 393; **V**, 424; **VI**, 142, 376, 731; **68**, 32. See also OS **69**, 66.

0-77 Reduction of Tosylates and Similar Compounds
Hydro-de-sulfonyloxy-substitution

$$\text{RCH}_2\text{OTs} + \text{LiAlH}_4 \longrightarrow \text{RCH}_3$$

Tosylates and other sulfonates can be reduced[1122] with LiAlH$_4$,[1123] with NaBH$_4$ in a dipolar aprotic solvent,[1124] with LiEt$_3$BH, with i-Bu$_2$AlH (DIBALH),[1125] or with Bu$_3$SnH–NaI.[1126] The scope of the reaction seems to be similar to that of **0-76**. When the reagent is LiAlH$_4$, alkyl tosylates are reduced more rapidly than iodides or bromides if the solvent is Et$_2$O,

[1111]Appleton; Fairlie; McCrindle *Chem. Commun.* **1967**, 690; Kraus; Chassin *Tetrahedron Lett.* **1970**, 1443.

[1112]Ashby; DePriest; Goel *Tetrahedron Lett.* **1981**, *22*, 1763, 3729; Singh; Khurana; Nigam *Tetrahedron Lett.* **1981**, *22*, 2901; Srivastava; le Noble *Tetrahedron Lett.* **1984**, *25*, 4871; Ashby; Pham *J. Org. Chem.* **1986**, *51*, 3598; Hatem; Meslem; Waegell *Tetrahedron Lett.* **1986**, *27*, 3723; Ashby; Pham; Amrollah-Majdjabadi *J. Org. Chem.* **1991**, *56*, 1596. See however Hirabe; Takagi; Muraoka; Nojima; Kusabayashi *J. Org. Chem.* **1985**, *50*, 1797; Park; Chung; Newcomb *J. Org. Chem.* **1987**, *52*, 3275.

[1113]Chung *J. Org. Chem.* **1980**, *45*, 3513.

[1114]McKinney; Anderson; Keyes; Schmidt *Tetrahedron Lett.* **1982**, *23*, 3443; Hatem; Waegell *Tetrahedron* **1990**, *46*, 2789.

[1115]Bell; Brown *J. Am. Chem. Soc.* **1966**, *88*, 1473.

[1116]Matsumura; Tokura *Tetrahedron Lett.* **1969**, 363.

[1117]Jacobus *Chem. Commun.* **1970**, 338; Ref. 1074.

[1118]For an exception, see Carey; Tramper *Tetrahedron Lett.* **1969**, 1645.

[1119]Kuivila; Menapace *J. Org. Chem.* **1963**, *28*, 2165; Menapace; Kuivila *J. Am. Chem. Soc.* **1964**, *86*, 3047; Tanner; Singh *J. Org. Chem.* **1986**, *51*, 5182.

[1120]Nelson; Detre; Tanabe *Tetrahedron Lett.* **1973**, 447; Freidlina et al., Ref. 1085.

[1121]Bryce-Smith; Wakefield; Blues *Proc. Chem. Soc.* **1963**, 219.

[1122]For a list of substrate types and reagents, with references, see Ref. 508, pp. 28-31.

[1123]For examples, see Rapoport; Bonner *J. Am. Chem. Soc.* **1951**, *73*, 2872; Eschenmoser; Frey *Helv. Chim. Acta* **1952**, *35*, 1660; Dimitriadis; Massy-Westropp *Aust. J. Chem.* **1982**, *35*, 1895.

[1124]Hutchins; Hoke; Keogh; Koharski, Ref. 1073.

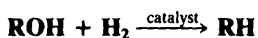[1125]Janssen; Hendriks; Godefroi *Recl. Trav. Chim. Pays-Bas* **1984**, *103*, 220.

[1126]Ueno; Tanaka; Okawara *Chem. Lett.* **1983**, 795.

but the order is reversed in diglyme.[1127] The reactivity difference is great enough so that a tosylate function can be reduced in the presence of a halide and vice versa.

OS **VI**, 376, 762; **68**, 138. See also OS **VII**, 66.

0-78   Hydrogenolysis of Alcohols[1128]
Hydro-de-hydroxylation or **Dehydroxylation**

$$ROH + H_2 \xrightarrow{\text{catalyst}} RH$$

The hydroxyl groups of most alcohols can seldom be cleaved by catalytic hydrogenation and alcohols are often used as solvents for hydrogenation of other compounds. However, benzyl-type alcohols undergo the reaction readily and have often been reduced.[1129] Diaryl and triarylcarbinols are similarly easy to reduce and this has been accomplished with $LiAlH_4$–$AlCl_3$,[1130] with $NaBH_4$ in F_3CCOOH,[1131] and with iodine, water, and red phosphorus (OS **I**, 224). Other reagents have been used,[1132] among them $Fe(CO)_5$,[1133] Me_3SiCl–MeI–MeCN,[1134] Et_3SiH–BF_3,[1135] SmI_2–THF–HMPA,[1136] $NaBH_4$–F_3CCOOH,[1137] P_2I_4,[1138] Me_2SiI_2,[1139] and tin and HCl. 1,3-Diols are especially susceptible to hydrogenolysis. Tertiary alcohols can be reduced by catalytic hydrogenolysis when the catalyst is Raney nickel.[1140] Allylic alcohols (and ethers and acetates) can be reduced (often with accompanying allylic rearrangement) with Zn amalgam and HCl, as well as with certain other reagents.[1141] α-Acetylenic alcohols are converted to alkynes by reduction of their cobalt carbonyl complexes with $NaBH_4$ and CF_3COOH.[1142] Reagents that reduce the OH group of α-hydroxy ketones without affecting the C=O group include lithium diphenylphosphide Ph_2PLi,[1143] red phosphorus–iodine,[1144] and Me_3SiI.[1145]

Alcohols can also be reduced indirectly by conversion to a sulfonate and reduction of that compound (**0-77**). The two reactions can be carried out without isolation of the sulfonate if the alcohol is treated with pyridine–SO_3 in THF, and $LiAlH_4$ then added.[1146] Another indirect reduction that can be done in one step involves treatment of the alcohol (primary, secondary, or benzylic) with NaI, Zn, and Me_3SiCl.[1147] In this case the alcohol is first converted to the iodide, which is reduced. For other indirect reductions of OH, see **0-81**.

[1127]Krishnamurthy *J. Org. Chem.* **1980**, *45*, 2550.
[1128]For a review, see Müller, in Patai *The Chemistry of Functional Groups, Supplement E*, pt. 1; Wiley: New York, 1980, pp. 515-522.
[1129]For reviews, see Rylander, Ref. 1090, pp. 157-163, *Catalytic Hydrogenation over Platinum Metals*; Academic Press: New York, 1967, pp. 449-468. For a review of the stereochemistry of hydrogenolysis, see Klabunovskii *Russ. Chem. Rev.* **1966**, *35*, 546-558.
[1130]Blackwell; Hickinbottom *J. Chem. Soc.* **1961**, 1405; Avendaño; de Diego; Elguero *Monatsh. Chem.* **1990**, *121*, 649.
[1131]For a review, see Gribble; Nutaitis *Org. Prep. Proced. Int.* **1985**, *17*, 317-384.
[1132]For a list of reagents, with references, see Ref. 508, pp. 27-28.
[1133]Alper; Sališová *Tetrahedron Lett.* **1980**, *21*, 801.
[1134]Sakai; Miyata; Utaka; Takeda *Tetrahedron Lett.* **1987**, *28*, 3817.
[1135]Orfanopoulos; Smonou *Synth. Commun.* **1988**, *18*, 833; Smonou; Orfanopoulos *Tetrahedron Lett.* **1988**, *29*, 5793.
[1136]Kusuda; Inanaga; Yamaguchi *Tetrahedron Lett.* **1989**, *30*, 2945.
[1137]Nutaitis; Bernardo *Synth. Commun.* **1990**, *20*, 487.
[1138]Suzuki; Tani; Kubota; Sato; Tsuji; Osuka *Chem. Lett* **1983**, 247.
[1139]Ando; Ikeno *Tetrahedron Lett.* **1979**, 4941; Wiggins *Synth. Commun.* **1988**, *18*, 741.
[1140]Krafft; Crooks *J. Org. Chem.* **1988**, *53*, 432. For another catalyst, see Parnes; Shaapuni; Kalinkin; Kursanov *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1974**, *23*, 1592.
[1141]For discussion, see Elphimoff-Felkin; Sarda *Org. Synth. VI*, 769; *Tetrahedron* **1977**, *33*, 511. For another reagent, see Lee; Alper *Tetrahedron Lett.* **1990**, *31*, 4101.
[1142]Nicholas; Siegel *J. Am. Chem. Soc.* **1985**, *107*, 4999.
[1143]Leone-Bay *J. Org. Chem.* **1986**, *51*, 2378.
[1144]Ho; Wong *Synthesis* **1975**, 161.
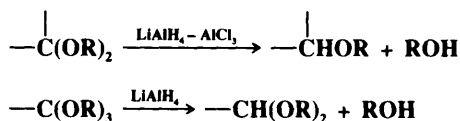[1145]Ho *Synth. Commun.* **1979**, *9*, 665.
[1146]Corey; Achiwa *J. Org. Chem.* **1969**, *34*, 3667.
[1147]Morita; Okamoto; Sakurai *Synthesis* **1981**, 32.

The mechanisms of most alcohol reductions are obscure.[1148] Hydrogenolysis of benzyl alcohols can give inversion or retention of configuration, depending on the catalyst.[1149]
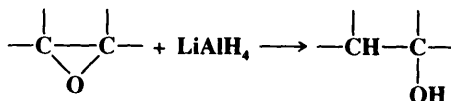
OS **I**, 224; **IV**, 25, 218, 482; **V**, 339; **VI**, 769.

0-79 Replacement of Alkoxyl by Hydrogen
Hydro-de-alkoxylation or **Dealkoxylation**

$$-\overset{|}{C}(OR)_2 \xrightarrow{\text{LiAlH}_4 - \text{AlCl}_3} -\overset{|}{C}HOR + ROH$$

$$-C(OR)_3 \xrightarrow{\text{LiAlH}_4} -CH(OR)_2 + ROH$$

Simple ethers are not normally cleaved by reducing agents, although such cleavage has sometimes been reported (for example, tetrahydrofuran treated with LiAlH$_4$–AlCl$_3$[1150] or with a mixture of LiAlH(O-t-Bu)$_3$ and Et$_3$B[1151] gave 1-butanol; the latter reagent also cleaves methyl alkyl ethers).[1152] Certain types of ethers can be cleaved quite well by reducing agents.[1153] Among these are allyl aryl,[1154] vinyl aryl,[1155] and benzylic ethers[1129] (for epoxides, see **0-80**). Acetals and ketals are resistant to LiAlH$_4$ and similar hydrides, and carbonyl groups are often converted to acetals or ketals for protection. However, a combination of LiAlH$_4$ and AlCl$_3$[1156] does reduce acetals and ketals, removing one group, as shown above.[1157] The actual reducing agents in this case are primarily chloroaluminum hydride AlH$_2$Cl and dichloroaluminum hydride AlHCl$_2$, which are formed from the reagents.[1158] This conversion can also be accomplished with DIBALH,[1159] with Nafion-H,[1160] with monochloroborane–etherate BH$_2$Cl-Et$_2$O,[1161] as well as with other reagents.[1162] Ortho esters are easily reduced to acetals by LiAlH$_4$ alone, offering a route to aldehydes, which are easily prepared by hydrolysis of the acetals (**0-6**).

OS **III**, 693; **IV**, 798; **V**, 303. Also see OS **III**, 742; **VII**, 386.

0-80 Reduction of Epoxides
(3)*OC-seco***-Hydro-de-alkoxylation**

$$-\overset{|}{\underset{\diagdown}{C}}\overset{|}{\underset{\diagup}{C}}- + \text{LiAlH}_4 \longrightarrow -\overset{|}{C}H-\overset{|}{\underset{|}{C}}-$$
$$\overset{}{O} \qquad\qquad\qquad OH$$

[1148]For discussions of the mechanisms of the hydrogenolysis of benzyl alcohols, see Khan; McQuillin; Jardine *Tetrahedron Lett.* **1966**, 2649, *J. Chem. Soc. C* **1967**, 136; Garbisch; Schreader; Frankel *J. Am. Chem. Soc.* **1967, 89**, 4233; Mitsui; Imaizumi; Esashi *Bull. Chem. Soc. Jpn.* **1970**, *43*, 2143.

[1149]Mitsui; Kudo; Kobayashi *Tetrahedron* **1969**, *25*, 1921; Mitsui; Imaizumi; Esashi, Ref. 1148.

[1150]Bailey; Marktscheffel *J. Org. Chem.* **1960**, *25*, 1797.

[1151]Krishnamurthy; Brown *J. Org. Chem.* **1979**, *44*, 3678.

[1152]For a review of ether reduction, see Müller, Ref. 1128, pp. 522-528.

[1153]For a list of reagents, with references, see Ref. 508, pp. 501-504.

[1154]Tweedie; Cuscurida *J. Am. Chem. Soc.* **1957**, *79*, 5463.

[1155]Tweedie; Barron *J. Org. Chem.* **1960**, *25*, 2023. See also Hutchins; Learn *J. Org. Chem.* **1982**, *47*, 4380.

[1156]For a review of reductions by metal hydride–Lewis acid combinations, see Rerick, in Augustine *Reduction*; Marcel Dekker: New York, 1968, pp. 1-94.

[1157]Eliel; Badding; Rerick *J. Am. Chem. Soc.* **1962**, *84*, 2371.

[1158]Ashby; Prather *J. Am. Chem. Soc.* **1966**, *88*, 729; Diner; Davis; Brown *Can. J. Chem.* **1967**, *45*, 207.

[1159]See, for example, Zakharkin; Khorlina *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1959**, 2156; Takano; Akiyama; Sato; Ogasawara *Chem. Lett.* **1983**, 1593.

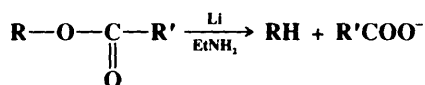[1160]Olah; Yamato; Iyer; Prakash *J. Org. Chem.* **1986**, *51*, 2826.

[1161]Borders; Bryson *Chem. Lett.* **1984**, 9.

[1162]For lists of other reagents that accomplish this conversion, with references, see Tsunoda; Suzuki; Noyori *Tetrahedron Lett.* **1979**, 4679; Kotsuki; Ushio; Yoshimura; Ochi *J. Org. Chem.* **1987**, *52*, 2594; Ref. 508, pp. 463-465.

Reduction of epoxides is a special case of **0-79** and is easily carried out.[1163] The most common reagent is LiAlH$_4$, which reacts by the S_N2 mechanism, giving inversion of configuration. An epoxide on a substituted cyclohexane ring cleaves in such a direction as to give an axial alcohol. As expected for an S_N2 mechanism, cleavage usually occurs so that a tertiary alcohol is formed if possible. If not, a secondary alcohol is preferred. However, for certain substrates, the epoxide ring can be opened the other way by reduction with NaBH$_3$CN–BF$_3$,[1164] with Me$_3$SiCl–Zn,[1165] with dicyclopentadienyltitanium chloride and 1,4-cyclohexadiene,[1166] or with BH$_3$ in tetrahydrofuran.[1167] The reaction has also been carried out with other reagents, for example, sodium amalgam in EtOH, Li in ethylenediamine,[1168] Bu$_3$SnH–NaI,[1169] and by catalytic hydrogenolysis.[1170] Chemoselective and regioselective ring opening (e.g., of allylic epoxides and of epoxy ketones and esters) has been achieved with NaHTe,[1171] SmI$_2$,[1172] sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al),[1173] and H$_2$ and a Pd-phosphine catalyst.[1174] Highly hindered epoxides can be conveniently reduced, without rearrangement, with lithium triethylborohydride.[1175]

Epoxides can be reductively halogenated (the product is the alkyl bromide or iodide rather than the alcohol) with Me$_3$SiCl–NaX–(Me$_2$SiH)$_2$O (1,1,3,3-tetramethyldisiloxane).[1176]

See **9-46** for another type of epoxide reduction.

0-81   Reductive Cleavage of Carboxylic Esters
Hydro-de-acyloxylation or **Deacyloxylation**

$$R\!-\!O\!-\!\underset{\underset{O}{\|}}{C}\!-\!R' \xrightarrow[\text{EtNH}_2]{\text{Li}} RH + R'COO^-$$

The alkyl group R of certain carboxylic esters can be reduced to RH[1177] by treatment with lithium in ethylamine.[1178] The reaction is successful when R is a tertiary or a sterically hindered secondary alkyl group. A free-radical mechanism is likely.[1179] Similar reduction, also by a free-radical mechanism, has been reported with sodium in HMPA–t-BuOH.[1180] In the latter case, tertiary R groups give high yields of RH, but primary and secondary R are converted to a mixture of RH and ROH. Both of these methods provide an indirect method

[1163]For a list of reagents, with references, see Ref. 508, pp. 505-508.
[1164]Hutchins; Taffer; Burgoyne *J. Org. Chem.* **1981**, *46*, 5214.
[1165]Vankar; Arya; Rao *Synth. Commun.* **1983**, *13*, 869. See also Vankar; Chaudhuri; Rao *Tetrahedron Lett.* **1987**, *28*, 551.
[1166]RajanBabu; Nugent; Beattie *J. Am. Chem. Soc.* **1990**, *112*, 6408.
[1167]For a review of epoxide reduction with BH$_3$, see Cragg, *Organoboranes in Organic Synthesis*; Marcel Dekker: New York, 1973, pp. 345-348. See also Yamamoto; Toi; Sonoda; Murahashi *J. Chem. Soc., Chem. Commun.* **1976**, 672.
[1168]Brown; Ikegami; Kawakami *J. Org. Chem.* **1970**, *35*, 3243.
[1169]Bonini; Di Fabio *Tetrahedron Lett.* **1988**, *29*, 819.
[1170]For a review, see Rylander, *Catalytic Hydrogenation over Platinum Metals*, Ref. 1129, pp. 478-485.
[1171]Osuka; Taka-Oka; Suzuki *Chem. Lett.* **1984**, 271.
[1172]Molander; La Belle; Hahn *J. Org. Chem.* **1986**, *51*, 5259; Otsubo; Inanaga; Yamaguchi *Tetrahedron Lett.* **1987**, *28*, 4437. See also Miyashita; Hoshino; Suzuki; Yoshikoshi *Chem. Lett.* **1988**, 507.
[1173]Gao; Sharpless *J. Org. Chem.* **1988**, *53*, 4081.
[1174]Oshima; Yamazaki; Shimizu; Nizar; Tsuji *J. Am. Chem. Soc.* **1989**, *111*, 6280.
[1175]Krishnamurthy; Schubert; Brown *J. Am. Chem. Soc.* **1973**, *95*, 8486.
[1176]Aizpurua; Palomo *Tetrahedron Lett.* **1984**, *25*, 3123.
[1177]For a review of some of the reactions in this section and some others, see Hartwig *Tetrahedron* **1983**, *39*, 2609-2645.
[1178]Barrett; Godfrey; Hollinshead; Prokopiou; Barton; Boar; Joukhadar; McGhie; Misra *J. Chem. Soc., Perkin Trans. 1* **1981**, 1501.
[1179]Barrett; Prokopiou; Barton; Boar; McGhie *J. Chem. Soc., Chem. Commun.* **1979**, 1173.
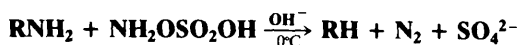[1180]Deshayes; Pete *Can. J. Chem.* **1984**, *62*, 2063.

of accomplishing **0-78** for tertiary R.[1181] The same thing can be done for primary and secondary R by treating alkyl chloroformates ROCOCl with tri-*n*-propylsilane in the presence of *t*-butyl peroxide[1182] and by treating thiono ethers ROC(=S)W (where W can be OAr or other groups) with Ph_2SiH_2 and a free radical initiator.[1183] Allylic acetates can be reduced with $NaBH_4$ and a palladium complex,[1184] with *p*-bis(diphenylhydrosilyl)benzene,[1185] and with SmI_2–Pd(0).[1186] The last reagent converts propargylic acetates to allenes $R^1C \equiv CR^2R^3OAc \rightarrow R^1CH = C = CR^2R^3$.[1186] For other carboxylic ester reductions, see **9-40, 9-42**, and **9-43**.

OS **VII**, 139.

0-82   Reduction of the C—N Bond
Hydro-de-amination or Deamination

$$RNH_2 + NH_2OSO_2OH \xrightarrow[0^\circ C]{OH^-} RH + N_2 + SO_4^{2-}$$

Primary amines have been reduced to RH with hydroxylamine-O-sulfonic acid and aqueous NaOH.[1187] It is postulated that R—N=N—H is an intermediate that decomposes to the carbocation. The reaction has also been accomplished with difluoroamine HNF_2;[1188] the same intermediates are postulated in this case. An indirect means of achieving the same result is the conversion of the primary amine to the sulfonamide $RNHSO_2R'$ (**0-116**) and treatment of this with NH_2OSO_2OH.[1189] Other indirect methods involve reduction of N,N-ditosylates (p. 354) with $NaBH_4$ in HMPA[1190] and modifications of the Katritzky pyrylium–pyridinium method.[1191] Allylic and benzylic amines[1129] can be reduced by catalytic hydrogenolysis. Enamines are cleaved to olefins with alane AlH_3,[1192] e.g.,

and with 9-BBN (p. 785) or borane methyl sulfide (BMS).[1193] Since enamines can be prepared from ketones (**6-14**), this is a way of converting ketones to alkenes. In the latter case BMS gives retention of configuration [an (*E*) isomer gives the (*E*) product] while 9-BBN gives the other isomer.[1193] Diazo ketones are reduced to methyl ketones by HI: $RCOCHN_2$ + HI $\rightarrow RCOCH_3$.[1194]

[1181]For other methods, see Barton; Crich; Löbberding; Zard *J. Chem. Soc., Chem. Commun.* **1985,** 646; Barton; Crich *J. Chem. Soc., Perkin Trans. 1* **1986,** 1603.
[1182]Jackson; Malek *J. Chem. Soc., Perkin Trans. 1* **1980,** 1207.
[1183]See Barton; Jang; Jaszberenyi *Tetrahedron Lett.* **1990,** *31,* 4681 and references cited therein. For similar methods, see Nozaki; Oshima; Utimoto *Bull. Chem. Soc. Jpn.* **1990,** *63,* 2578; Kirwan; Roberts; Willis *Tetrahedron Lett.* **1990,** *31,* 5093.
[1184]Hutchins; Learn; Fulton *Tetrahedron Lett.* **1980,** *21,* 27. See also Ipaktschi *Chem. Ber.* **1984,** *117,* 3320.
[1185]Sano; Takeda; Migita *Chem. Lett.* **1988,** 119. See also Keinan; Greenspoon *Isr. J. Chem.* **1984,** *24,* 82.
[1186]Tabuchi; Inanaga; Yamaguchi *Tetrahedron Lett.* **1986,** *27,* 601, 5237. See also Ref. 1136.
[1187]Doldouras; Kollonitsch *J. Am. Chem. Soc.* **1978,** *100,* 341.
[1188]Bumgardner; Martin; Freeman *J. Am. Chem. Soc.* **1963,** *85,* 97.
[1189]Nickon; Hill *J. Am. Chem. Soc.* **1964,** *86,* 1152.
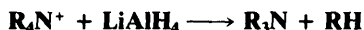[1190]Hutchins; Cistone; Goldsmith; Heuman *J. Org. Chem.* **1975,** *40,* 2018.
[1191]See Katritzky; Bravo-Borja; El-Mowafy; Lopez-Rodriguez *J. Chem. Soc., Perkin Trans. 1* **1984,** 1671.
[1192]Coulter; Lewis; Lynch *Tetrahedron* **1968,** *24,* 4489.
[1193]Singaram; Goralski; Rangaishenvi; Brown *J. Am. Chem. Soc.* **1989,** *111,* 384.
[1194]For example, see Pojer; Ritchie; Taylor *Aust. J. Chem.* **1968,** *21,* 1375.

Quaternary ammonium salts can be cleaved with $LiAlH_4$

$$R_4N^+ + LiAlH_4 \longrightarrow R_3N + RH$$

as can quaternary phosphonium salts R_4P^+. Other reducing agents have also been used, for example, lithium triethylborohydride (which preferentially cleaves methyl groups)[1195] and sodium in liquid ammonia. When quaternary salts are reduced with sodium amalgam in water, the reaction is known as the *Emde reduction*. However, this reagent is not applicable to the cleavage of ammonium salts with four *saturated* alkyl groups. Of course, aziridines[1170] can be reduced in the same way as epoxides (**0-80**).

Nitro compounds RNO_2 can be reduced to RH[1196] by sodium methylmercaptide CH_3SNa in an aprotic solvent[1197] or by Bu_3SnH.[1198] Both reactions have free-radical mechanisms.[1199] Tertiary nitro compounds can be reduced to RH by NaHTe.[1200] Bu_3SnH also reduces iso-cyanides RNC (prepared from RNH_2 by formylation followed by **7-41**) to RH,[1201] a reaction that can also be accomplished with Li or Na in liquid NH_3,[1202] or with K and a crown ether in toluene.[1203] α-Nitro ketones can be reduced to ketones with $Na_2S_2O_4$–Et_3SiH in HMPA–H_2O.[1204]

Hydrogenolysis with a Pt catalyst in the gas phase has been reported to reduce nitro compounds, as well as primary and secondary amines.[1205]
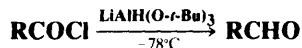
OS **III**, 148; **IV**, 508; **68**, 227.

For reduction of the C—S bond, see **4-36**.

B.   Attack at an Acyl Carbon

0-83   Reduction of Acyl Halides
Hydro-de-halogenation or **Dehalogenation**

$$RCOCl \xrightarrow[-78°C]{LiAlH(O\text{-}t\text{-}Bu)_3} RCHO$$

Acyl halides can be reduced to aldehydes[1206] by treatment with lithium tri-*t*-butoxyaluminum hydride in diglyme at $-78°C$.[1207] R may be alkyl or aryl and may contain many types of substituents, including NO_2, CN, and EtOOC groups. The reaction stops at the aldehyde stage because steric hindrance prevents further reduction under these conditions. Acyl halides can also be reduced to aldehydes by hydrogenolysis with palladium-on-barium sulfate

[1195]Cooke; Parlman *J. Org. Chem.* **1975**, *40*, 531.

[1196]For a method of reducing allylic nitro groups, see Ono; Hamamoto; Kamimura; Kaji *J. Org. Chem.* **1986**, *51*, 3734.

[1197]Kornblum; Carlson; Smith *J. Am. Chem. Soc.* **1979**, *101*, 647; Kornblum; Widmer; Carlson *J. Am. Chem. Soc.* **1979**, *101*, 658.

[1198]For reviews, see Ono, in Feuer; Nielsen *Nitro Compounds; Recent Advances in Synthesis and Chemistry*; VCH: New York, 1990, pp. 1-135, pp. 1-45; Rosini; Ballini *Synthesis* **1988**, 833-847, pp. 835-837; Ono; Kaji *Synthesis* **1986**, 693-704. For discussions of the mechanism, see Korth; Sustmann; Dupuis; Geise *Chem. Ber.* **1987**, *120*, 1197; Kamimura; Ono *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3629.

[1199]For a discussion of the mechanism with Bu_3SnH, see Tanner; Harrison; Chen; Kharrat; Wayner; Griller; McPhee *J. Org. Chem.* **1990**, *55*, 3321. If an α substituent is present, it may be reduced instead of the NO_2. For a mechanistic discussion, see Bowman; Crosby; Westlake *J. Chem. Soc., Perkin Trans. 2* **1991**, 73.

[1200]Suzuki; Takaoka; Osuka *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1067.

[1201]Barton; Bringmann; Motherwell *Synthesis* **1980**, 68.

[1202]See Niznik; Walborsky *J. Org. Chem.* **1978**, *43*, 2396; Yadav; Reddy; Joshi *Tetrahedron Lett.* **1988**, *44*, 7243.

[1203]Ohsawa; Mitsuda; Nezu; Oishi *Tetrahedron Lett.* **1989**, *30*, 845.

[1204]Kamimura; Kurata; Ono *Tetrahedron Lett.* **1989**, *30*, 4819.

[1205]Guttieri; Maier *J. Org. Chem.* **1984**, *49*, 2875.

[1206]For a review of the formation of aldehydes from acid derivatives, see Fuson, in Patai, Ref. 446, pp. 211-232. For a review of the reduction of acyl halides, see Wheeler, in Patai, Ref. 502, pp. 231-251.

[1207]Brown; McFarlin *J. Am. Chem. Soc.* **1958**, *80*, 5372; Brown; Subba Rao *J. Am. Chem. Soc.* **1958**, *80*, 5377.

as catalyst. This is called the *Rosenmund reduction*.[1208] A more convenient hydrogenolysis procedure involves palladium-on-charcoal as the catalyst, with ethyldiisopropylamine as acceptor of the liberated HCl and acetone as the solvent.[1209] The reduction of acyl halides to aldehydes has also been carried out[1210] with Bu_3SnH,[1211] with $Bu_3GeH-Pd(PPh_3)_4$,[1212] with $NaBH_4$ in a mixture of DMF and THF,[1213] and with ions of the form $HM(CO)_4^-$ ($M = Fe, Cr, W$).[1214] In some of these cases, the mechanisms are free-radical. There are several indirect methods for the conversion of acyl halides to aldehydes, most of them involving prior conversion of the halides to certain types of amides (see **0-85**). There is also a method in which the COOH group is replaced by a completely different CHO group (**0-110**). Also see **9-45**.

OS **III**, 551, 627; **VI**, 529, 1007. Also see OS **III**, 818; **VI**, 312.

0-84   Reduction of Carboxylic Acids, Esters, and Anhydrides to Aldehydes[1215]
  Hydro-de-hydroxylation or **Dehydroxylation** (overall transformation)

$$RCOOH \xrightarrow[MeNH_2]{Li} RCH=N-Me \xrightarrow{H_2O} RCHO$$

With most reducing agents, reduction of carboxylic acids generally gives the primary alcohol (**9-38**) and the isolation of aldehydes is not feasible. However, simple straight-chain carboxylic acids have been reduced to aldehydes[1216] by treatment with Li in $MeNH_2$ or NH_3 followed by hydrolysis of the resulting imine,[1217] with borane–Me_2S followed by pyridinium chlorochromate,[1218] with isobutylmagnesium bromide and a titanium-complex catalyst followed by hydrolysis,[1219] with thexylchloroborane–Me_2S[1220] or thexylbromoborane–Me_2S[1221] (see **5-12** for the thexyl group), with $LiAlH(O-t-Bu)_3$ and chloromethylene dimethylammonium chloride[1222] $Me_2N=CHCl^+$ Cl^- in pyridine,[1223] and with diaminoaluminum hydrides.[1224] Caproic and isovaleric acids have been reduced to aldehydes in 50% yields or better with DIBALH (i-Bu_2AlH) at -75 to $-70°C$.[1225]

[1208]For a review, see Ref. 1170, pp. 398-404. For a discussion of the Pt catalyst, see Maier; Chettle; Rai; Thomas *J. Am. Chem. Soc.* **1986**, *108*, 2608.
[1209]Peters; van Bekkum *Recl. Trav. Chim. Pays-Bas* **1971**, *90*, 1323, **1981**, *100*, 21. See also Burgstahler; Weigel; Shaefer *Synthesis* **1976**, 767.
[1210]For some other methods, see Wagenknecht *J. Org. Chem.* **1972**, *37*, 1513; Smith; Smith *J. Chem. Soc., Chem. Commun.* **1975**, 459; Leblanc; Moise; Tirouflet *J. Organomet. Chem.* **1985**, *292*, 225; Corriu; Lanneau; Perrot *Tetrahedron Lett.* **1988**, *29*, 1271. For a list of reagents, with references, see Ref. 508, pp. 620-621.
[1211]Kuivila *J. Org. Chem.* **1960**, *25*, 284; Walsh; Stoneberg; Yorke; Kuivila *J. Org. Chem.* **1969**, *34*, 1156; Four; Guibe *J. Org. Chem.* **1981**, *46*, 4439; Lusztyk; Lusztyk; Maillard; Ingold *J. Am. Chem. Soc.* **1984**, *106*, 2923.
[1212]Geng; Lu *J. Organomet. Chem.* **1989**, *376*, 41.
[1213]Babler; Invergo *Tetrahedron Lett.* **1981**, *22*, 11; Babler *Synth. Commun.* **1982**, *12*, 839. For the use of $NaBH_4$ and metal ions, see Entwistle, Boehm; Johnstone; Telford *J. Chem. Soc., Perkin Trans. 1* **1980**, 27.
[1214]Cainelli; Manescalchi; Umani-Ronchi *J. Organomet. Chem.* **1984**, *276*, 205; Kao; Gaus; Youngdahl; Darensbourg *Organometallics* **1984**, *3*, 1601.
[1215]For a review, see Cha *Org. Prep. Proced. Int.* **1989**, *21*, 451-477.
[1216]For other reagents, see Hubert; Eyman; Wiemer *J. Org. Chem.* **1984**, *49*, 2279; Corriu; Lanneau; Perrot *Tetrahedron Lett.* **1987**, *28*, 3941; Cha; Kim; Yoon; Kim *Tetrahedron Lett.* **1987**, *28*, 6231. See also the lists in Ref. 508, pp. 619-622.
[1217]Bedenbaugh; Bedenbaugh; Bergin; Adkins *J. Am. Chem. Soc.* **1970**, *92*, 5774; Burgstahler; Worden; Lewis *J. Org. Chem.* **1963**, *28*, 2918.
[1218]Brown; Rao; Kulkarni *Synthesis* **1979**, 704.
[1219]Sato; Jinbo; Sato *Synthesis* **1981**, 871.
[1220]Brown; Cha; Yoon; Nazer *J. Org. Chem.* **1987**, *52*, 5400.
[1221]Cha; Kim; Lee *J. Org. Chem.* **1987**, *52*, 5030.
[1222]For the preparation of this reagent, see Fujisawa; Sato *Org. Synth.* 66, 121.
[1223]Fujisawa; Mori; Tsuge; Sato *Tetrahedron Lett.* **1983**, *24*, 1543.
[1224]Muraki; Mukaiyama *Chem. Lett.* **1974**, 1447, **1975**, 215.
[1225]Zakharkin; Khorlina *J. Gen. Chem. USSR* **1964**, *34*, 1021; Zakharkin; Sorokina *J. Gen. Chem. USSR* **1967**, *37*, 525.
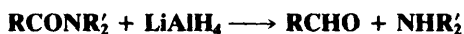
Carboxylic esters have been reduced to aldehydes with DIBALH at −70°C, with di-aminoaluminum hydrides,[1224] with LiAlH$_4$–Et$_2$NH,[1226] and with NaAlH$_4$ at −65 to −45°C, and (for phenolic esters) with LiAlH(O-t-Bu)$_3$ at 0°C.[1227] Aldehydes have also been prepared by reducing ethyl thiol esters RCOSEt with Et$_3$SiH and a Pd–C catalyst.[1228]

Anhydrides, both aliphatic and aromatic, as well as mixed anhydrides of carboxylic and carbonic acids, have been reduced to aldehydes in moderate yields with disodium tetracar-bonylferrate Na$_2$Fe(CO)$_4$.[1229]

Also see **9-40** and **9-42**.

OS **VI**, 312; **66**, 121; **69**, 55.

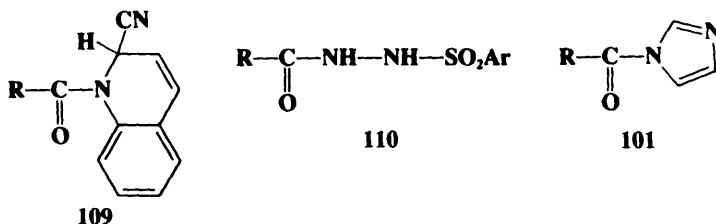**0-85** Reduction of Amides to Aldehydes
Hydro-de-dialkylamino-substitution

$$\textbf{RCONR}_2' + \textbf{LiAlH}_4 \longrightarrow \textbf{RCHO} + \textbf{NHR}_2'$$

N,N-Disubstituted amides can be reduced to amines with LiAlH$_4$ (see **9-39**), but also to aldehydes.[1230] Keeping the amide in excess gives the aldehyde rather than the amine. Some-times it is not possible to prevent further reduction and primary alcohols are obtained instead. Other reagents[1231] that give good yields of aldehydes are DIBALH,[1232] LiAlH(O-t-Bu)$_3$, LiAlH$_4$–EtOH,[1233] NaAlH$_4$,[1234] and diaminoaluminum hydrides.[1235]

Aldehydes have been prepared from carboxylic acids or acyl halides by first converting them to certain types of amides that are easily reducible. The following are some exam-ples:[1236]

1. *Reissert compounds*[1237] (**109**) are prepared from the acyl halide by treatment with quinoline and cyanide ion. Treatment of **109** with sulfuric acid gives the corresponding aldehyde.

$$\text{109} \qquad \text{110} \qquad \text{101}$$

2. Acyl sulfonylhydrazides (**110**) are cleaved with base to give aldehydes. This is known as the *McFadyen–Stevens reduction* and is applicable only to aromatic aldehydes or aliphatic

[1224]Cha; Kwon *J. Org. Chem.* **1987**, *52*, 5486.
[1227]Zakharkin; Khorlina *Tetrahedron Lett.* **1962**, 619, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1963**, 288, **1964**, 435; Zakharkin; Gavrilenko; Maslin; Khorlina *Tetrahedron Lett.* **1963**, 2087; Zakharkin; Gavrilenko; Maslin *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1964**, 867; Weissman; Brown *J. Org. Chem.* **1966**, *31*, 283.
[1228]Fukuyama; Lin; Li *J. Am. Chem. Soc.* **1990**, *112*, 7050.
[1229]Watanabe; Yamashita; Mitsudo; Igami; Takegami *Bull. Chem. Soc. Jpn.* **1975**, *48*, 2490; Watanabe; Yamashita; Mitsudo; Igami; Tomi; Takegami *Tetrahedron Lett.* **1975**, 1063.
[1230]For a review, see Fuson, in Patai, Ref. 446, pp. 220-225.
[1231]For a list of reagents, with references, see Ref. 508, pp. 623-624.
[1232]Zakharkin; Khorlina *Bull. Acad. Sci. USSR, Div. Chem. Sci* **1959**, 2046.
[1233]Brown; Tsukamoto *J. Am. Chem. Soc.* **1964**, 86, 1089.
[1234]Zakharkin; Maslin; Gavrilenko *Tetrahedron* **1969**, *25*, 5555.
[1235]Muraki; Mukaiyama *Chem. Lett.* **1975**, 875.
[1236]For other examples, see Brown; Tsukamoto *J. Am. Chem. Soc.* **1961**, *83*, 4549; Doleschall *Tetrahedron* **1976**, *32*, 2549; Atta-ur-Rahman; Basha *J. Chem. Soc., Chem. Commun.* **1976**, 594; Izawa; Mukaiyama *Bull. Chem. Soc. Jpn.* **1979**, *52*, 555; Craig; Ekwuribe; Fu; Walker *Synthesis* **1981**, 303.
[1237]For reviews of Reissert compounds, see Popp; Uff *Heterocycles* **1985**, *23*, 731-740; Popp *Bull. Soc. Chim Belg* **1981**, *90*, 609-613, *Adv. Heterocycl. Chem.* **1979**, 24, 187-214, **1968**, *9*, 1-25.

aldehydes with no α hydrogen.[1238] RCON=NH (see **0-82**) has been proposed as an intermediate in this reaction.[1239]

   3. Imidazoles (**101**)[664] can be reduced to aldehydes with $LiAlH_4$.
   4. See also the Sonn-Müller method (**6-28**).

OS **67**, 69. See OS **IV**, 641, **VI**, 115 for the preparation of Reissert compounds.

Carbon Nucleophiles

In any heterolytic reaction in which a new carbon–carbon bond is formed[1240] 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, **1-12** to **1-28** and **2-15** to **2-20** 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 (**0-86** to **0-113**) would be called electrophilic substitution (aromatic or aliphatic) if we were to consider the reagent as the substrate.

A.   Attack at an Alkyl Carbon. In **0-86** to **0-93** 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 **0-86** to **0-93** include both symmetrical and unsymmetrical coupling reactions. The latter are also called *cross-coupling reactions*. Other coupling reactions are considered in later chapters.

0-86   Coupling of Alkyl Halides. The Wurtz Reaction
      De-halogen-coupling

$$2RX + Na \longrightarrow RR$$

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*).[1241] However, the coupling of two aryl halides with sodium is impractical (but see **3-16**). Other metals have also been used to effect Wurtz reactions,[1242] notably silver, zinc,[1243] iron,[1244] activated copper,[1245] and pyrophoric lead.[1246] Lithium, under the influence of ultrasound,

[1238]Babad; Herbert; Stiles *Tetrahedron Lett.* **1966**, 2927; Dudman; Grice; Reese *Tetrahedron Lett.* **1980**, *21*, 4645.
[1239]For discussions, see Cacchi; Paolucci *Gazz. Chem. Ital.* **1974**, *104*, 221; Matin; Craig; Chan *J. Org. Chem.* **1974**, *39*, 2285.
[1240]For a monograph that discusses most of the reactions in this section, see Stowell *Carbanions in Organic Synthesis*; Wiley: New York, 1979. For a review, see Noyori, in Alper *Transition Metal Organometallics in Organic Synthesis*, vol. 1; Academic Press: New York, 1976, pp. 83-187.
[1241]For an example, see Kwa; Boelhouwer *Tetrahedron* **1970**, *25*, 5771.
[1242]For a list of reagents, including metals and other reagents, with references, see Ref. 508, pp. 47-48.
[1243]See, for example, Nosek *Collect. Czech. Chem. Commun.* **1964**, *29*, 597.
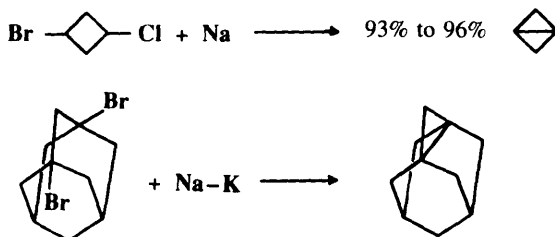[1244]Nozaki; Noyori *Tetrahederon* **1966**, *22*, 2163; Onsager *Acta Chem. Scand.*, *Ser. B* **1978**, *32*, 15.
[1245]Ginah; Donovan; Suchan; Pfennig; Ebert *J. Org. Chem.* **1990**, *55*, 584.
[1246]Mészáros *Tetrahedron Lett.* **1967**, 4951; Azoo; Grimshaw *J. Chem. Soc. C* **1968**, 2403.
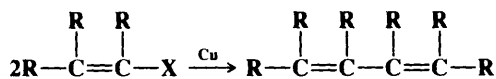
has been used to couple alkyl, aryl, and benzylic halides.[1247] Metallic nickel, prepared by the reduction of nickel halides with Li, dimerizes benzylic halides to give $ArCH_2CH_2Ar$.[1248] The coupling of alkyl halides has also been achieved electrochemically.[1249]

One type of Wurtz reaction that is quite useful is the closing of small rings, especially three-membered rings.[1250] For example, 1,3-dibromopropane can be converted to cyclopropane by Zn and NaI.[1251] Two highly strained molecules that have been prepared this way are bicyclobutane[1252] and tetracyclo[3.3.1.1^{3,7}.0^{1,3}]decane.[1253] Three- and four-membered

rings can also be closed in this manner with certain other reagents,[1254] including benzoyl peroxide,[1255] *t*-BuLi,[1256] (phenylsulfonyl)methylene dilithium $PhSO_2CHLi_2$[1257] and lithium amalgam,[1258] as well as electrochemically.[1259]

Vinylic halides can be coupled to give 1,3-butadienes by treatment with activated copper powder in a reaction analogous to the Ullmann reaction (**3-16**).[1260] This reaction is stereospecific, with retention of configuration at both carbons. Vinylic halides can also be

coupled[1261] with $CuCl$,[1262] with $Zn-NiCl_2$,[1263] and with *n*-BuLi in ether in the presence of $MnCl_2$.[1264]

[1247]Han; Boudjouk *Tetrahedron Lett.* **1981**, *22*, 2757.
[1248]Inaba; Matsumoto; Rieke *J. Org. Chem.* **1984**, *49*, 2093. For some other reagents that accomplish this, see Sayles; Kharasch *J. Org. Chem.* **1961**, *26*, 4210; Cooper *J. Am. Chem. Soc.* **1973**, *95*, 4158; Ho; Olah *Synthesis* **1977**, 170; Ballatore; Crozet; Surzur *Tetrahedron Lett.* **1979**, 3073; Yamada; Momose *Chem. Lett.* **1981**, 1277; Iyoda; Sakaitani; Otsuka; Oda *Chem. Lett.* **1985**, 127.
[1249]Folest; Nedelec; Perichon *J. Chem. Res. (S)* **1989**, 394.
[1250]For a review, see Freidlina; Kamyshova; Chukovskaya *Russ. Chem. Rev.* **1982**, *51*, 368-376. For reviews of methods of synthesizing cyclopropane rings, see, in Rappoport *The Chemistry of the Cyclopropyl Group*, pt. 1; Wiley: New York, 1987, the reviews by Tsuji; Nishida, pp. 307-373, and Verhé; De Kimpe, pp. 445-564.
[1251]For a discussion of the mechanism, see Applequist; Pfohl *J. Org. Chem.* **1978**, *43*, 867.
[1252]Wiberg; Lampman *Tetrahedron Lett.* **1963**, 2173; Lampman; Aumiller *Org. Synth. VI*, 133.
[1253]Pincock; Schmidt; Scott; Torupka *Can. J. Chem.* **1972**, *50*, 3958.
[1254]For a list of reagents, with references, see Ref. 508, pp. 87-88.
[1255]Kaplan *J. Am. Chem. Soc.* **1967**, *89*, 1753, *J. Org. Chem.* **1967**, *32*, 4059.
[1256]Bailey; Gagnier *Tetrahedron Lett.* **1982**, *23*, 5123.
[1257]Eisch; Dua; Behrooz *J. Org. Chem.* **1985**, *50*, 3674.
[1258]Connor; Wilson *Tetrahedron Lett.* **1967**, 4925.
[1259]Rifi *J. Am. Chem. Soc.* **1967**, *89*, 4442, *Org. Synth. VI*, 153.
[1260]Cohen; Poeth *J. Am. Chem. Soc.* **1972**, *94*, 4363.
[1261]For some other methods, see Jones *J. Org. Chem.* **1967**, *32*, 1667; Semmelhack; Helquist; Gorzynski *J. Am. Chem. Soc.* **1972**, *94*, 9234; Wellmann; Steckhan *Synthesis* **1978**, 901; Miyahara; Shiraishi; Inazu; Yoshino *Bull. Chem. Soc. Jpn.* **1979**, *52*, 953; Grigg; Stevenson; Worakun *J. Chem. Soc., Chem. Commun.* **1985**, 971; Vanderesse; Fort; Becker; Caubere *Tetrahedron Lett.* **1986**, *27*, 3517.
[1262]Kauffmann; Sahm *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 85 [*Angew. Chem. 79*, 101]; Toda; Takehira *J. Chem. Soc., Chem. Commun.* **1975**, 174.
[1263]Takagi; Mimura; Inokawa *Bull. Chem. Soc. Jpn.* **1984**, *57*, 3517.
[1264]Cahiez; Bernard; Normant *J. Organomet. Chem.* **1976**, *113*, 99.

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 → RM), which in many cases can be isolated (2-38). Following this, the organometallic compound reacts with a second molecule of alkyl halide (RX + RM → RR). This reaction and its mechanism are considered in the next section (0-87).

OS III, 157; V, 328, 1058; VI, 133, 153.

0-87 The Reaction of Alkyl Halides with Organometallic Reagents[1265]
Alkyl-de-halogenation

$$RX + R'_2CuLi \longrightarrow R—R'$$

The reagents lithium dialkylcopper[1266] (also called *Gilman reagents*) react with alkyl bromides, chlorides, and iodides in ether or THF to give good yields of the cross-coupling products.[1267] The reaction is of wide scope.[1268] R may be primary alkyl, allylic, benzylic, aryl, vinylic, or allenic, and may contain keto, COOH, COOR, or $CONR_2$ groups. The reaction at a vinylic substrate occurs stereospecifically, with retention of configuration.[1269] When the reagent and substrate are both vinylic, yields are low, but the reaction can be made to go (to give 1,3-butadienes) stereospecifically in high yields by the use of $ZnBr_2$ and a Pd(0) complex.[1270] Many *gem*-dihalides do not react, but when the two halogens are on a carbon α to an aromatic ring[1271] or on a cyclopropane ring,[1272] both halogens can be replaced by R, e.g., $PhCHCl_2$ → $PhCHMe_2$. However, 1,2-dibromides give exclusive elimination[1273] (7-29). R' in R'_2CuLi may be primary alkyl, vinylic, allylic, or aryl. Thus, in the reaction as so far described, neither R nor R' may be secondary or tertiary alkyl. However, secondary and tertiary alkyl coupling can be achieved (on primary RX) by the use of $R'_2CuLi·PBu_3$[1274] (though this procedure introduces problems in the workup) or by the use of $PhS(R')CuLi$,[1275] which selectively couples a secondary or tertiary R' with a primary iodide RI to give RR'.[1276] From the opposite standpoint, coupling to a secondary R can be achieved in high yield with the reagents $R'_2Cu(CN)Li_2$,[1277] where R' is primary alkyl or vinylic (but not aryl).[1278] The reagents $RCu(PPh_2)Li$, $RCu(NR'_2)Li$, and $Cu(PR'_2)Li$ (R' = cyclohexyl) are more stable than R_2CuLi and can be used at higher

[1265]For a review of the reactions in this section, see Naso; Marchese, in Patai; Rappoport, Ref. 88, pt. 2, pp. 1353-1449.
[1266]For the structure of Me_2CuLi (a cyclic dimer), see Pearson; Gregory *J. Am. Chem. Soc.* **1976**, *98*, 4098. See also Lipshutz; Kozlowski; Breneman *Tetrahedron Lett.* **1985**, *26*, 5911. For reviews of the structure and reactions of organocopper compounds, see Power *Prog. Inorg. Chem.* **1991**, *39*, 75-112; Collman; Hegedus; Norton; Finke *Principles and Applications of Organotransition Metal Chemistry*, 2nd ed.; University Science Books: Mill Valley, CA, 1987, pp. 682-698.
[1267]Corey; Posner *J. Am. Chem. Soc.* **1967**, *89*, 3911, **1968**, *90*, 5615; Whitesides; Fischer; San Filippo; Bashe; House *J. Am. Chem. Soc.* **1969**, *91*, 4871; Bergbreiter; Whitesides *J. Org. Chem.* **1975**, *40*, 779.
[1268]For a review of this reaction, see Posner *Org. React.* **1975**, *22*, 253-400. For a review of organocopper reagents, see Normant *Synthesis* **1972**, 63-80. For examples of the use of this reaction in this synthesis of natural products, see Posner *An Introduction to Synthesis Using Organocopper Reagents*; Wiley: New York, 1980, pp. 68-81. For lists of substrates and reagents, with references, see Ref. 508, pp. 206-210, 304-306, 788.
[1269]Corey; Posner, Ref. 1267; Klein; Levene *J. Am. Chem. Soc.* **1972**, *94*, 2520.
[1270]Jabri; Alexakis; Normant *Tetrahedron Lett.* **1981**, *22*, 959, **1982**, *23*, 1589, *Bull. Soc. Chim. Fr.* **1983**, II-321, II-332.
[1271]Posner; Brunelle *Tetrahedron Lett.* **1972**, 293.
[1272]See, for example, Kitatani; Hiyama; Nozaki *Bull. Chem. Soc. Jpn* **1977**, *50*, 1600.
[1273]Posner; Ting *Synth. Commun.* **1973**, *3*, 281.
[1274]Whitesides; Fischer; San Filippo; Bashe; House, Ref. 1267.
[1275]Prepared as in Ref. 1285 or treatment of PhSCu with RLi: Posner; Brunelle; Sinoway *Synthesis* **1974**, 662.
[1276]Posner; Whitten; Sterling *J. Am. Chem. Soc.* **1973**, *95*, 7788; Posner; Whitten *Tetrahedron Lett.* **1973**, 1815.
[1277]For reviews of these and other "higher order" organocuprates, see Lipshutz; Wilhelm; Kozlowski *Tetrahedron* **1984**, *40*, 5005-5038, Lipshutz *Synthesis* **1987**, 325-341, *Synlett* **1990**, 119-128. See also Bertz *J. Am. Chem. Soc.* **1990**, *112*, 4031; Lipshutz; Sharma; Ellsworth *J. Am. Chem. Soc.* **1990**, *112*, 4032.
[1278]Lipshutz; Wilhelm; Floyd *J. Am. Chem. Soc.* **1981**, *103*, 7672.

temperatures.[1279] With an allenic substrate, reaction with R(CN)CuLi can give ordinary displacement (with retention of configuration)[1280] or an S$_N$2' reaction to produce an alkyne.[1281] In the latter case, a chiral allene gave a chiral alkyne. The fact that R$_2'$CuLi do not react with ketones provides a method for the alkylation of ketones[1282] (see also **0-95** and **0-99**), though halogen–metal exchange (**2-39**) is a side reaction and can become the main reaction.[1283]
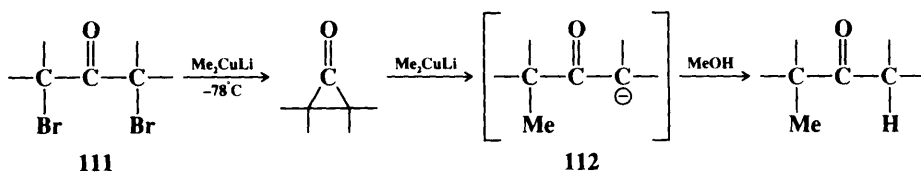
$$R_2C{-}C{-}R'' + R_2'CuLi \longrightarrow R_2C{-}C{-}R''$$
$$\underset{Br\ \ \ O}{|\ \ \ ||} \qquad\qquad\qquad \underset{R'\ \ \ O}{|\ \ \ ||}$$

When α,α'-dibromo ketones (**111**) are treated with Me$_2$CuLi in ether at $-78°C$ and the mixture quenched with methanol, *mono*methylation takes place[1284] (no dimethylation is observed). It has been suggested that the reaction involves cyclization (**0-86**) to a cyclopropanone followed by nucleophilic attack to give the enolate ion **112** which is protonated by

the methanol. If methyl iodide is added instead of methanol, an α,α'-dimethyl ketone is obtained, presumably from S$_N$2 attack by **112** on methyl iodide (**0-95**). Only halides that are highly reactive to S$_N$2 attack (e.g., methyl and benzylic halides) react successfully with **112**. Primary, secondary, *and tertiary* monoalkylation of **111** can be achieved if **111** is treated with a lithium *t*-butoxy(alkyl)copper reagent[1285] instead of Me$_2$CuLi. For example, 2,6-dibromocyclohexanone, treated with lithium *t*-butoxy(*t*-butyl)copper, gave 66% 2-*t*-butylcyclohexanone. This is one of the few methods for introducing a tertiary alkyl group α to a carbonyl group. When dialkylcopperzinc reagents R$_2$CuZnCl couple with allylic halides, almost complete allylic rearrangement occurs (S$_N$2'), and the reaction is diastereoselective if the allylic halide contains a δ alkoxy group.[1286]

For the preparation of R$_2'$CuLi reagents, see **2-35**.

A much older reaction is the coupling of alkyl halides with Grignard reagents.[1287] Grignard reagents have the advantage that they are usually simpler to prepare than the corresponding R$_2'$CuLi, 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.[1288] Aryl Grignard

[1279]Bertz; Dabbagh; Villacorta *J. Am. Chem. Soc.* **1982**, *104*, 5824; Bertz; Dabbagh *J. Org. Chem.* **1984**, *49*, 1119.

[1280]Mooiweer; Elsevier; Wijkens; Vermeer *Tetrahedron Lett.* **1985**, *26*, 65.

[1281]Corey; Boaz *Tetrahedron Lett.* **1984**, *25*, 3059, 3063. For the reaction of these reagents with haloalkynes, see Yeh; Knochel *Tetrahedron Lett.* **1989**, *30*, 4799.

[1282]Dubois; Lion; Moulineau *Tetrahedron Lett.* **1971**, 177; Dubois; Fournier; Lion *Bull. Soc. Chim. Fr.* **1976**, 1871.

[1283]See Corey; Posner, Ref. 1267; Wakselman; Mondon *Tetrahedron Lett.* **1973**, 4285.

[1284]Posner; Sterling *J. Am. Chem. Soc.* **1973**, *95*, 3076. See also Posner; Sterling; Whitten; Lentz; Brunelle *J. Am. Chem. Soc.* **1975**, *97*, 107; Lion; Dubois *Tetrahedron* **1975**, *31*, 1223. Ph$_2$CuLi behaves similarly: see Lei; Doubleday; Turro *Tetrahedron Lett.* **1986**, *27*, 4671.

[1285]Prepared by treating CuI with *t*-BuOLi in THF at 0°C and adding RLi to this solution.

[1286]Nakamura; Sekiya; Arai; Aoki *J. Am. Chem. Soc.* **1989**, *111*, 3091.

[1287]For reviews, see Raston; Salem, in Hartley *The Chemistry of the Metal–Carbon Bond*, vol. 4; Wiley: New York, 1987, pp. 161-306, pp. 269-283; Kharasch; Reinmuth *Grignard Reactions of Nonmetallic Substances*; Prentice-Hall: Englewood Cliffs, NJ, 1954, pp. 1046-1165.

[1288]See, for example, Ohno; Shimizu; Ishizaki; Sasaki; Eguchi *J. Org. Chem.* **1988**, *53*, 729.

reagents usually give better yields in these reactions than alkyl Grignard reagents. Furthermore, because Grignard reagents react with the C=O group (6-29, 6-32), they cannot be used to couple with halides containing ketone, COOR, or amide functions. Though 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. Grignard reagents can be made to couple with alkyl halides in good yields by the use of certain catalysts.[1289] Among these are Cu(I) salts, which permit the coupling of Grignard reagents with primary alkyl halides in good yield[1290] (organocopper salts are probably intermediates here), and iron(III)[1291] or palladium[1292] complexes, which allow the coupling of Grignard reagents and vinylic halides. Grignard reagents prepared from primary or secondary[1293] alkyl or aryl halides can be coupled with vinylic or aryl halides in high yields in the presence of a nickel(II) catalyst.[1294] When a chiral nickel(II) catalyst is used, optically active hydrocarbons can be prepared from achiral reagents.[1295] Neopentyl iodides also couple with aryl Grignard reagents in the presence of a nickel(II) catalyst.[1295a]

Other organometallic compounds[1296] have also been used to couple with alkyl halides.[1297] Organosodium and organopotassium compounds are more reactive than Grignard reagents and couple even with less reactive halides. 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[1298] or of vinylic halides with alkyllithiums in the presence of a Pd or Ru catalyst.[1299] 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.[1300]

Organoaluminum compounds couple very well with tertiary (to give products containing a quaternary carbon) and benzylic halides at $-78°C$.[1301] This reaction can also be applied to allylic, secondary, and some primary halides, but several days standing at room temperature is required (see also 0-90). Products containing a quaternary carbon can also be

[1289]For reviews, see Erdik *Tetrahedron* **1984**, *40*, 641-657; Kochi, Ref. 1077, pp. 374-398.

[1290]Tamura; Kochi *J. Am. Chem. Soc.* **1971**, *93*, 1485, *Synthesis* **1971**, 303, *J. Organomet. Chem.* **1972**, *42*, 205; Onuma; Hashimoto *Bull. Chem. Soc. Jpn.* **1972**, *45*, 2582; Derguini-Boumechal; Linstrumelle *Tetrahedron Lett.* **1976**, 3225; Mirviss *J. Org. Chem.* **1989**, *54*, 1948.

[1291]Tamura; Kochi *Synthesis* **1971**, 303, *J. Am. Chem. Soc.* **1971**, *93*, 1487; Smith; Kochi *J. Org. Chem.* **1976**, *41*, 502; Walborsky; Banks *J. Org. Chem.* **1981**, *46*, 5074; Molander; Rahn; Shubert; Bonde *Tetrahedron Lett.* **1983**, *24*, 5449.

[1292]Dang; Linstrumelle *Tetrahedron Lett.* **1978**, 191; Ratovelomanana; Linstrumelle; Normant *Tetrahedron Lett.* **1985**, *26*, 2575; Rossi; Carpita *Tetrahedron Lett.* **1986**, *27*, 2529; Minato; Suzuki; Tamao *J. Am. Chem. Soc.* **1987**, *109*, 1257; Fiandanese; Marchese; Mascolo; Naso; Ronzini *Tetrahedron Lett.* **1988**, *29*, 3705. For other references, see Ref. 508, pp. 201-202.

[1293]Hayashi; Konishi; Kobori; Kumada; Higuchi; Hirotsu *J. Am. Chem. Soc.* **1984**, *106*, 158.

[1294]Corriu; Masse *J. Chem. Soc., Chem. Commun.* **1972**, 144; Tamao; Sumitani; Kumada *J. Am. Chem. Soc.* **1972**, *94*, 4374. For a review, see Kumada *Pure Appl. Chem.* **1980**, *52*, 669-679.

[1295]For a review, see Hayashi; Kumada, in Morrison *Asymmetric Synthesis*, vol. 5; Academic Press: New York, 1985, pp. 147-169. See also Cross; Kellogg *J. Chem. Soc., Chem. Commun.* **1987**, 1746; Iida; Yamashita *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2365.

[1295a]Yuan; Scott *Tetrahedron Lett.* **1991**, *32*, 189.

[1296]For lists of reagents and substrates, with references, see Ref. 508, pp. 57-67.

[1297]For a review of the coupling of organic halides with organotin, mercury, and copper compounds catalyzed by palladium complexes, see Beletskaya *J. Organomet. Chem.* **1983**, *250*, 551-564. For a review of palladium-assisted coupling, see Larock *Organomercury Compounds in Organic Synthesis*; Springer: New York, 1985, pp. 249-262.

[1298]Linstrumelle *Tetrahedron Lett.* **1974**, 3809; Millon; Lorne; Linstrumelle *Synthesis* **1975**, 434; Duhamel; Poirier *J. Am. Chem. Soc.* **1977**, *99*, 8356.

[1299]Murahashi; Yamamura; Yanagisawa; Mita; Kondo *J. Org. Chem.* **1979**, *44*, 2408.

[1300]Yamamoto; Yamamoto; Yatagai; Maruyama *J. Am. Chem. Soc.* **1980**, *102*, 2318. See also Lipshutz; Ellsworth; Dimock *J. Am. Chem. Soc.* **1990**, *112*, 5869.

[1301]Miller *J. Org. Chem.* **1966**, *31*, 908; Kennedy *J. Org. Chem.* **1970**, *35*, 532. See also Kennedy; Sivaram *J. Org. Chem.* **1973**, *38*, 2262; Sato; Kodama; Sato *J. Organomet. Chem.* **1978**, *157*, C30.

obtained by treatment of tertiary halides with dialkyl or diaryl zinc reagents in CH_2Cl_2,[1302] with Me_4Si and $AlCl_3$,[1303] or with alkyltitanium reagents $RTiCl_3$ and R_2TiCl_2.[1304] 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 ($R_2CCl_2 \rightarrow R_2CMe_2$).[1305] 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,[1306] and with vinylic and benzylic halides to give 1,3-dienes and allylic arenes, respectively.[1307] Arylpalladium salts "ArPdX" prepared from arylmercury compounds and lithium palladium chloride couple with allylic chlorides in moderate yields, though allylic rearrangements can occur.[1308] The advantage of this procedure is that the aryl group may contain nitro, ester, or aldehyde groups, etc., which cannot be present in a Grignard reagent. Allylic, benzylic, vinylic, and aryl halides couple with organotin reagents in a reaction catalyzed by palladium complexes.[1309] 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. 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.[1310] Alkenylboranes ($R_2'C=CHBZ_2$; Z = various groups) couple in high yields with vinylic, alkynyl, aryl, benzylic, and allylic halides in the presence of tetra-kis(triphenylphosphine)palladium $Pd(PPh_3)_4$ and a base to give $R_2'C=CHR$.[1311] 9-Alkyl-9-BBN compounds (p. 785) also couple with vinylic and aryl halides[1312] as well as with α-halo ketones, nitriles, and esters.[1313]

gem-Dichlorides have been prepared by coupling alkyl halides to $RCCl_3$ compounds electrochemically, in an undivided cell with a sacrificial anode:[1314]

$$RCCl_3 + R'X + 2e^- \longrightarrow RCCl_2R' + Cl^- + X^-$$

R' could also be Cl, in which case the product bears a CCl_3 group.[1315]

Much study has been devoted to the mechanisms of these reactions,[1316] 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 envi-

[1302]Reetz; Wenderoth; Peter; Steinbach; Westermann *J. Chem. Soc., Chem. Commun.* **1980**, 1202. See also Klingstedt; Frejd *Organometallics* **1983**, *2*, 598.

[1303]Bolestova; Parnes; Latypova; Kursanov *J. Org. Chem. USSR* **1981**, *17*, 1203.

[1304]Reetz; Westermann; Steinbach *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 900, 901 [*Angew. Chem. 92*, 931, 933].

[1305]Reetz; Steinbach; Wenderoth *Synth. Commun.* **1982**, *11*, 261.

[1306]Lynd; Zweifel *Synthesis* **1974**, 658; Matsushita; Negishi *J. Am. Chem. Soc.* **1981**, *103*, 2882, *J. Chem. Soc., Chem. Commun.* **1982**, 160. For similar reactions with other metals, see Larock; Bernhardt; Driggs *J. Organomet. Chem.* **1978**, *156*, 45; Yoshida; Tamao; Takahashi; Kumada *Tetrahedron Lett.* **1978**, 2161; Brown; Campbell *J. Org. Chem.* **1980**, *45*, 550; Baeckström; Björkling; Högberg; Norin *Acta Chem. Scand., Ser. B* **1984**, *38*, 779.

[1307]Negishi *Acc. Chem. Res.* **1982**, *15*, 340-348; Negishi; Luo *J. Org. Chem.* **1983**, *48*, 1560; Negishi; Takahashi; Baba; Van Horn; Okukado *J. Am. Chem. Soc.* **1987**, *109*, 2393; Negishi; Takahashi; Baba *Org. Synth. 66*, 60.

[1308]Heck *J. Am. Chem. Soc.* **1968**, *90*, 5531. For a review of palladium-assisted coupling, see Heck *Palladium Reagents in Organic Syntheses*; Academic Press: New York, 1985, pp. 208-214, 242-249.

[1309]For a review, see Stille *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508-524 [*Angew. Chem. 98*, 504-519]. See also Stille; Simpson *J. Am. Chem. Soc.* **1987**, *109*, 2138; Bumagin; Andryukhova; Beletskaya *Doklad. Chem.* **1989**, *307*, 211; Stork; Isaacs *J. Am. Chem. Soc.* **1990**, *112*, 7399; Laborde; Lesheski; Kiely *Tetrahedron Lett.* **1990**, *31*, 1837. For a review of the mechanism, see Bumagin; Beletskaya *Russ. Chem. Rev.* **1990**, *59*, 1174-1184.

[1310]Hatanaka; Hiyama *J. Org. Chem.* **1988**, *53*, 918, **1989**, *54*, 268.

[1311]Brown; Molander *J. Org. Chem.* **1981**, *46*, 645; Miyaura; Yamada; Suginome; Suzuki *J. Am. Chem. Soc.* **1985**, *107*, 972; Sato; Miyaura; Suzuki *Chem. Lett.* **1989**, 1405; Rivera; Soderquist *Tetrahedron Lett.* **1991**, *32*, 2311; and references cited in these papers. For a review, see Matteson *Tetrahedron* **1989**, *45*, 1859-1885.

[1312]Miyaura; Ishiyama; Sasaki; Ishikawa; Satoh; Suzuki *J. Am. Chem. Soc.* **1989**, *111*, 314. See also Soderquist; Santiago *Tetrahedron Lett.* **1990**, *31*, 5541.

[1313]Brown; Joshi; Pyun; Singaram *J. Am. Chem. Soc.* **1989**, *111*, 1754. For another such coupling, see Matteson; Tripathy; Sarkar; Sadhu *J. Am. Chem. Soc.* **1989**, *111*, 4399.

[1314]Nédélec; Aït Haddou Mouloud; Folest; Périchon *J. Am. Chem. Soc.* **1988**, *53*, 4720.

[1315]For the transformation RX → RCF_3, see Chen; Wu *J. Chem. Soc., Chem. Commun.* **1989**, 705.

[1316]For a review, see Beletskaya; Artamkina; Reutov *Russ. Chem. Rev.* **1976**, *45*, 330-347.

sioned: 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:

$$RX + R'M \longrightarrow \begin{bmatrix} R\cdot + R'\cdot \\ + MX \end{bmatrix} \longrightarrow RR'$$

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.[1317] 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.[1318] Similarly, inversion has been shown in the reaction of 2-bromobutane with Ph_2CuLi[1274] (though the same reaction with 2-iodobutane has been reported to proceed with racemization[1319]). The fact that in some of these cases the 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 → 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[1320] is the observation of CIDNP in reactions of alkyl halides with simple organolithium reagents[1321] (see p. 187), the detection of free radicals by esr spectroscopy[1322] (p. 186), and the formation of 2,3-dimethyl-2,3-diphenylbutane when the reaction was carried out in the presence of cumene[1323] (this product is formed when a free radical abstracts a hydrogen from cumene to give PhĊMe$_2$, which dimerizes). Evidence for free-radical mechanisms has also been found for the coupling of alkyl halides with simple organosodium compounds (Wurtz),[1324] with Grignard reagents,[1325] and with lithium dialkylcopper reagents.[1326] Free radicals have also been implicated in the metal-ion-catalyzed coupling of alkyl and aryl halides with Grignard reagents.[1327]

For symmetrical coupling of organometallic reagents (2RM → RR), see **4-33** to **4-35**.

OS I, 186; III, 121; IV, 748; V, 1092; VI, 407, 675; VII, 77, 172, 245, 326, 485; **66,** 60; **68,** 130, 162; **69,** 120.

[1317]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.

[1318]Sauer; Braig *Tetrahedron Lett.* **1969,** 4275; Sommer; Korte *J. Org. Chem.* **1970,** *35,* 22; Korte; Kinner; Kaska *Tetrahedron Lett.* **1970,** 603. See also Schlosser; Fouquet *Chem. Ber.* **1974,** *107,* 1162, 1171.

[1319]Lipshutz; Wilhelm *J. Am. Chem. Soc.* **1982,** *104,* 4696; Lipshutz; Wilhelm; Nugent; Little; Baizer *J. Org. Chem.* **1983,** *48,* 3306.

[1320]For other evidence, see Muraoka; Nojima; Kusabayashi; Nagase *J. Chem. Soc., Perkin Trans. 2* **1986,** 761.

[1321]Ward; Lawler; Cooper *J. Am. Chem. Soc.* **1969,** *91,* 746; Lepley; Landau *J. Am. Chem. Soc.* **1969,** *91,* 748; Podoplelov; Leshina; Sagdeev; Kamkha; Shein *J. Org. Chem. USSR* **1976,** *12,* 488. For a review, see Ward; Lawler; Cooper, in Lepley; Closs *Chemically Induced Magnetic Polarization*; Wiley: New York, 1973, pp. 281-322.

[1322]Russell; Lamson *J. Am. Chem. Soc.* **1969,** *91,* 3967.

[1323]Bryce-Smith *Bull. Soc. Chim. Fr.* **1963,** 1418.

[1324]Garst; Cox *J. Am. Chem. Soc.* **1970,** *92,* 6389; Kasukhin; Gragerov *J. Org. Chem. USSR* **1971,** *7,* 2087; Garst; Hart *J. Chem. Soc., Chem. Commun.* **1975,** 215.

[1325]Gough; Dixon *J. Org. Chem.* **1968,** *33,* 2148; Ward; Lawler; Marzilli *Tetrahedron Lett.* **1970,** 521; Kasukhin; Ponomarchuk; Buteiko *J. Org. Chem. USSR* **1972,** *8,* 673; Singh; Tayal; Nigam *J. Organomet. Chem.* **1972,** *42,* C9.

[1326]Ashby; DePriest; Tuncay; Srivastava *Tetrahedron Lett.* **1982,** *23,* 5251; Ashby; Coleman *J. Org. Chem.* **1987,** *52,* 4554; Bertz; Dabbagh; Mujsce *J. Am. Chem. Soc.* **1991,** *113,* 631.

[1327]Norman; Waters *J. Chem. Soc.* **1957,** 950; Frey *J. Org. Chem.* **1961,** *26,* 5187; Slaugh *J. Am. Chem. Soc.* **1961,** *83,* 2734; Davies; Done; Hey *J. Chem. Soc.* C **1969,** 1392, 2021, 2056; Abraham; Hogarth *J. Organomet. Chem.* **1968,** *12,* 1, 497; Tamura; Kochi *J. Am. Chem. Soc.* **1971,** *93,* 1483, 1485, 1487, *J. Organomet. Chem.* **1971,** *31,* 289, **1972,** *42,* 205; Lehr; Lawler *J. Am. Chem. Soc.* **1986,** *106,* 4048.

0-88   Allylic and Propargylic Coupling with a Halide Substrate
De-halogen-coupling

$$2R-\overset{\overset{\displaystyle R}{|}}{C}=\overset{\overset{\displaystyle R}{|}}{C}-CH_2Br + Ni(CO)_4 \longrightarrow R-\overset{\overset{\displaystyle R}{|}}{C}=\overset{\overset{\displaystyle R}{|}}{C}-CH_2CH_2-\overset{\overset{\displaystyle R}{|}}{C}=\overset{\overset{\displaystyle R}{|}}{C}-R + NiBr_2 + 4CO$$

Because of the presence of the 1,5-diene moiety in many naturally occurring compounds, a great deal of effort has been expended in searching for methods to couple[1328] allylic groups.[1329] In one of these methods, allylic halides, tosylates, and acetates can be symmetrically coupled by treatment with nickel carbonyl[1330] at room temperature in a solv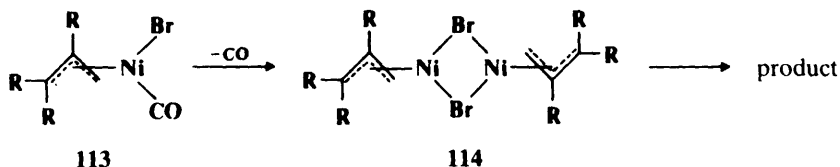ent such as THF or DMF to give 1,5-dienes.[1331] The order of halide reactivity is I > Br > Cl. With unsymmetrical allylic substrates, coupling nearly always takes place at the less-substituted end. The reaction can be performed intramolecularly; large (11- to 20-membered) rings can be made in good yields (60 to 80%) by the use of high dilution. An example[1332] is
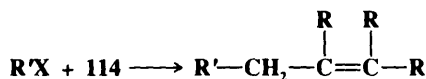
$$\begin{array}{l} CH{=}CH{-}CH_2Br \\ | \\ (CH_2)_{12} \\ | \\ CH{=}CH{-}CH_2Br \end{array} \quad + \ Ni(CO)_4 \ \xrightarrow{\text{DMF}} \ 84\%$$

It is likely that the mechanism involves reaction of the allylic compound with Ni(CO)$_4$ to give one or more π-allyl complexes, one of which may be **113**, which can then lose CO to

113   114

give a π-allylnickel bromide (**114**) which reacts further, perhaps with CO, to give the product. The complexes **114** can be isolated from the solution and crystallized as stable solids.

Unsymmetrical coupling can be achieved by treating an alkyl halide directly with **114**, in a polar aprotic solvent.[1333] In this case too, unsymmetrical allylic groups couple at the less

$$R'X + 114 \longrightarrow R'-CH_2-\overset{\overset{\displaystyle R}{|}}{C}=\overset{\overset{\displaystyle R}{|}}{C}-R$$

[1328]For a review of some allylic coupling reactions, see Magid *Tetrahedron* **1980**, *36*, 1901-1930, pp. 1910-1924.

[1329]In this section are discussed methods in which one molecule is a halide. For other allylic coupling reactions, see **0-87, 0-90**, and **0-91**.

[1330]For a review of the use of organonickel compounds in organic synthesis, see Tamao; Kumada, in Hartley, Ref. 1287, pp. 819-887.

[1331]For reviews, see Collman et al., Ref. 1266, pp. 739-748; Billington *Chem. Soc. Rev.* **1985**, *14*, 93-120; Kochi, Ref. 1077, pp. 398-408; Semmelhack *Org. React.* **1972**, *19*, 115-198, pp. 162-170; Baker *Chem. Rev.* **1973**, *73*, 487-530, pp. 512-517; Heimbach; Jolly; Wilke *Adv. Organomet. Chem.* **1970**, *8*, 29-86, pp. 30-39.

[1332]Corey; Wat *J. Am. Chem. Soc.* **1967**, *89*, 2757. See also Corey; Helquist *Tetrahedron Lett.* **1975**, 4091; Reijnders; Blankert; Buck *Recl. Trav. Chim. Pays-Bas* **1978**, *97*, 30.
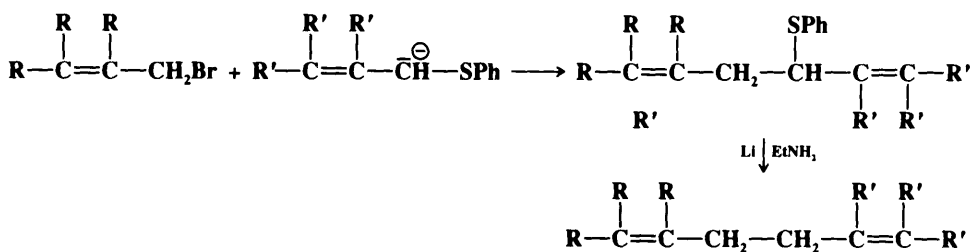
[1333]Corey; Semmelhack *J. Am. Chem. Soc.* **1967**, *89*, 2755. For a review, see Semmelhack, Ref. 1331, pp. 147-162. For a discussion of the preparation and handling of π-allylnickel halides, see Semmelhack, Ref. 1331, pp. 144-146.

substituted end. The mechanism here cannot be simple nucleophilic substitution, since aryl and vinylic halides undergo the reaction as well as or better than simple primary bromides. There is evidence that free radicals are involved.[1334] Hydroxy or carbonyl groups in the alkyl halide do not interfere. When **114** reacts with an allylic halide, a mixture of three products is obtained because of halogen–metal interchange. For example, allyl bromide treated with **114** 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.[1335]

The reaction between primary and secondary halides and allyltributylstannane provides another method for unsymmetrical coupling RX + $CH_2=CHCH_2SnBu_3$ → $RCH_2CH=CH_2$.[1336]

Symmetrical coupling of allylic halides can also be accomplished by heating with magnesium in ether,[1337] with a cuprous iodide–dialkylamide complex,[1338] with $CrCl_3$–$LiAlH_4$,[1339] with Te^{2-} ions,[1340] with ion powder in DMF,[1341] or electrochemically.[1342] 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,[1343] or with an allylic tin reagent.[1344] 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 ($RCH=CHCH_2\overset{\ominus}{B}R_3''\ Li^+$).[1345]

In another method for the coupling of two different allylic groups,[1346] a carbanion derived from a β,γ-unsaturated thioether couples with an allylic halide.[1347] The product contains an SPh group that must be removed (with Li in ethylamine) to give the 1,5-diene, but this

method has the advantage that, unlike most of the methods previously discussed, the coupling preserves the original positions and configurations of the two double bonds; no allylic rearrangements take place.

[1334]Hegedus; Thompson *J. Am. Chem. Soc.* **1985**, *107*, 5663.

[1335]Corey; Semmelhack; Hegedus *J. Am. Chem. Soc.* **1968**, *90*, 2416.

[1336]See Keck; Yates *J. Am. Chem. Soc.* **1982**, *104*, 5829; Migita; Nagai; Kosugi *Bull. Chem. Soc. Jpn* **1983**, *56*, 2480.

[1337]Turk; Chanan *Org. Synth. III*, 121.

[1338]Kitagawa; Oshima; Yamamoto; Nozaki *Tetrahedron Lett.* **1975**, 1859.

[1339]Okude; Hiyama; Nozaki *Tetrahedron Lett.* **1977**, 3829.

[1340]Clive; Anderson; Moss; Singh *J. Org. Chem.* **1982**, *47*, 1641.

[1341]Hall; Hurley *Can. J. Chem.* **1969**, *47*, 1238.

[1342]Tokuda; Endate; Suginome *Chem. Lett.* **1988**, 945.

[1343]Stork; Grieco; Gregson *Tetrahedron Lett.* **1969**, 1393; Grieco *J. Am. Chem. Soc.* **1969**, *91*, 5660.

[1344]Godschalx; Stille *Tetrahedron Lett.* **1980**, *21*, 2599; **1983**, *24*, 1905; Hosomi; Imai; Endo; Sakurai *J. Organomet. Chem.* **1985**, *285*, 95. See also Yanagisawa; Norikate; Yamamoto *Chem. Lett.* **1988**, 1899.

[1345]Yamamoto; Yatagai; Maruyama *J. Am. Chem. Soc.* **1981**, *103*, 1969.

[1346]For other procedures, see Axelrod; Milne; van Tamelen *J. Am. Chem Soc.* **1970**, *92*, 2139; Morizawa; Kanemoto; Oshima; Nozaki *Tetrahedron Lett.* **1982**, *23*, 2953.

[1347]Biellmann; Ducep *Tetrahedron Lett.* **1969**, 3707.

In a method for propargylating an alkyl halide without allylic rearrangement, the halide is treated with lithio-1-trimethylsilylpropyne (115) which is a lithium compound protected

$$RX + Li\overset{3}{C}H_2\overset{}{-}C\overset{1}{\equiv}C\overset{}{-}SiMe_3 \longrightarrow RCH_2\overset{}{-}C\equiv C\overset{}{-}SiMe \xrightarrow[2.CN^-]{1.Ag^+} R\overset{}{-}CH_2\overset{}{-}C\equiv CH$$

$$\mathbf{115}$$

by an $SiMe_3$ group.[1348] 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^-. 115 is prepared by treating propynyllithium with Me_3SiCl to give $MeC\equiv CSiMe_3$ from which a proton is removed with BuLi. R may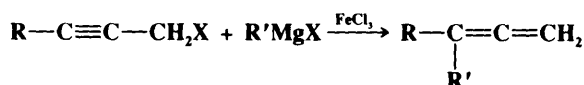 be primary or allylic.[1349] On the other hand, propargylic halides can be alkylated with essentially complete allylic rearrangement, to give allenes, by treatment with Grignard reagents and metallic salts,[1350] or with dialkylcuprates R_2Cu.[1351]

$$R\overset{}{-}C\equiv C\overset{}{-}CH_2X + R'MgX \xrightarrow{FeCl_3} R\overset{}{-}\underset{\underset{R'}{|}}{C}{=}C{=}CH_2$$

OS **III**, 121; **IV**, 748; **VI**, 722.

0-89 Coupling of Organometallic Reagents with Esters of Sulfuric and Sulfonic Acids
Alkyl-de-sulfonyloxy-substitution, etc.

$$ROSO_2OR' + R_2'CuLi \longrightarrow RR''$$

Lithium dialkylcopper reagents couple with alkyl tosylates.[1352] High yields are obtained with primary tosylates; secondary tosylates give lower yields.[1353] Aryl tosylates do not react. Vinylic triflates[1354] couple very well to give alkenes.[1355] Vinylic triflates also couple with allylic cuprates, to give 1,4-dienes.[1356] Tosylates and other sulfonates and sulfates also couple with Grignard reagents,[1357] most often those prepared from aryl or benzylic halides.[1358] Alkyl sulfates and sulfonates generally make better substrates in reactions with Grignard reagents than the corresponding halides (0-87). The method is useful for primary and secondary R. Allylic tosylates can be symmetrically coupled with $Ni(CO)_4$ (see **0-88**). Propargylic tosylates couple with vinylic cuprates to give vinylic allenes.[1359] Vinylic triflates, in the presence of $Pd(Ph_3P)_4$ and LiCl, couple with organotin compounds $R'SnMe_3$, where R' can be alkyl,

[1348]Corey; Kirst; Katzenellenbogen *J. Am. Chem. Soc.* **1970**, *92*, 6314.
[1349]For an alternative procedure, see Ireland; Dawson; Lipinski *Tetrahedron Lett.* **1970**, 2247.
[1350]Pasto; Chou; Waterhouse; Shults; Hennion *J. Org. Chem.* **1978**, *43*, 1385; Jeffery-Luong; Linstrumelle *Tetrahedron Lett.* **1980**, *21*, 5019.
[1351]Pasto; Chou; Fritzen; Shults; Waterhouse; Hennion *J. Org. Chem.* **1978**, *43*, 1389. See also Tanigawa; Murahashi *J. Org. Chem.* **1980**, *45*, 4536.
[1352]Johnson; Dutra *J. Am. Chem. Soc.* **1973**, *95*, 7777, 7783. For examples, see Posner *An Introduction to Synthesis Using Organocopper Reagents*, Ref. 1268, pp. 85-90.
[1353]Secondary tosylates give higher yields when they contain an O or S atom: Hanessian; Thavonekham; DeHoff *J. Org. Chem.* **1989**, *54*, 5831.
[1354]For a review of coupling reactions of vinylic triflates, see Scott; McMurry *Acc. Chem. Res.* **1988**, *21*, 47-54.
[1355]McMurry; Scott *Tetrahedron Lett.* **1980**, *21*, 4313; Tsushima; Araki; Murai *Chem. Lett.* **1989**, 1313.
[1356]Lipshutz; Elworthy *J. Org. Chem.* **1990**, *55*, 1695.
[1357]For a review, see Kharasch; Reinmuth, Ref. 1287, pp. 1277-1286.
[1358]For an example involving an allylic rearrangement (conversion of a silylalkyne to a silylallene), see Danheiser; Tsai; Fink *Org. Synth.* 66, 1.
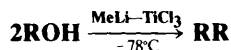[1359]Baudouy; Goré *J. Chem. Res. (S)* **1981**, 278. See also Elsevier; Vermeer *J. Org. Chem.* **1989**, *54*, 3726.

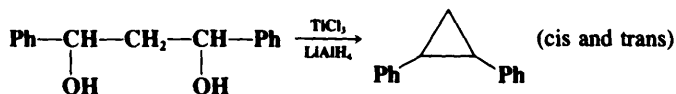allylic, vinylic, or alkynyl.[1360] The reaction has been performed intramolecularly, to prepare large-ring lactones.[1361]

OS **I**, 471; **II**, 47, 360; **VII**, 351; **66**, 1; **68**, 116.

0-90   Coupling Involving Alcohols
De-hydroxyl-coupling

$$2ROH \xrightarrow[-78°C]{MeLi-TiCl_3} RR$$

Allylic or benzylic alcohols can be symmetrically coupled[1362] by treatment with methyllithium and titanium trichloride at -78°C[1363] or by refluxing with $TiCl_3$ and $LiAlH_4$.[1364] 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.[1365] Another reagent that symmetrically couples allylic and benzylic alcohols is $NbCl_5$–$NaAlH_4$.[1366] The $TiCl_3$–$LiAlH_4$ reagent can also convert 1,3-diols to cyclopropanes, provided that at least one α phenyl is present,[1367] e.g.,

$$Ph-\underset{\underset{OH}{|}}{CH}-CH_2-\underset{\underset{OH}{|}}{CH}-Ph \xrightarrow[LiAlH_4]{TiCl_3} \quad \underset{Ph}{\triangle}\underset{Ph}{} \quad \text{(cis and trans)}$$

Tertiary alcohols react with trimethylaluminum at 80 to 200°C to give methylation.[1368] The presence of side products from elimination and rearrangement, as well as the lack of

$$R_3COH + Me_3Al \xrightarrow{80-200°C} R_3CMe$$

stereospecificity,[1369] indicate an S_N1 mechanism. The reaction can also be applied to primary and secondary alcohols if these contain an aryl group in the α position. Higher trialkylaluminums are far less suitable, because reduction competes with alkylation (see also reactions of Me_3Al with ketones, **6-29**, and with carboxylic acids, **6-32**). Me_2TiCl_2 also reacts with tertiary alcohols in the same way.[1370] Allylic alcohols couple with a reagent prepared from MeLi, CuI, and R′Li in the presence of $(Ph_3PNMePh)^+ I^-$ to give alkenes that are products of allylic rearrangement.[1371] The reaction gives good yields with primary, secondary, and

[1360]Scott; Stille *J. Am. Chem. Soc.* **1986**, *108*, 3033; Kwon; McKee; Stille *J. Org. Chem.* **1990**, *55*, 3114. For discussions of the mechanism, see Stang; Kowalski; Schiavelli; Longford *J. Am. Chem. Soc.* **1989**, *111*, 3347; Stang; Kowalski *J. Am. Chem. Soc.* **1989**, *111*, 3356.

[1361]Stille; Tanaka *J. Am. Chem. Soc.* **1987**, *109*, 3785.

[1362]For a review, see Lai *Org. Prep. Proceed. Int.* **1980**, *12*, 363-391, pp. 377-388.

[1363]Sharpless; Hanzlik; van Tamelen *J. Am. Chem. Soc.* **1968**, *90*, 209.

[1364]McMurry; Silvestri; Fleming; Hoz; Grayston *J. Org. Chem.* **1978**, *43*, 3249. For another method, see Nakanishi; Shundo; Nishibuchi; Otsuji *Chem. Lett.* **1979**, 955.

[1365]van Tamelen; Åkermark; Sharpless *J. Am. Chem. Soc.* **1969**, *91*, 1552.

[1366]Sato; Oshima *Chem. Lett.* **1982**, 157. For a reagent that couples benzhydrols, see Pri-Bar; Buchman; Blum *Tetrahedron Lett.* **1977**, 1443.

[1367]Baumstark; McCloskey; Tolson; Syriopoulos *Tetrahedron Lett.* **1977**, 3003; Walborsky; Murati *J. Am. Chem. Soc.* **1980**, *102*, 426.

[1368]Meisters; Mole *J. Chem. Soc., Chem. Commun.* **1972**, 595; Harney; Meisters; Mole *Aust. J. Chem.* **1974**, *27*, 1639.

[1369]Salomon; Kochi *J. Org. Chem.* **1973**, *38*, 3715.

[1370]Reetz; Westermann; Steinbach *J. Chem. Soc., Chem. Commun.* **1981**, 237.

[1371]Tanigawa; Ohta; Sonoda; Murahashi *J. Am. Chem. Soc.* **1978**, *100*, 4610; Goering; Tseng *J. Org. Chem.* **1985**, *50*, 1597. For another procedure, see Yamamoto; Maruyama *J. Organomet. Chem.* **1978**, *156*, C9.

$$
\begin{array}{ccc}
\text{R} & \text{R} & \text{R} \\
| & | & | \\
\text{R}-\text{C}=\text{C}-\text{C}-\text{OH} \\
& & | \\
& & \text{R}
\end{array}
\xrightarrow[\text{(Ph}_3\text{PNMePh)}^+\ \text{I}^-]{\text{MeLi}-\text{CuI}-\text{R'Li}}
\begin{array}{ccc}
\text{R} & \text{R} & \text{R} \\
| & | & | \\
\text{R}-\text{C}-\text{C}=\text{C}-\text{R} \\
| \\
\text{R'}
\end{array}
$$

tertiary alcohols, and with alkyl and aryllithiums.[1372] Allylic alcohols also couple with certain Grignard reagents[1373] in the presence of a nickel complex to give both normal products and the products of allylic rearrangement.
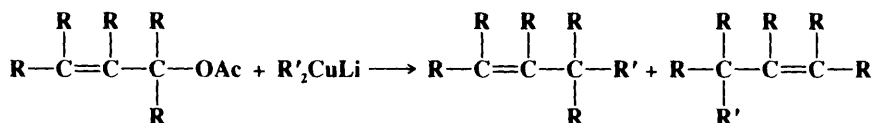
0-91   Coupling of Organometallic Reagents with Carboxylic Esters
Alkyl-de-acyloxy-substitution

$$
\begin{array}{ccc}
\text{R} & \text{R} & \text{R} \\
| & | & | \\
\text{R}-\text{C}=\text{C}-\text{C}-\text{OAc} \\
& & | \\
& & \text{R}
\end{array}
+ \text{R}'_2\text{CuLi} \longrightarrow
\begin{array}{ccc}
\text{R} & \text{R} & \text{R} \\
| & | & | \\
\text{R}-\text{C}=\text{C}-\text{C}-\text{R}' \\
& & | \\
& & \text{R}
\end{array}
+
\begin{array}{ccc}
\text{R} & \text{R} & \text{R} \\
| & | & | \\
\text{R}-\text{C}-\text{C}=\text{C}-\text{R} \\
| \\
\text{R}'
\end{array}
$$

Lithium dialkylcopper reagents couple with allylic acetates to give normal coupling products or those resulting from allylic rearrangement, depending on the substrate.[1374] A mechanism involving a σ-allylic copper(III) complex has been suggested.[1375] With propargyl substrates, the products are allenes.[1376] Allenes are also obtained when propargyl acetates are treated

$$\text{RC}\equiv\text{C}-\text{CR}_2-\text{OAc} + \text{R}'_2\text{CuLi} \longrightarrow \text{RR'C}=\text{C}=\text{CR}_2$$

with methylmagnesium iodide.[1377] Lithium dialkylcopper reagents also give normal coupling products with enol acetates of β-dicarbonyl compounds.[1378] It is also possible to carry out the coupling of allylic acetates with Grignard reagents, if catalytic amounts of cuprous salts are present.[1379] 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,[1380] and allylic acetates couple with aryl and vinylic tin reagents, in the presence of a palladium-complex catalyst.[1381] Allylic acetates can be symmetrically

[1372]For the allylation of benzylic alcohols, see Cella *J. Org. Chem.* **1982**, *47*, 2125.

[1373]Buckwalter; Burfitt; Felkin; Joly-Goudket; Naemura; Salomon; Wenkert; Wovkulich *J. Am. Chem. Soc.* **1978**, *100*, 6445; Felkin; Joly-Goudket; Davies *Tetrahedron Lett.* **1981**, *22*, 1157; Consiglio; Morandini; Piccolo *J. Am. Chem. Soc.* **1981**, *103*, 1846, and references cited in these papers. For a review, see Felkin; Swierczewski *Tetrahedron* **1975**, *31*, 2735-2748. For other procedures, see Mukaiyama; Imaoka; Izawa *Chem. Lett.* **1977**, 1257; Fujisawa; Iida; Yukizaki; Sato *Tetrahedron Lett.* **1983**, *24*, 5745.

[1374]Rona; Tökes; Tremble; Crabbé *Chem. Commun.* **1969**, 43; Anderson; Henrick; Siddall *J. Am. Chem. Soc.* **1970**, *92*, 735; Goering; Singleton *J. Am. Chem. Soc.* **1976**, *98*, 7854; Gallina; Ciattini *J. Am. Chem. Soc.* **1979**, *101*, 1035; Goering; Kantner *J. Org. Chem.* **1984**, *49*, 422. For examples of the use of this reaction with allylic and propargyl substrates, see Posner, Ref. 1352, pp. 91-104.

[1375]Goering; Kantner *J. Org. Chem.* **1983**, *48*, 721; Goering; Kantner; Seitz *J. Org. Chem.* **1985**, *50*, 5495.

[1376]Crabbé; Barreiro; Dollat; Luche *J. Chem. Soc., Chem. Commun.* **1976**, 183, and references cited therein.

[1377]Roumestant; Gore *Bull. Soc. Chim. Fr.* **1972**, 591, 598.

[1378]Casey; Marten *Synth. Commun.* **1973**, *3*, 321, *Tetrahedron Lett.* **1974**, 925. See also Posner; Brunelle *J. Chem. Soc., Chem. Commun.* **1973**, 907; Kobayashi; Takei; Mukaiyama *Chem. Lett.* **1973**, 1097.

[1379]Tseng; Paisley; Goering *J. Org. Chem.* **1986**, *51*, 2884; Tseng; Yen; Goering *J. Org. Chem.* **1986**, *51*, 2892; Underiner; Paisley; Schmitter; Lesheski; Goering *J. Org. Chem.* **1989**, *54*, 2369; Bäckvall; Sellén; Grant *J. Am. Chem. Soc.* **1990**, *112*, 6615. See also Hiyama; Wakasa *Tetrahedron Lett.* **1985**, *26*, 3259.
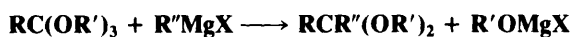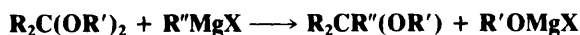
[1380]Itoh; Oshima; Sasaki; Yamamoto; Hiyama; Nozaki *Tetrahedron Lett.* **1979**, 4751; Gallina *Tetrahedron Lett.* **1985**, *26*, 519; Tolstikov; Dzhemilev *J. Organomet. Chem.* **1985**, *292*, 133.

[1381]Del Valle; Stille; Hegedus *J. Org. Chem.* **1990**, *55*, 3019. For another method, see Legros; Fiaud *Tetrahedron Lett.* **1990**, *31*, 7453.
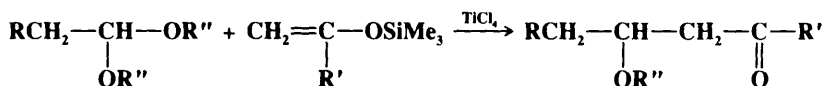
coupled by treatment with $Ni(CO)_4$ (reaction **0-88**) or with Zn and a palladium-complex catalyst,[1382] or converted to unsymmetrical 1,5-dienes by treatment with an allylic stannane $R_2C{=}CHCH_2SnR_3$ in the presence of a palladium complex.[1383]

0-92   Coupling of Organometallic Reagents with Compounds Containing the Ether Linkage[1384]
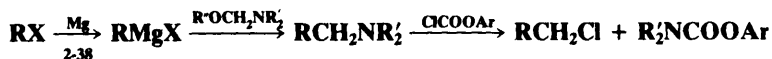**Alkyl-de-alkoxy-substitution**

$$R_2C(OR')_2 + R''MgX \longrightarrow R_2CR''(OR') + R'OMgX$$

$$RC(OR')_3 + R''MgX \longrightarrow RCR''(OR')_2 + R'OMgX$$

Acetals,[1385] ketals, and ortho esters[1386] react with Grignard reagents to give, respectively, ethers and acetals (or ketals). The latter can be hydrolyzed to aldehydes or ketones (**0-6**). 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 **0-102**). The ketone synthesis generally gives lower yields. Acetals, including allylic acetals, also give this reaction with organocopper compounds and BF_3.[1387] Acetals also undergo substitution when treated with silyl enol ethers or allylic silanes, with a Lewis acid catalyst,[1388] e.g.,

$$RCH_2{-}\underset{\underset{OR''}{|}}{CH}{-}OR'' + CH_2{=}\underset{\underset{R'}{|}}{C}{-}OSiMe_3 \xrightarrow{TiCl_4} RCH_2{-}\underset{\underset{OR''}{|}}{CH}{-}CH_2{-}\underset{\underset{O}{\|}}{C}{-}R'$$

Tertiary amines can be prepared by the reaction of amino ethers with Grignard reagents,[1389] $(R_2NCH_2{-}OR' + R''MgX \rightarrow R_2NCH_2{-}R'')$ or with lithium dialkylcopper reagents.[1390] This method, when followed by treatment of the amine with a chloroformate (see **0-72**) allows an alkyl halide RX to be converted to its homolog RCH_2X in only two laboratory steps[1391] (see also p. 476):

$$RX \xrightarrow[\text{2-38}]{Mg} RMgX \xrightarrow{R'OCH_2NR_2'} RCH_2NR_2' \xrightarrow{ClCOOAr} RCH_2Cl + R_2'NCOOAr$$

Ordinary ethers are not cleaved by Grignard reagents (in fact, diethyl ether and THF are the most common solvents for Grignard reagents), though more active organometallic compounds often do cleave them.[1392] Allylic ethers can be cleaved by Grignard reagents in

[1382]Sasaoka; Yamamoto; Kinoshita; Inomata; Kotake *Chem. Lett.* **1985**, 315.

[1383]Trost; Keinan *Tetrahedron Lett.* **1980**, *21*, 2595.

[1384]For a review, see Trofimov; Korostova *Russ. Chem. Rev.* **1975**, *44*, 41-55.

[1385]For a review of coupling reactions of acetals, see Mukaiyama; Murakami *Synthesis* **1987**, 1043-1054. For a discussion of the mechanism, see Abell; Massy-Westropp *Aust. J. Chem.* **1985**, *38*, 1031. For a list of substrates and reagents, with references, see Ref. 508, pp. 404-405.

[1386]For a review of the reaction with ortho esters, see DeWolfe, Ref. 457, pp. 44-45, 224-230.

[1387]Normant; Alexakis; Ghribi; Mangeney *Tetrahedron* **1989**, *45*, 507; Alexakis; Mangeney; Ghribi; Marek; Sedrani; Guir; Normant *Pure Appl. Chem.* **1988**, *60*, 49-56.

[1388]See Mori; Ishihara; Flippen; Nozaki; Yamamoto; Bartlett; Heathcock *J. Org. Chem.* **1990**, *55*, 6107, and references cited therein.

[1389]For example, see Miginiac; Mauzé *Bull. Soc. Chim. Fr.* **1968**, 2544; Eisele; Simchen *Synthesis* **1978**, 757; Kapnang; Charles *Tetrahedron Lett.* **1983**, *24*, 1597; Morimoto; Takahashi; Sekiya *J. Chem. Soc., Chem. Commun.* **1984**, 794; Mesnard; Miginiac *J. Organomet. Chem.* **1989**, *373*, 1. See also Bourhis; Bosc; Golse *J. Organomet. Chem.* **1983**, *256*, 193.

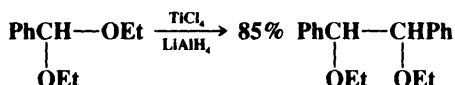[1390]Germon; Alexakis; Normant *Bull. Soc. Chim. Fr.* **1984**, II-377.

[1391]Yankep; Charles *Tetrahedron Lett.* **1987**, *28*, 427.

[1392]For a review of the reactions of ethers with Grignard reagents, see Kharasch; Reinmuth, Ref. 1287, pp. 1013-1045.

THF if CuBr is present.[1393] The reaction takes place either with or without allylic rearrangement.[1394] Propargylic ethers give allenes.[1395] Vinylic ethers can also be cleaved by Grignard reagents in the presence of a catalyst, in this case, a nickel complex.[1396] Silyl enol ethers R_2C=CROSiMe$_3$ behave similarly.[1397]
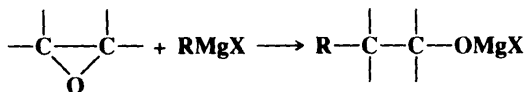
Certain acetals and ketals can be dimerized in a reaction similar to **0-86** by treatment with TiCl$_4$–LiAlH$_4$, e.g.,[1398]

$$PhCH-OEt \xrightarrow[\text{LiAlH}_4]{\text{TiCl}_4} 85\% \; PhCH-CHPh$$

with OEt below the left PhCH, and OEt OEt below the right PhCH—CHPh.

Also see **0-93**.
OS **II**, 323; **III**, 701. Also see OS **V**, 431.

0-93   The Reaction of Organometallic Reagents with Epoxides
3(*OC*)-*seco*-Alkyl-de-alkoxy-substitution

$$-\overset{|}{\underset{\diagdown}{C}}\underset{O}{\overset{|}{\diagup}}\overset{|}{C}- \; + \; RMgX \longrightarrow R-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-OMgX$$

The reaction between Grignard reagents and epoxides is very valuable and is often used to increase the length of a carbon chain by two carbons.[1399] The Grignard reagent may be aromatic or aliphatic, though tertiary Grignard reagents give low yields. As expected for an S_N2 process, attack is at the less substituted carbon. Lithium dialkylcopper reagents also give the reaction,[1400] often producing higher yields, and 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 in a regioselective manner.[1401] The use of BF$_3$ increases the reactivity of R$_2$CuLi, enabling it to be used with thermally unstable epoxides.[1402] The reaction has also been performed with other organometallic compounds, e.g., of Li, Al, etc.[1403]

[1393]Commercon; Bourgain; Delaumeny; Normant; Villieras *Tetrahedron Lett.* **1975**, 3837; Claesson; Olsson *Chem. Soc., Chem. Commun.* **1987**, 621.
[1394]Normant; Commercon; Gendreau; Bourgain; Villieras *Bull. Soc. Chim. Fr.* **1979**, II-309; Gendreau; Normant *Tetrahedron* **1979**, *35*, 1517; Calo; Lopez; Pesce *J. Chem. Soc., Perkin Trans. 1* **1988**, 1301. See also Valverde; Bernabé; Garcia-Ochoa; Gómez *J. Org. Chem.* **1990**, *55*, 2294.
[1395]Alexakis; Marek; Mangeney; Normant *Tetrahedron Lett.* **1989**, *30*, 2387. *J. Am. Chem. Soc.* **1990**, *112*, 8042.
[1396]Wenkert; Michelotti; Swindell; Tingoli *J. Org. Chem.* **1984**, *49*, 4894; Kocieński; Dixon; Wadman *Tetrahedron Lett.* **1988**, *29*, 2353.
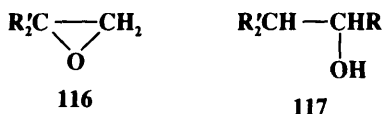[1397]Hayashi; Katsuro; Kumada *Tetrahedron Lett.* **1980**, *21*, 3915.
[1398]Ishikawa; Mukaiyama *Bull Chem. Soc. Jpn.* **1978**, *51*, 2059.
[1399]For a review, see Kharasch; Reinmuth, Ref. 1287, pp. 961-1012. For a thorough discussion, see Schaap; Arens *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 1249. For improved procedures, see Huynh; Derguini-Boumechal; Linstrumelle *Tetrahedron Lett.* **1979**, 1503; Schrumpf; Grätz; Meinecke; Fellenberger *J. Chem. Res. (S)* **1982**, 162.
[1400]For examples of the use of this reactions, see Posner, Ref. 1352, pp. 103-113. See also Lipshutz; Kozlowski; Wilhelm *J. Am. Chem. Soc.* **1982**, *104*, 2305.
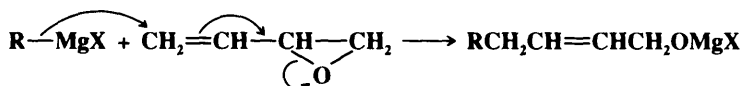[1401]Johnson; Herr; Wieland *J. Org. Chem.* **1973**, *38*, 4263; Hartman; Livinghouse; Rickborn *J. Org. Chem.* **1973**,

When *gem*-disubstituted epoxides (**116**) are treated with Grignard reagents (and sometimes other epoxides), the product may be **117**, that is, the new alkyl group may appear on

$$R_2'C \overset{\displaystyle\diagdown O \diagup}{\quad} CH_2 \qquad\qquad R_2'CH - CHR$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\overset{|}{OH}$$
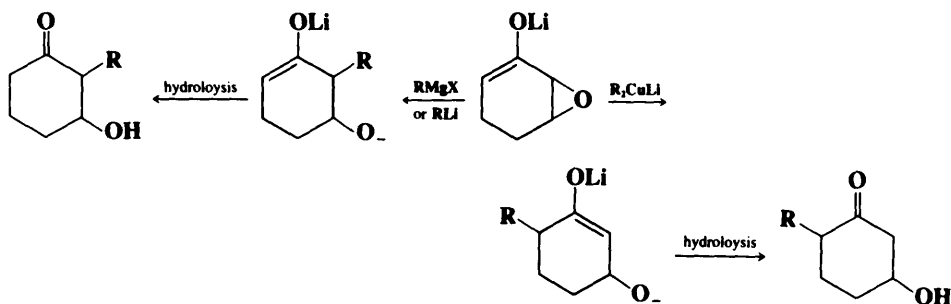
$$\textbf{116} \qquad\qquad\qquad \textbf{117}$$

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.
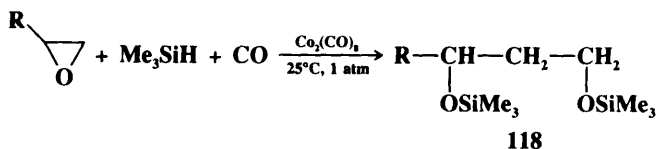
When the substrate is a vinylic epoxide,[1404] Grignard reagents generally give a mixture of the normal product and the product of allylic rearrangement.[1405]

$$R\overset{\frown}{-}MgX + CH_2\overset{\frown}{=}CH\overset{\frown}{-}CH\overset{\frown}{-}CH_2 \longrightarrow RCH_2CH=CHCH_2OMgX$$

The latter often predominates. In the case of R_2CuLi,[1406] acyclic substrates give mostly allylic rearrangement.[1405] The double bond of the "vinylic" epoxide can be part of an enolate ion if the substrate is cyclic. In this case R_2CuLi give exclusive allylic rearrangement (SN2'), while Grignard and organolithium reagents give normal substitution, e.g.,[1407]

An organometallic equivalent that opens epoxides is a hydrosilane, e.g., Me_3SiH, and carbon monoxide, catalyzed by dicobalt octacarbonyl:[1408]

$$\textbf{118}$$

[1404]For a list of organometallic reagents that react with vinylic epoxides, with references, see Ref. 508, pp. 123-124.

[1405]Anderson *J. Am. Chem. Soc.* **1970**, *92*, 4978; Johnson; Herr; Wieland, Ref. 1401; Marshall; Trometer; Blough; Crute *J. Org. Chem.* **1988**, *53*, 4274; Marshall; Trometer; Cleary *Tetrahedron* **1989**, *45*, 391.

[1406]For a review of the reactions of vinylic epoxides with organocopper reagents, see Marshall *Chem. Rev.* **1989**, *89*, 1503-1511.

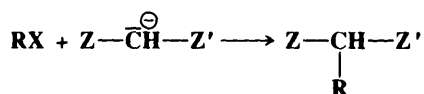[1407]Wender; Erhardt; Letendre *J. Am. Chem. Soc.* **1981**, *103*, 2114.

[1408]Murai; Kato; Murai; Toki; Suzuki; Sonoda *J. Am. Chem. Soc.* **1984**, *106*, 6093.

The 1,3-disilyl ether **118** can be hydrolyzed to a 1,3-diol.[1409]
Aziridines have been similarly opened, to give amines.[1410]
OS **I**, 306; **VII**, 501; **69**, 1, 80.

0-94 Alkylation at a Carbon Bearing an Active Hydrogen
Bis(ethoxycarbonyl)methyl-de-halogenation, etc.

$$RX + Z-\overset{\ominus}{C}H-Z' \longrightarrow Z-CH-Z'$$
$$\underset{R}{|}$$

Compounds that contain two (or three, but this is rare) strong electron-withdrawing groups
on a carbon atom are more acidic than compounds without such groups (p. 264) and are
easily converted to their corresponding enolate ions (p. 72). These enolate ions can attack
alkyl halides, resulting in their alkylation.[1411] Z and Z' may be COOR', CHO, COR',
CONR$_2'$, COO⁻, CN,[1412] NO$_2$, SOR', SO$_2$R',[1413] SO$_2$OR', SO$_2$NR$_2'$ or similar groups.[1414] A
carbon atom with any two of these (the same or different) will give up a proton (if it has
one) to a suitable base. Some commonly used bases are sodium ethoxide and potassium *t*-
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,[1415] 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.[1416] The solvent
used in the reaction must not be acidic enough to protonate either the enolate ion or the
base, which in most cases rules out water. The use of polar aprotic solvents, e.g., DMF or
Me$_2$SO, markedly increases the rate of alkylation[1417] but also increases the extent of alkyl-
ation at the oxygen rather than the carbon (p. 368). Phase transfer catalysis has also been
used.[1418]

Usually the reaction is carried out on a CH$_2$ group connected to two Z groups. In such
cases it is possible to alkylate twice, first removing the proton with a base, then alkylating
with RX, then removing the proton from ZCHRZ', and finally alkylating the resulting
enolate ion with the same or a different RX. 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,

[1409]For another method of converting epoxides to 1,3-diols, see Pelter; Bugden; Rosser *Tetrahedron Lett.* **1985**,
26, 5097.
[1410]See, for example Eis; Ganem *Tetrahedron Lett.* **1985**, *26*, 1153; Onistschenko; Buchholz; Stamm *Tetrahedron*
1987, *43*, 565.
[1411]For dicussions of reactions **0-94** and **0-95**, see House *Modern Synthetic Reactions*, 2nd ed.; W. A. Benjamin:
New York, 1972, pp. 492-570, 586-595; Carruthers *Some Modern Methods of Organic Synthesis*, 3rd ed.; Cambridge
University Press: Cambridge, 1986, pp. 1-26.
[1412]For reviews of the reactions of malononitrile CH$_2$(CN)$_2$, see Fatiadi *Synthesis* **1978**, 165-204, 241-282; Freeman
Chem. Rev. **1969**, *69*, 591-624.
[1413]For a review of compounds with two SO$_2$R groups on the same carbon (*gem*-disulfones), see Neplyuev; Bazarova;
Lozinskii *Russ. Chem. Rev.* **1986**, *55*, 883-900.
[1414]For lists of examples, with references, see Ref. 508, pp. 764-772*ff*, 894-896.
[1415]See, for example, Fedoryński; Wojciechowski; Matacz; Mąkosza *J. Org. Chem.* **1978**, *43*, 4682.
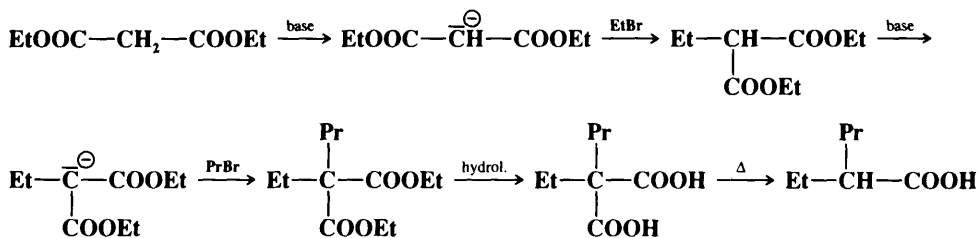[1416]Murphy; Hamrick; Hauser *Org. Synth.* V. 523.
[1417]Zaugg; Horrom; Borgwardt, Ref. 306; Zaugg; Dunnigan; Michaels; Swett; Wang; Sommers; DeNet *J. Org.
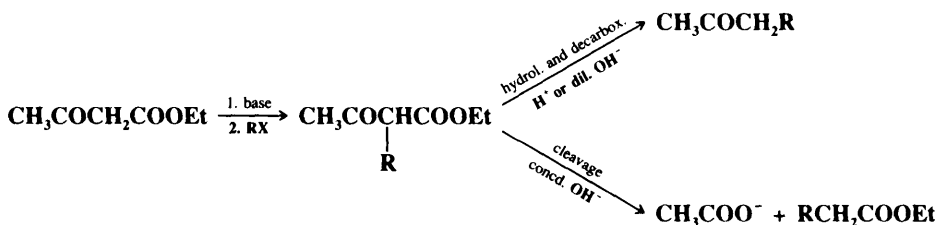Chem.* **1961**, *26*, 644; Johnstone; Tuli; Rose *J. Chem. Res. (S)* **1980**, 283.
[1418]See Sukhanov; Trappel'; Chetverikov; Yanovskaya *J. Org. Chem. USSR* **1985**, *21*, 2288; Tundo; Venturello;
Angeletti *J. Chem. Soc., Perkin Trans. 1* **1987**, 2159.

p. 466). 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 ion is a strong enough base), and dialkylation.
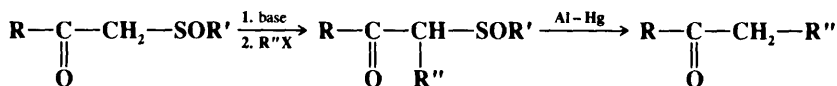
An important example of this reaction is the *malonic ester synthesis*, in which both Z groups are COOEt. The product can be hydrolyzed and decarboxylated (**2-40**) to give a carboxylic acid. An illustration is the preparation of 2-ethylpentanoic acid from malonic ester:

$$\text{EtOOC—CH}_2\text{—COOEt} \xrightarrow{\text{base}} \text{EtOOC—}\overset{\ominus}{\text{CH}}\text{—COOEt} \xrightarrow{\text{EtBr}} \underset{\underset{\text{COOEt}}{|}}{\text{Et—CH—COOEt}} \xrightarrow{\text{base}}$$

$$\underset{\underset{\text{COOEt}}{|}}{\text{Et—}\overset{\ominus}{\text{C}}\text{—COOEt}} \xrightarrow{\text{PrBr}} \underset{\underset{\text{COOEt}}{|}}{\overset{\overset{\text{Pr}}{|}}{\text{Et—C—COOEt}}} \xrightarrow{\text{hydrol.}} \underset{\underset{\text{COOH}}{|}}{\overset{\overset{\text{Pr}}{|}}{\text{Et—C—COOH}}} \xrightarrow{\Delta} \overset{\overset{\text{Pr}}{|}}{\text{Et—CH—COOH}}$$

It is obvious that many carboxylic acids of the formulas RCH$_2$COOH and RR'CHCOOH can be synthesized by this method (for some other ways of preparing such acids, see **0-96, 0-98**, and **0-99**). 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 (**2-40**) to give a ketone or cleaved with concentrated base (**2-43**) to give a carboxylic ester and a salt of acetic acid:

$$\text{CH}_3\text{COCH}_2\text{COOEt} \xrightarrow[\text{2. RX}]{\text{1. base}} \underset{\underset{\text{R}}{|}}{\text{CH}_3\text{COCHCOOEt}} \begin{array}{c} \xrightarrow[\text{H}^+\text{ or dil. OH}^-]{\text{hydrol. and decarbox.}} \text{CH}_3\text{COCH}_2\text{R} \\ \\ \xrightarrow[\text{concd. OH}^-]{\text{cleavage}} \text{CH}_3\text{COO}^- + \text{RCH}_2\text{COOEt} \end{array}$$

Another way of preparing ketones involves alkylation[1419] of β-keto sulfoxides[1420] or sulfones,[1421] e.g.,

$$\underset{\underset{\text{O}}{\|}}{\text{R—C—CH}_2\text{—SOR'}} \xrightarrow[\text{2. R''X}]{\text{1. base}} \underset{\underset{\text{O}}{\|}}{\underset{\underset{\text{R''}}{|}}{\text{R—C—CH—SOR'}}} \xrightarrow{\text{Al–Hg}} \underset{\underset{\text{O}}{\|}}{\text{R—C—CH}_2\text{—R''}}$$

since the product in this case is easily reduced to a ketone in high yields with aluminum amalgam or by electrolysis.[1422] The β-keto sulfoxides or sulfones are easily prepared (**0-109**). 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 the reaction is applied to N-acetylaminomalonic ester (EtOOC)$_2$CHNHCOCH$_3$. 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.

[1419]For a review of the synthetic uses of β-keto sulfoxides, sulfones, and sulfides, see Trost *Chem. Rev.* **1978**, *78*, 363-382. For a review of asymmetric synthesis with chiral sulfoxides, see Solladié *Synthesis* **1981**, 185-196.

[1420]Gassman; Richmond *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; Iwasawa *Tetrahedron Lett.* **1974**, 107.
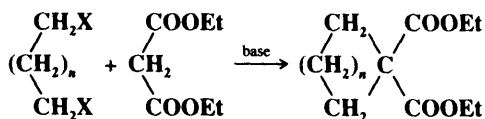
[1421]House; Larson *J. Org. Chem.* **1968**, *33*, 61; Kurth; O'Brien *J. Org. Chem.* **1985**, 3846.

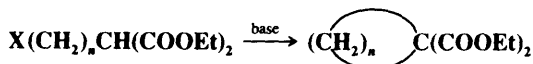[1422]Lamm; Samuelsson *Acta Chem. Scand.* **1969**, *23*, 691.

The reaction is not limited to Z—CH$_2$—Z' compounds. Other acidic CH hydrogens, which include, for example, the methyl hydrogens of α-aminopyridines, the methyl hydrogens of ynamines of the form CH$_3$C≡CNR$_2$[1423] (the product in this case can be hydrolyzed to an amide RCH$_2$CH$_2$CONR$_2$), the CH$_2$ hydrogens of cyclopentadiene and its derivatives (p. 46), hydrogens connected to a triple-bond carbon (**0-100**), and the hydrogen of HCN (**0-101**) can also be removed with a base and the resulting ion alkylated (see also **0-95** to **0-98**).

Alkylation takes place at the most acidic position of a reagent molecule; for example, acetoacetic ester (CH$_3$COCH$_2$COOEt) 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 moles 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 then takes place at the less acidic position (see p. 366). This technique has been used to alkylate many compounds in the second most acidic position.[1424]

When ω,ω'-dihalides are used, ring closures can be effected:[1425]

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.[1426]

$$X(CH_2)_nCH(COOEt)_2 \xrightarrow{\text{base}} (CH_2)_n \quad C(COOEt)_2$$

This method has been shown to be applicable to medium rings (10 to 14 members) without the use of high-dilution techniques.[1427]

The mechanism of these reactions is usually S$_N$2 with inversion taking place at a chiral RX, though there is strong evidence that an SET[1428] mechanism is involved in certain cases,[1429] especially where the nucleophile is an α-nitro carbanion[1430] and/or the substrate contains a nitro or cyano[1431] group. Tertiary alkyl groups can be introduced by an S$_N$1 mechanism if the ZCH$_2$Z' compound (not the enolate ion) is treated with a tertiary carbocation generated in situ from an alcohol or alkyl halide and BF$_3$ or AlCl$_3$,[1432] or with a tertiary alkyl perchlorate.[1433]

[1423]Corey; Cane *J. Org. Chem.* **1970**, *35*, 3405.

[1424]For a list of references, see Ref. 508, pp. 772-773. See also Ref. 426.

[1425]Zefirov; Kuznetsova; Kozhushkov; Surmina; Rashchupkina *J. Org. Chem. USSR* **1983**, *19*, 474.

[1426]For example, see Knipe; Stirling *J. Chem. Soc. B* **1968**, 67; Gosselck; Winkler *Tetrahedron Lett.* **1970**, 2437; Walborsky; Murari *Can. J. Chem.* **1984**, *62*, 2464. For a review of this method as applied to the synthesis of β-lactams, see Bose; Manhas; Chatterjee; Abdulla *Synth. Commun.* **1971**, *1*, 51-73. For a list of examples, see Ref. 508, pp. 81, 83-84.

[1427]Deslongchamps; Lamothe; Lin *Can. J. Chem.* **1984**, *62*, 2395, **1987**, *65*, 1298; Brillon; Deslongchamps *Can. J. Chem.* **1987**, *65*, 43, 56.

[1428]These SET mechanisms are often called S$_{RN}$1 mechanisms. See also Ref. 75.

[1429]Kerber; Urry; Kornblum *J. Am. Chem. Soc.* **1965**, *87*, 4520; Kornblum; Michel; Kerber *J. Am. Chem. Soc.* **1966**, *88*, 5660, 5662; Russell; Danen *J. Am. Chem. Soc.* **1966**, *88*, 5663; Russell; Ros *J. Am. Chem. Soc.* **1985**, *107*, 2506; Ashby; Argyropoulos *J. Org. Chem.* **1985**, *50*, 3274; Bordwell; Wilson *J. Am. Chem. Soc.* **1987**, *109*, 5470; Bordwell; Harrelson *J. Am. Chem. Soc.* **1989**, *111*, 1052.
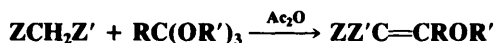
[1430]For a review of mechanisms with these nucleophiles, see Bowman *Chem. Soc. Rev.* **1988**, *17*, 283-316.

[1431]Kornblum; Fifolt *Tetrahedron* **1989**, *45*, 1311.
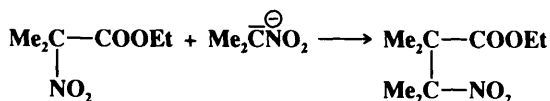
[1432]For example, see Boldt; Militzer *Tetrahedron Lett* **1966**, 3599; Crimmins; Hauser *J. Org. Chem.* **1967**, *32*, 2615; Boldt; Militzer; Thielecke; Schulz *Liebigs Ann. Chem.* **1968**, *718*, 101.

[1433]Boldt; Thielecke *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 1044 [*Angew. Chem. 78*, 1058]; Boldt; Ludwieg; Militzer *Chem. Ber.* **1970**, *103*, 1312.

Other leaving groups are sometimes used. Sulfates, sulfonates, and epoxides give the expected products. Acetals can behave as substrates, one OR group being replaced by $ZCHZ'$ in a reaction similar to **0-92**.[1434] Ortho esters behave similarly, but the product loses $R'OH$ to give an enol ether.[1435]

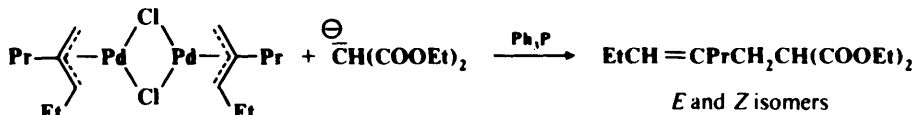$$ZCH_2Z' + RC(OR')_3 \xrightarrow{Ac_2O} ZZ'C{=}CROR'$$

The SO_2Ph group of allylic sulfones can be a leaving group if a palladium(0) complex is present.[1436] 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. 338). A nitro group can be displaced[1437] from α-nitro esters, ketones, nitriles, and α,α-dinitro compounds,[1438] and even from simple tertiary nitro compounds of the form R_3CNO_2[1439] or ArR_2CNO_2[1440] by salts of nitroalkanes, e.g.,

$$\underset{\underset{\text{NO}_2}{|}}{\text{Me}_2\text{C}}{-}\text{COOEt} + \text{Me}_2\overset{\ominus}{\text{C}}\text{NO}_2 \longrightarrow \underset{\underset{\text{Me}_2\text{C}{-}\text{NO}_2}{|}}{\text{Me}_2\text{C}}{-}\text{COOEt}$$

These reactions take place by SET mechanisms.[1441] However, with α-nitro sulfones it is the sulfone group that is displaced, rather than the nitro group.[1442] 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.[1443] Alkylation α to a nitro group can be achieved with the Katritzky pyrylium–pyridinium reagents.[1444] This reaction probably has a free-radical mechanism.[1445]

Palladium can be the leaving atom if the substrate is a π-allylpalladium complex (an η^3 complex). Ions of $ZCHZ'$ compounds react with such complexes[1446] in the presence of triphenylphosphine,[1447] e.g.,

E and Z isomers

[1434]Yufit; Krasnaya; Levchenko; Kucherov *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1967**, 123; Aleskerov; Yufit; Kucherov *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1972**, *21*, 2279.

[1435]For a review, see DeWolfe, Ref. 457, pp. 231-266.

[1436]Trost; Schmuff; Miller *J. Am. Chem. Soc.* **1980**, *102*, 5979.

[1437]For reviews, see Kornblum, in Patai, Ref. 346, pt. 1, pp. 361-393; Kornblum *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 734-745 [*Angew. Chem.* **87**, 797-808]. For reviews of aliphatic S$_N$ reactions in which NO$_2$ is a leaving group, see Tamura; Kamimura; Ono *Synthesis* **1991**, 423-434; Kornblum, in Feuer; Nielsen, Ref. 1198, pp. 46-85.

[1438]Kornblum; Kelly; Kestner *J. Org. Chem.* **1985**, *50*, 4720.

[1439]Kornblum; Erickson *J. Org. Chem.* **1981**, *46*, 1037.

[1440]Kornblum; Carlson; Widmer; Fifolt; Newton; Smith *J. Org. Chem.* **1978**, *43*, 1394.

[1441]For a review of the mechanism, see Beletskaya; Drozd *Russ. Chem. Rev.* **1979**, *48*, 431-448. See also Kornblum; Wade *J. Org. Chem.* **1987**, *52*, 5301; Ref. 1430; Ref. 1437.

[1442]Kornblum; Boyd; Ono *J. Am. Chem. Soc.* **1974**, *96*, 2580.

[1443]Trost; Merlic *J. Org. Chem.* **1990**, *55*, 1127.

[1444]Katritzky; de Ville; Patel *Tetrahedron* **1981**, *37*, Suppl. 1, 25; Katritzky; Kashmiri; Wittmann *Tetrahedron* **1984**, *40*, 1501.

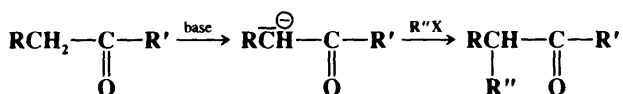[1445]Katritzky; Chen; Marson; Maia; Kashmiri *Tetrahedron* **1986**, *42*, 101.

[1446]For a review of the use of η^3-allylpalladium complexes to form C—C bonds, see Tsuji, in Hartley; Patai, Ref. 1403, vol. 3, 1985, pp. 163-199.

[1447]For reviews, see Trost *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1173-1192 [*Angew. Chem. 101*, 1199-1219], *Chemtracts: Org. Chem.* **1988**, *1*, 415-435, *Aldrichimica Acta* **1981**, *14*, 43-50, *Acc. Chem. Res.* **1980**, *13*, 385-393, *Tetrahedron* **1977**, *33*, 2615-2649; Tsuji; Minami *Acc. Chem. Res.* **1987**, *20*, 140-145; Tsuji *Tetrahedron* **1986**, *42*, 4361-4401, *Organic Synthesis with Palladium Compounds*; Springer: Berlin, 1981, pp. 45-51, 125-132; Heck *Palladium Reagents in Organic Synthesis*; Academic Press: New York, 1985, pp. 130-166; Hegedus, in Buncel; Durst *Comprehensive Carbanion Chemistry*, vol. 5, pt. B; Elsevier: New York, 1984, pp. 30-44.

When the Pd bears chiral ligands, these reactions can be enantioselective.[1448] π-Allylmolybdenum compounds behave similarly.[1449] Because palladium compounds are expensive, a catalytic synthesis, which uses much smaller amounts of the complex, was developed. That is, a substrate such as an allylic acetate, alcohol, amine, or nitro compound[1450] is treated with the nucleophile, and a catalytic amount of a palladium salt is added. The π-allylpalladium complex is generated in situ. Alkene–palladium complexes (introducing the nucleophile at a vinylic rather than an allylic carbon) can also be used.[1451]

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; **66**, 75; **68**, 56; **69**, 38. See also OS **68**, 210.

0-95 Alkylation of Ketones, Nitriles, and Carboxylic Esters
α-**Acylalkyl-de-halogenation**, etc.

$$\text{RCH}_2\text{—C—R}' \xrightarrow{\text{base}} \text{R}\overset{\ominus}{\text{CH}}\text{—C—R}' \xrightarrow{\text{R}''\text{X}} \text{RCH—C—R}'$$

Ketones,[1452] nitriles,[1453] and carboxylic esters[1454] can be alkylated in the α position in a reaction similar to **0-94**,[1411] but a stronger base must be employed, since only one activating group is present. The most common bases[1455] are Et_2NLi (LDA), (iso-Pr)$_2$NLi, t-BuOK, NaNH$_2$, and KH. The base lithium N-isopropyl-N-cyclohexylamide is particularly successful for carboxylic esters[1456] and nitriles.[1457] Solid KOH in Me$_2$SO has been used to methylate ketones, in high yields.[1458] Some of these bases are strong enough to convert the ketone, nitrile, or ester completely to its enolate ion conjugate base; others (especially t-BuOK) convert a significant fraction of the molecules. In the latter case, the aldol reaction (**6-39**) or Claisen condensation (**0-108**) 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. 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.[1459]

As in **0-94**, the alkyl halide may be primary or secondary. Tertiary halides give elimination. Even primary and secondary halides give predominant elimination if the enolate ion is a strong enough base (e.g., the enolate ion from Me$_3$CCOMe).[1460] Tertiary alkyl groups, as

[1448]For a review, see Consiglio; Waymouth *Chem. Rev.* **1989**, *89*, 257-276.
[1449]Trost; Lautens *Tetrahedron* **1987**, *43*, 4817; *J. Am. Chem. Soc.* **1987**, *109*, 1469.
[1450]Tamura; Kai; Kakihana; Hayashi; Tsuji; Nakamura; Oda *J. Org. Chem.* **1986**, *51*, 4375.
[1451]Hegedus; Williams; McGuire; Hayashi *J. Am. Chem. Soc.* **1980**, *102*, 4973; Hegedus, Ref. 1447, pp. 9-20.
[1452]For a review of the alkylation and acylation of ketones and aldehydes, see Caine, in Augustine *Carbon–Carbon Bond Formation*, vol. 1; Marcel Dekker: New York, 1979, pp. 85-352.
[1453]For a review, see Arseniyadis; Kyler; Watt *Org. React.* **1984**, *31*, 1-364. For a list of references, see Ref. 508, pp. 910-913.
[1454]For a review, see Petragnani; Yonashiro *Synthesis* **1982**, 521-578. For a list of references, see Ref. 508, pp. 873-890ff.
[1455]For a list of some bases, with references, see Ref. 508, pp. 738-740.
[1456]Rathke; Lindert *J. Am. Chem. Soc.* **1971**, *93*, 2319; Bos; Pabon *Recl. Trav. Chim. Pays-Bas* **1980**, *99*, 141. See also Cregge; Herrmann; Lee; Richman; Schlessinger *Tetrahedron Lett.* **1973**, 2425.
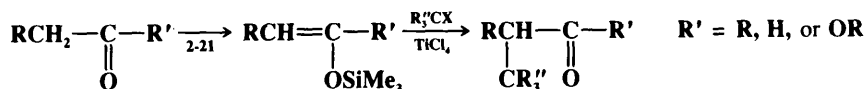[1457]Watt *Tetrahedron Lett.* **1974**, 707.
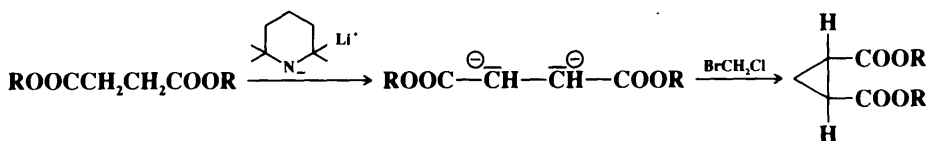[1458]Langhals; Langhals *Tetrahedron Lett.* **1990**, *31*, 859.
[1459]For reviews, see Makosza *Russ. Chem. Rev.* **1977**, *46*, 1151-1166; *Pure Appl. Chem.* **1975**, *43*, 439-462; Starks; Liotta, Ref. 404, pp. 170-217; Weber; Gokel *Phase Transfer Catalysis in Organic Synthesis*, Ref. 404, pp. 136-204.
[1460]Zook; Kelly; Posey *J. Org. Chem.* **1968**, *33*, 3477.

well as other groups that normally give S_N1 reactions, can be introduced if the reaction is performed on a silyl enol ether[1461] of a ketone, aldehyde, or ester with a Lewis acid catalyst.[1462]
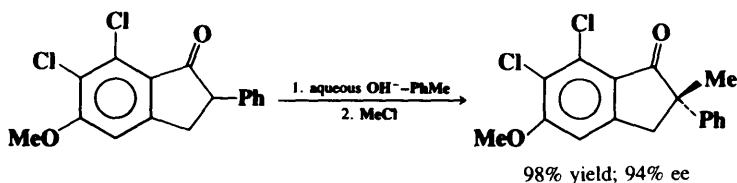
$$RCH_2\text{—}\underset{\underset{O}{\|}}{C}\text{—}R' \xrightarrow{2\text{-}21} RCH\text{=}\underset{\underset{OSiMe_3}{|}}{C}\text{—}R' \xrightarrow[TiCl_4]{R_3''CX} RCH\text{—}\underset{\underset{O}{\|}}{C}\text{—}R' \quad\quad R' = R, H, \text{ or } OR$$
$$\underset{CR_3''}{|}$$

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.[1463] However, ketones have been vinylated by treating their enol acetates with vinylic bromides in the presence of a Pd compound catalyst.[1464] Also as in **0-94**, this reaction can be used to close rings.[1465] In one example of this, rings have been closed by treating a diion of a dialkyl succinate with a 1,ω-dihalide or ditosylate,[1466], e.g.:

$$ROOCCH_2CH_2COOR \xrightarrow{\quad} ROOC\text{—}\overset{\ominus}{CH}\text{—}\overset{\ominus}{CH}\text{—}COOR \xrightarrow{BrCH_2Cl} $$

This was applied to the synthesis of 3-, 4-, 5-, and 6-membered rings. When the R groups were chiral (e.g., menthyl) the product was formed with greater than 90% enantiomeric excess.[1466]

An efficient enantioselective alkylation has been reported:[1467]

98% yield; 94% ee

The indanone substrate was methylated in 94% enantiomeric excess, by the use of a chiral catalyst, N-(p-(trifluoromethyl)benzyl)cinchoninium bromide, under phase transfer conditions.[1468] In another method enantioselective alkylation can be achieved by using a chiral base to form the enolate.[1469]

[1461]For a list of alkylations of silyl enol ethers, see Ref. 508, pp. 750-754.
[1462]Chan; Paterson; Pinsonnault *Tetrahedron Lett.* **1977**, 4183; Reetz; Maier *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 48 [*Angew. Chem. 90*, 50]; Reetz; Schwellnus; Hübner; Massa; Schmidt *Chem. Ber.* **1983**, *116*, 3708. Lion; Dubois *Bull. Soc. Chim. Fr.* **1982**, II-375; Reetz; Sauerwald *J. Organomet. Chem.* **1990**, *382*, 121; Reetz; Chatziiosifidis; Hübner; Heimbach *Org. Synth. VII*, 424. For a review, see Reetz *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 96-108 [*Angew. Chem. 94*, 97-109].
[1463]Millard; Rathke *J. Am. Chem. Soc.* **1977**, *99*, 4833.
[1464]Kosugi; Hagiwara; Migita *Chem. Lett.* **1983**, 839. For other methods, see Negishi; Akiyoshi *Chem. Lett.* **1987**, 1007; Chang; Rosenblum; Simms *Org. Synth. 66*, 95.
[1465]For example, see Etheredge *J. Org. Chem.* **1966**, *31*, 1990; Wilcox; Whitney *J. Org. Chem.* **1967**, *32*, 2933; Bird; Stirling *J. Chem. Soc. B* **1968**, 111; Stork; Boeckman *J. Am. Chem. Soc.* **1973**, *95*, 2016; Stork; Cohen *J. Am. Chem. Soc.* **1974**, *96*, 5270. In the last case, the substrate moiety is an epoxide function.
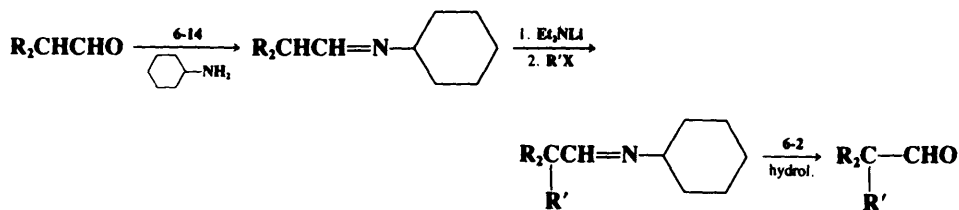[1466]Misumi; Iwanaga; Furuta; Yamamoto *J. Am. Chem. Soc.* **1985**, *107*, 3343; Furuta; Iwanaga; Yamamoto *Org. Synth. 67*, 76.
[1467]For reviews of stereoselective alkylation of enolates, see Nógrádi *Stereoselective Synthesis*; VCH: New York, 1986, pp. 236-245; Evans, in Morrison *Asymmetric Synthesis*, vol. 3; Academic Press: New York, 1984, pp. 1-110.
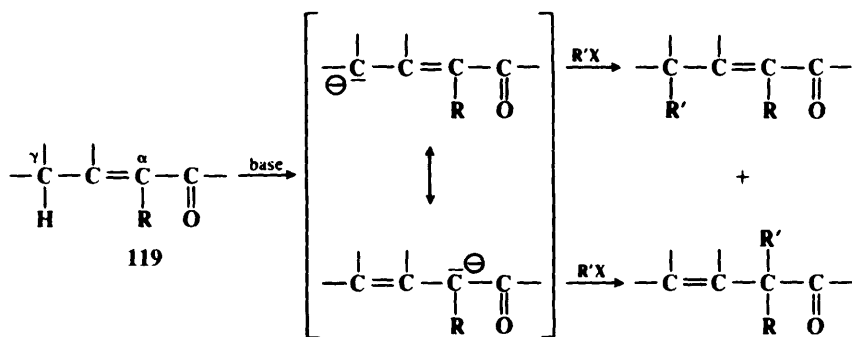[1468]Hughes; Dolling; Ryan; Schoenewaldt; Grabowski *J. Org. Chem.* **1987**, *52*, 4745.
[1469]For example, see Murakata; Nakajima; Koga *J. Chem. Soc., Chem. Commun.* **1990**, 1657. For a review, see Cox; Simpkins *Tetrahedron: Asymmetry* **1991**, *2*, 1-26, pp. 6-13.

The reaction can be applied to aldehydes, indirectly, by alkylating an imine derivative of the aldehyde.[1470] The derivative is easily prepared (**6-14**) and the product easily hydrolyzed to the aldehyde (**6-2**). 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. Direct alkylation of aldehydes is not generally possible because base treatment of aldehydes normally gives rapid aldol reaction (**6-39**), though 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,[1471] or in moderate yields, by the use of a phase transfer catalyst.[1472] Hydrazones and other compounds with C=N bonds can be similarly alkylated.[1470] The use of chiral amines or hydrazines[1473] (followed by hydrolysis **6-2** of the alkylated imine) can lead to chiral alkylated ketones in high optical yields[1474] (for an example, see p. 118).

In α,β-unsaturated ketones, nitriles, and esters (e.g., **119**), 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 *vinylology*, 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.

[1470]Cuvigny; Normant *Bull. Soc. Chim. Fr.* **1970,** 3976. For reviews, see Fraser, in Buncel; Durst, Ref. 1447, pp. 65-105; Whitesell; Whitesell *Synthesis* **1983,** 517-536. For a list of references, see Ref. 508, pp. 758-761. For a method in which the metalated imine is prepared from a nitrile, see Goering; Tseng *J. Org. Chem.* **1981,** *46,* 5250.
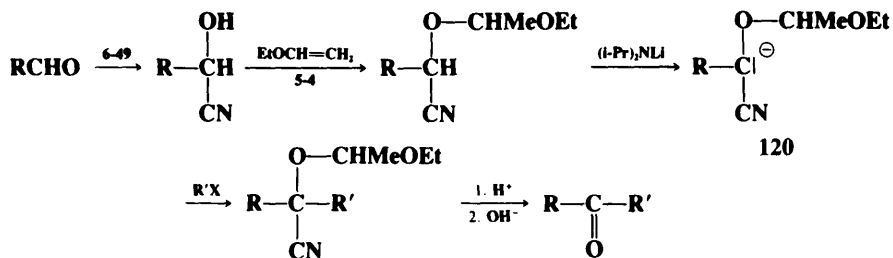
[1471]Groenewegen; Kallenberg; van der Gen *Tetrahedron Lett.* **1978,** 491; Artaud; Torossian; Viout *Tetrahedron* **1985,** *41,* 5031.

[1472]Dietl; Brannock *Tetrahedron Lett.* **1973,** 1273; Purohit; Subramanian *Chem. Ind. (London)* **1978,** 731; Buschmann; Zeeh *Liebigs Ann. Chem.* **1979,** 1585.

[1473]For a review of the alkylation of chiral hydrazones, see Enders, in Morrison, Ref. 1467, pp. 275-339.

[1474]Meyers; Williams; Erickson; White; Druelinger *J. Am. Chem. Soc.* **1981,** *103,* 3081; Meyers; Williams; White; Erickson *J. Am. Chem. Soc.* **1981,** *103,* 3088; Enders; Bockstiegel *Synthesis* **1989,** 493; Enders; Kipphardt; Fey *Org. Synth.* 65, 183.

α-Hydroxynitriles (cyanohydrins), protected by conversion to acetals with ethyl vinyl ether (**5-4**), can be easily alkylated with primary or secondary alkyl or allylic halides.[1475]

$$\text{RCHO} \xrightarrow{\text{6-49}} \underset{\underset{CN}{|}}{\overset{\overset{OH}{|}}{R-CH}} \xrightarrow[\text{5-4}]{\text{EtOCH=CH}_2} \underset{\underset{CN}{|}}{\overset{\overset{O-CHMeOEt}{|}}{R-CH}} \xrightarrow{(i\text{-Pr})_2\text{NLi}} \underset{\underset{CN}{|}}{\overset{\overset{O-CHMeOEt}{|}}{R-\overset{\ominus}{C}l}}$$

120

$$\xrightarrow{R'X} \underset{\underset{CN}{|}}{\overset{\overset{O-CHMeOEt}{|}}{R-\overset{|}{C}-R'}} \xrightarrow[2.\ OH^-]{1.\ H^+} \underset{\overset{\|}{O}}{R-\overset{|}{C}-R'}$$

R can be aryl or saturated or unsaturated alkyl. Since the cyanohydrins[1476] are easily formed from aldehydes (**6-49**) and the product is easily hydrolyzed to a ketone, this is a method for converting an aldehyde RCHO to a ketone RCOR'[1477] (for other methods, see **0-97, 0-105**, and **8-9**).[1478] 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.[1479] The German word *umpolung*[1480] is used to describe this kind of reversal (another example is found in **0-97**). Since the ion **120** serves as a substitute for the unavailable $R-\overset{\ominus}{\underset{}{C}}=O$ anion, it is often called a "masked" $R-\overset{\ominus}{\underset{}{C}}=O$ ion. This method fails for formaldehyde (R = H), but other masked formaldehydes have proved successful.[1481]

When the compound to be alkylated is a nonsymmetrical ketone, the question arises as to which side will be alkylated. If an α phenyl or α 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,[1482] the cation, and the solvent. In any case, di- and trisubstitution are frequent[1483] and it is often difficult to stop with the introduction of just one alkyl group.[1484]

[1475]Stork; Maldonado *J. Am. Chem. Soc.* **1971,** *93,* 5286; Stork; Depezay; D'Angelo *Tetrahedron Lett.* **1975,** 389. See also Rasmussen; Heilmann *Synthesis* **1978,** 219; Ahlbrecht; Raab; Vonderheid *Synthesis* **1979,** 127; Hünig; Marschner; Peters; von Schnering *Chem. Ber.* **1989,** *122,* 2131, and other papers in this series.
[1476]For a review of **120,** see Albright *Tetrahedron* **1983,** *39,* 3207-3233.
[1477]For similar methods, see Stetter; Schmitz; Schreckenberg *Chem. Ber.* **1977,** *110,* 1971; Hünig; *Chimia* **1982,** *36,* 1.
[1478]For a review of methods of synthesis of aldehydes, ketones, and carboxylic acids by coupling reactions, see Martin, *Synthesis* **1979,** 633-665.
[1479]For reviews of such reversals of carbonyl group reactivity, see Block *Reactions of Organosulfur Compounds*; Academic Press: New York, 1978, pp. 56-67; Gröbel; Seebach *Synthesis* **1977,** 357-402; Lever *Tetrahedron* **1976,** *32,* 1943-1971; Seebach; Kolb *Chem. Ind. (London)* **1974,** 687-692; Seebach *Angew. Chem. Int. Ed. Engl.* **1969,** *8,* 639-649 [*Angew. Chem. 81,* 690-700]. For a compilation of references to masked acyl and formyl anions, see Hase; Koskimies *Aldrichimica Acta* **1981,** *14,* 73-77. For tables of masked reagents, see Hase, Ref. 1480, pp. xiii-xiv, 7-18, 219-317. For lists of references, see Ref. 508, pp. 709-711.
[1480]For a monograph, see Hase *Umpoled Synthons*; Wiley: New York, 1987. For a review see Seebach *Angew. Chem. Int. Ed. Engl.* **1979,** *18,* 239-258 [*Angew. Chem. 91,* 259-278].
[1481]Possel; van Leusen *Tetrahedron Lett.* **1977,** 4229; Stork; Ozorio; Leong *Tetrahedron Lett.* **1978,** 5175.
[1482]Sterically hindered bases may greatly favor one enolate over the other. See, for example, Prieto; Suarez; Larson *Synth. Commun.* **1988,** *18,* 253; Gaudemar; Bellassoued *Tetrahedron Lett.* **1989,** *30,* 2779.
[1483]For a procedure for completely methylating the α positions of a ketone, see Lissel; Neumann; Schmidt *Liebigs Ann. Chem.* **1987,** 263.
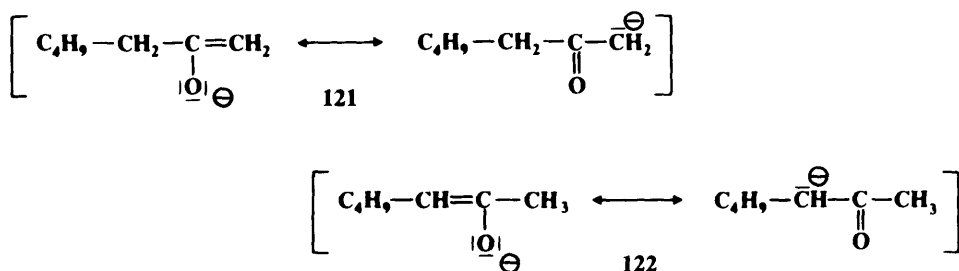[1484]For some methods of reducing dialkylation, see Hooz; Oudenes *Synth. Commun.* **1980,** *10,* 139; Morita; Suzuki; Noyori *J. Org. Chem.* **1989,** *54,* 1785.

Several methods have been developed for ensuring that alkylation takes place regioselectively on the *desired* side of a ketone.[1485] 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 (**0-109**); this generally blocks the less hindered side. The formyl group is easily removed by alkaline hydrolysis (**2-43**).

2. Introduce an activating group on one side; alkylation then takes place on that side (**0-94**); the activating group is then removed.

3. Prepare the desired one of the two possible enolate ions.[1486] The two ions, e.g., **121** and **122** for 2-heptanone,

$$\left[\ C_4H_9-CH_2-\underset{\underset{|\underline{O}|\ominus}{|}}{C}=CH_2 \quad \longleftrightarrow \quad C_4H_9-CH_2-\underset{\underset{O}{||}}{C}-\overset{\ominus}{CH_2} \ \right] \qquad \mathbf{121}$$

$$\left[\ C_4H_9-CH=\underset{\underset{|\underline{O}|\ominus}{|}}{C}-CH_3 \quad \longleftrightarrow \quad C_4H_9-\overset{\ominus}{CH}-\underset{\underset{O}{||}}{C}-CH_3 \ \right] \qquad \mathbf{122}$$

interconvert rapidly only in the presence of the parent ketone or any stronger acid.[1487] In the absence of such acids, it is possible to prepare either **121** or **122** and thus achieve selective alkylation on either side of the ketone.[1488] The desired enolate ion 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, e.g.,

$$C_4H_9-CH_2-\underset{\underset{OAc}{|}}{C}=CH_2 \ \xrightarrow{\text{MeLi}} \ \mathbf{121} \qquad\qquad C_4H_9-CH=\underset{\underset{OAc}{|}}{C}=CH_3 \ \xrightarrow{\text{MeLi}} \ \mathbf{122}$$

The enol acetates, in turn, can be prepared by treatment of the parent ketone with an appropriate reagent.[1488] 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.[1488] An alternate procedure involves conversion of a silyl enol ether[1489] (see **2-23**) or a dialkylboron enol ether[1490] (an enol borinate, see p. 481) to the corresponding enolate ion. If the less hindered enolate ion is desired (e.g., **121**), it can be prepared directly from the ketone by treatment with lithium diisopropylamide in THF or 1,2-dimethoxyethane at −78°C.[1491]

[1485]For a review, see House *Rec. Chem. Prog.* **1968**, *28*, 99-120. For a review with respect to cyclohexenones, see Podraza *Org. Prep. Proced. Int.* **1991**, *23*, 217-235.

[1486]For reviews, see d'Angelo *Tetrahedron* **1976**, *32*, 2979-2990; Stork *Pure Appl. Chem.* **1975**, *43*, 553-562.

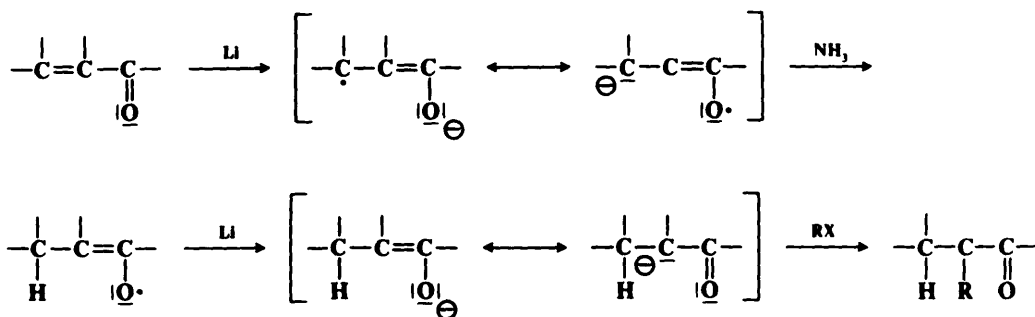[1487]House; Trost *J. Org. Chem.* **1965**, *30*, 1341.

[1488]House; Trost *J. Org. Chem.* **1965**, *30*, 2502; Whitlock; Overman *J. Org. Chem.* **1969**, *34*, 1962; House; Gall; Olmstead *J. Org. Chem.* **1971**, *36*, 2361. For an improved procedure, see Liotta; Caruso *Tetrahedron Lett.* **1985**, *26*, 1599.

[1489]Stork; Hudrlik *J. Am. Chem. Soc.* **1968**, *90*, 4462, 4464. For reviews, see Kuwajima; Nakamura *Acc. Chem. Res.* **1985**, *18*, 181-187; Fleming *Chimia* **1980**, *34*, 265-271; Rasmussen *Synthesis* **1977**, 91-110.

[1490]Pasto; Wojtkowski *J. Org. Chem.* **1971**, *36*, 1790.

[1491]House; Gall; Olmstead, Ref. 1488. See also Corey; Gross *Tetrahedron Lett.* **1984**, *25*, 495.

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 ion. When the alkyl halide is added,
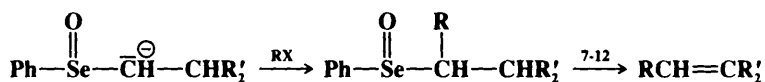

it must react with the enolate ion on the side where the double bond was.[1492] Of course, this method is not actually an alkylation of the ketone, but of the α,β-unsaturated ketone, though the product is the same as if the saturated ketone had been alkylated on the desired side.

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.[1493]

Among other methods for the preparation of alkylated ketones are: (1) the Stork enamine reaction (**2-19**), (2) the acetoacetic ester synthesis (**0-94**), (3) alkylation of β-keto sulfones or sulfoxides (**0-94**), (4) acylation of $CH_3SOCH_2^-$ followed by reductive cleavage (**0-109**), (5) treatment of α-halo ketones with lithium dialkylcopper reagents (**0-87**), and (6) treatment of α-halo ketones with trialkylboranes (**0-99**).

Sulfones[1494] and sulfonic esters can also be alkylated in the α position if strong enough bases are used.[1495] Alkylation at the α position of selenoxides allows the formation of alkenes, since selenoxides easily undergo elimination (**7-12**).[1496]

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; **65**, 32, 183; **66**, 87, 95; **67**, 76, 141; **69**, 55.

[1492]Stork; Rosen; Goldman; Coombs; Tsuji *J. Am. Chem. Soc.* **1965**, 87, 275. For a review, see Caine *Org. React.* **1976**, 23, 1-258. For similar approaches, see Coates; Sowerby *J. Am. Chem. Soc.* **1971**, 93, 1027; Näf; Decorzant *Helv. Chim. Acta* **1974**, 57, 1317; Wender; Eissenstat *J. Am. Chem. Soc.* **1978**, 100, 292.
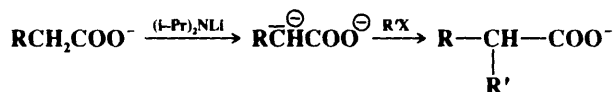
[1493]Yamashita; Matsuyama; Tanabe; Suemitsu *Bull. Chem. Soc. Jpn.* **1985**, 58, 407.

[1494]For a review, see Magnus *Tetrahedron* **1977**, 33, 2019-2045, pp. 2022-2025. For alkylation of sulfones containing the F_3CSO_2 group, see Hendrickson; Sternbach; Bair *Acc. Chem. Res.* **1977**, 10, 306-312.
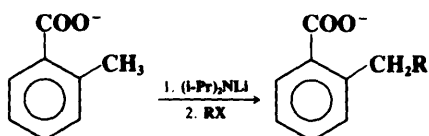
[1495]For examples, see Truce; Hollister; Lindy; Parr *J. Org. Chem.* **1968**, 33, 43; Julia; Arnould *Bull. Soc. Chim. Fr.* **1973**, 743, 746; Bird; Stirling, Ref. 1465.

[1496]Reich; Shah *J. Am. Chem. Soc.* **1975**, 97, 3250.

0-96 Alkylation of Carboxylic Acid Salts
α-**Carboxyalkyl-de-halogenation**

$$RCH_2COO^- \xrightarrow{(i\text{-}Pr)_2NLi} R\overset{\ominus}{C}HCOO^{\ominus} \xrightarrow{R'X} R-CH-COO^-$$
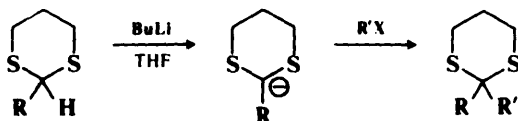$$\underset{R'}{|}$$

Carboxylic acids can be alkylated in the α position by conversion of their salts to dianions [which actually have the enolate structures $RCH=C(O^-)_2$[1497]] by treatment with a strong base such as lithium diisopropylamide.[1498] The use of Li^+ as the counterion is important, because it increases the solubility of the dianionic salt. The reaction has been applied[1499] to primary alkyl, allylic, and benzylic halides, and to carboxylic acids of the form RCH_2COOH and $RR''CHCOOH$.[1454] This method, which is an example of the alkylation of a dianion at its more nucleophilic position (see p. 368), is an alternative to the malonic ester synthesis (**0-94**) as a means of preparing carboxylic acids and has the advantage that acids of the form $RR'R''CCOOH$ can also be prepared. In a related reaction, methylated aromatic acids can be alkylated at the methyl group by a similar procedure.[1500]

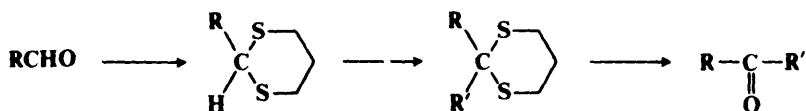OS **V**, 526; **VI**, 517; **VII**, 249. See also OS **VII**, 164.

0-97 Alkylation at a Position α to a Hetero Atom. Alkylation of 1,3-Dithianes
2-**(2-Alkyl-1,3-dithianyl)-de-halogenation**

1,3-Dithianes can be alkylated[1501] if a proton is first removed by treatment with butyllithium in THF.[1502] Since 1,3-dithianes can be prepared by treatment of an aldehyde or its acetal (see OS **VI**, 556) with 1,3-propanedithiol (**6-11**) and can be hydrolyzed (**0-6**), this is a method for the conversion of an aldehyde to a ketone[1503] (see also **0-95**, **0-105**, and **8-9**):

[1497]Mladenova; Blagoev; Gaudemar; Dardoize; Lallemand *Tetrahedron* **1981**, *37*, 2153.
[1498]Cregar *J. Am. Chem. Soc.* **1967**, *89*, 2500, **1970**, *92*, 1397; Pfeffer; Silbert; Chirinko *J. Org. Chem.* **1972**, *37*, 451.
[1499]For lists of reagents, with references, see Ref. 508, pp. 867-870ff.
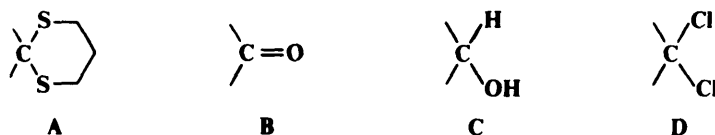[1500]Cregar *J. Am. Chem. Soc.* **1970**, *92*, 1396.
[1501]Corey; Seebach *Angew. Chem. Int. Ed. Engl.* **1965**, *4*, 1075, 1077 [*Angew. Chem. 77*, 1134, 1135]; Seebach; Corey *J. Org. Chem.* **1975**, *40*, 231. For reviews, see Page; van Niel; Prodger *Tetrahedron* **1989**, *45*, 7643-7677; Ager, in Hase, Ref. 1480, pp. 19-37; Seebach *Synthesis* **1969**, 17-36, especially pp. 24-27; Olsen; Currie, in Patai, Ref. 744, pt. 2, pp. 536-547.
[1502]For an improved method of removing the proton, see Lipshutz; Garcia *Tetrahedron Lett.* **1990**, *31*, 7261.
[1503]For examples of the use of this reaction, with references, see Ref. 508, pp. 721-725.

This is another example of umpolung (see **0-95**);[1478] 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.[1504] R' may be primary or secondary alkyl or benzylic. Iodides give the best results. The reaction has been used to close rings.[1505] A similar synthesis of aldehydes can be performed starting with ethyl ethylthiomethyl sulfoxide EtSOCH$_2$SEt.[1506]
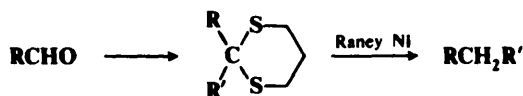
The group **A** may be regarded as a structural equivalent for the carbonyl group **B**, since introduction of **A** into a molecule is actually an indirect means of introducing **B**. It is

convenient to have a word for units within molecules; such a word is *synthon*, introduced by Corey,[1507] 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 **6-25** and **9-3**) and **D** (by reactions **0-2** and **6-24**).[1508]

Carbanions generated from 1,3-dithianes also react with epoxides[1509] to give the expected products.

Another useful application of this reaction stems from the fact that dithianes can be desulfurated with Raney nickel (**4-36**). Aldehydes can therefore be converted to chain-extended hydrocarbons:[1510]

Similar reactions have been carried out with other thioacetals, as well as with compounds containing three thioether groups on a carbon.[1511]

The carbanion derived from a 1,3-dithiane is stabilized by two thioether groups. If a strong enough base is used, it is possible to alkylate at a position adjacent to only one such group. For example, benzylic and allylic thioethers (RSCH$_2$Ar and RSCH$_2$CH=CH$_2$) and thioethers of the form RSCH$_3$ (R = tetrahydrofuranyl or 2-tetrahydropyranyl)[1512] have been successfully alkylated at the carbon adjacent to the sulfur atom.[1513] In the case of the RSCH$_3$

[1504]For a direct conversion of RX to RCHO, see **0-102**.

[1505]For example, see Seebach; Jones; Corey *J. Org. Chem.* **1968**, *33*, 300; Hylton; Boekelheide *J. Am. Chem. Soc.* **1968**, *90*, 6887; Ogura; Yamashita; Suzuki; Tsuchihashi *Tetrahedron Lett.* **1974**, 3653.

[1506]Richman; Herrmann; Schlessinger *Tetrahedron Lett.* **1973**, 3267. See also Ogura; Tsuchihashi *Tetrahedron Lett.* **1971**, 3151; Schill; Jones *Synthesis* **1974**, 117; Hori; Hayashi; Midorikawa *Synthesis* **1974**, 705.

[1507]Corey *Pure Appl. Chem.* **1967**, *14*, 19-37, pp. 20-23.

[1508]For a long list of synthons for RCO, with references, see Hase; Koskimies *Aldrichimica Acta* **1982**, *15*, 35-41.

[1509]For example, see Corey; Seebach, Ref. 1501; Jones; Grayshan *Chem. Commun.* **1970**, 141, 741.

[1510]For examples, see Hylton; Boekelheide, Ref. 1505; Jones; Grayshan, Ref. 1509.

[1511]For example, see Seebach *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 442 [*Angew. Chem. 79*, 468]; Olsson *Acta Chem. Scand.* **1968**, *22*, 2390; Mori; Hashimoto; Takenaka; Takigawa *Synthesis* **1975**, 720; Lissel *Liebigs Ann. Chem.* **1982**, 1589.

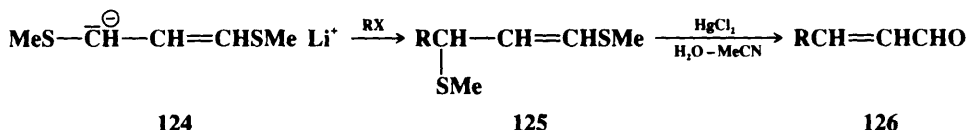[1512]Block; Aslam *J. Am. Chem. Soc.* **1985**, *107*, 6729.

[1513]Biellmann; Ducep *Tetrahedron Lett.* **1968**, 5629, **1969**, 3707, *Tetrahedron* **1971**, *27*, 5861. See also Narasaka; Hayashi; Mukaiyama *Chem. Lett.* **1972**, 259.

compounds, alkylation took place at the methyl group. Stabilization by one thioether group has also been used in a method for the homologization of primary halides.[1514] Thioanisole is treated with BuLi to give the corresponding anion[1515] which reacts with the halide to give

$$\text{PhSCH}_3 \xrightarrow{\text{BuLi}} \text{PhS}\overset{\ominus}{\text{CH}}_2 \text{ Li}^+ \xrightarrow{\text{RX}} \text{RCH}_2\text{SPh} \xrightarrow[\text{DMF}]{\text{CH}_3\text{I}} \left[\text{RCH}_2\overset{\oplus}{\underset{\underset{\text{CH}_3}{|}}{\text{SPh}}} \right] \xrightarrow[\text{DMF}]{\text{NaI}} \text{RCH}_2\text{I}$$
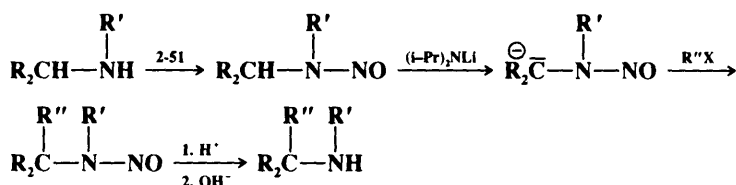
Thioanisole   **123**

the thioether **123. 123** is then refluxed with a mixture of methyl iodide and sodium iodide in dimethylformamide. By this sequence an alkyl halide RX is converted to its homolog RCH_2X by a pathway involving two laboratory steps (see also **0-92**).

Vinylic sulfides containing an α hydrogen can also be alkylated[1516] by alkyl halides or epoxides. In one application, the ion **124,** which can be prepared in three steps from epichlorohydrin, reacts with alkyl halides to give the bis(methylthio) compound **125,**[1517] which

$$\text{MeS}-\overset{\ominus}{\text{CH}}-\text{CH}{=}\text{CHSMe Li}^+ \xrightarrow{\text{RX}} \text{RCH}-\underset{\underset{\text{SMe}}{|}}{\text{CH}}{=}\text{CHSMe} \xrightarrow[\text{H}_2\text{O}-\text{MeCN}]{\text{HgCl}_2} \text{RCH}{=}\text{CHCHO}$$

          124   **125**   **126**

is easily hydrolyzed[1518] with $HgCl_2$ in aqueous MeCN. This is a method for converting an alkyl halide RX to an α,β-unsaturated aldehyde (**126**) using **124,** which is the synthetic equivalent of the unknown $\text{H}\overset{\ominus}{\text{C}}{=}\text{CH}-\text{CHO}$ ion.[1519] Even simple alkyl aryl sulfides RCH_2SAr and $RR'CHSAr$ have been alkylated α to the sulfur.[1520]

Alkylation can also be carried out, in certain compounds, at positions α to other hetero atoms,[1521] for example, at a position α to the nitrogen of tertiary amines.[1522] 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. It has been accomplished, however, by replacing the NH hydrogens with other (removable) groups.[1523] In one example, a secondary amine is converted to its N-nitroso derivative (**2-51**).[1524] The N-nitroso product is

$$\text{R}_2\text{CH}-\underset{\underset{\text{R}'}{|}}{\text{NH}} \xrightarrow{\text{2-51}} \text{R}_2\text{CH}-\underset{\underset{\text{R}'}{|}}{\text{N}}-\text{NO} \xrightarrow{(\text{i-Pr})_2\text{NLi}} \overset{\ominus}{\text{R}_2\text{C}}-\underset{\underset{\text{R}'}{|}}{\text{N}}-\text{NO} \xrightarrow{\text{R}''\text{X}}$$

$$\text{R}_2\text{C}-\underset{\underset{\text{R}'}{|}}{\overset{\overset{\text{R}''}{|}}{\text{N}}}-\text{NO} \xrightarrow[\text{2. OH}^-]{\text{1. H}^+} \text{R}_2\text{C}-\overset{\overset{\text{R}''}{|}}{\underset{\underset{\text{R}'}{|}}{\text{NH}}}$$

[1514]Corey; Jautelat *Tetrahedron Lett.* **1968**, 5787.

[1515]Corey; Seebach *J. Org. Chem.* **1966**, *31*, 4097.

[1516]Oshima; Shimoji; Takahashi; Yamamoto; Nozaki *J. Am. Chem. Soc.* **1973**, *95*, 2694.

[1517]Corey; Erickson; Noyori *J. Am. Chem. Soc.* **1971**, *93*, 1724.

[1518]Corey; Shulman *J. Org. Chem.* **1970**, *35*, 777. See, however, Mura; Majetich; Grieco; Cohen *Tetrahedron Lett.* **1975**, 4437.

[1519]For references to other synthetic equivalents of this ion, see Funk; Bolton *J. Am. Chem. Soc.* **1988**, *110*, 1290.

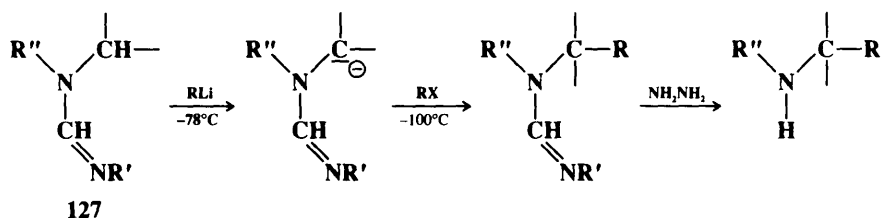[1520]Dolak; Bryson *Tetrahedron Lett.* **1977**, 1961.

[1521]For a review of anions α to a selenium atom on small rings, see Krief *Top. Curr. Chem.* **1987**, *135*, 1-75. For alkylation α to boron, see Pelter; Smith; Brown *Borane Reagents*; Academic Press: New York, 1988, pp. 336-341.

[1522]Lepley; Khan *J. Org. Chem.* **1966**, *31*, 2061, 2064, *Chem. Commun.* **1967**, 1198; Lepley; Giumanini *J. Org. Chem.* **1966**, *31*, 2055; Ahlbrecht; Dollinger *Tetrahedron Lett.* **1984**, *25*, 1353.
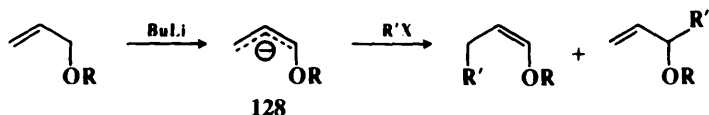
[1523]For a review, see Beak; Zajdel; Reitz *Chem. Rev.* **1984**, *84*, 471-523.

[1524]Seebach; Enders; Renger *Chem. Ber.* **1977**, *110*, 1852; Renger; Kalinowski; Seebach *Chem. Ber.* **1977**, *110*, 1866. For a review, see Seebach; Enders *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 15-32 [*Angew. Chem. 87*, 1-17].
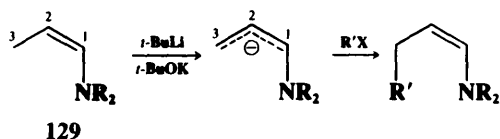
easily hydrolyzed to the product amine (9-53).[1525] Alkylation of secondary and primary amines has also been accomplished with more than ten other protecting groups, involving conversion of amines to amides, carbamates,[1526] formamidines,[1527] and phosphoramides.[1523] In the case of formamidines (127) use of a chiral R' leads to a chiral amine, in high enantiomeric excess, even when R is not chiral.[1528]

127

A proton can be removed from an allylic ether by treatment with an alkyllithium at about − 70°C (at higher temperatures the Wittig rearrangement—**8-23**—takes place) to give the ion **128**, which reacts with alkyl halides to give the two products shown.[1529] Similar

128

reactions[1530] have been reported for allylic[1531] and vinylic tertiary amines. In the latter case, enamines **129**, treated with a strong base, are converted to anions that are then alkylated, generally at C-3.[1532] (For direct alkylation of enamines at C-2, see **2-19**.)

129

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.[1533] Since esters can be hydrolyzed to alcohols, this constitutes an indirect alkylation of primary alcohols. Methanol has also been alkylated by converting it to $^\ominus CH_2 O^\ominus$.[1534]

OS **VI**, 316, 364, 542, 704, 869; **67**, 60.

[1525]Fridman; Mukhametshin; Novikov *Russ. Chem. Rev.* **1971**, *40*, 34-50, pp. 41-42.

[1526]For the use of *t*-butyl carbamates, see Beak; Lee *Tetrahedron Lett.* **1989**, *30*, 1197.

[1527]For a review, see Meyers *Aldrichimica Acta* **1985**, *18*, 59-68.

[1528]Meyers; Fuentes; Kubota *Tetrahedron* **1984**, *40*, 1361; Gawley; Hart; Goicoechea-Pappas; Smith *J. Org. Chem.* **1986**, *51*, 3076; Meyers; Dickman *J. Am. Chem. Soc.* **1987**, *109*, 1263; Gawley *J. Am. Chem. Soc.* **1987**, *109*, 1265; Meyers; Miller; White *J. Am. Chem. Soc.* **1988**, *110*, 4778; Gonzalez; Meyers *Tetrahedron Lett.* **1989**, *30*, 43, 47.

[1529]Evans; Andrews; Buckwalter *J. Am. Chem. Soc.* **1974**, *96*, 5560; Still; Macdonald *J. Am. Chem. Soc.* **1974**, *96*, 5561; Ref. 1519. For a similar reaction with triple-bond compounds, see Hommes; Verkruijsse; Brandsma *Recl. Trav. Chim. Pays-Bas* **1980**, *99*, 113, and references cited therein.
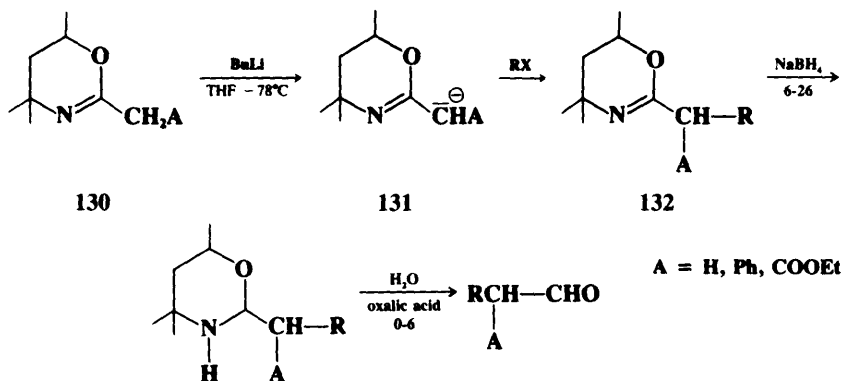
[1530]For a review of allylic and benzylic carbanions substituted by hetero atoms, see Biellmann; Ducep *Org. React.* **1982**, *27*, 1-344.

[1531]Martin; DuPriest *Tetrahedron Lett.* **1977**, 3925 and references cited therein.

[1532]For a review, see Ahlbrecht *Chimia* **1977**, *31*, 391-403.

[1533]Beak; McKinnie *J. Am. Chem. Soc.* **1977**, *99*, 5213; Beak; Carter *J. Org. Chem.* **1981**, *46*, 2363.
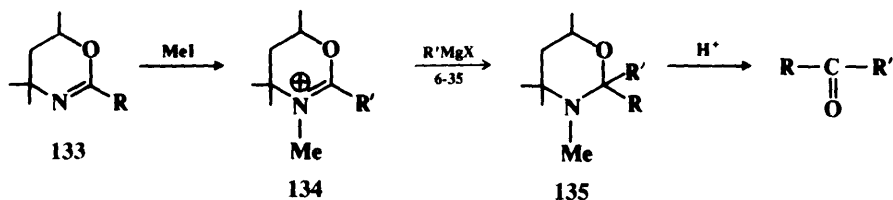
[1534]Seebach; Meyer *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 438 [*Angew. Chem. 88*, 484].

0-98   Alkylation of Dihydro-1,3-Oxazine. The Meyers Synthesis of Aldehydes, Ketones, and Carboxylic Acids

$$\text{BuLi} \xrightarrow{\text{THF} -78°C} \quad \text{RX} \quad \xrightarrow{} \quad \text{NaBH}_4 \xrightarrow{6\text{-}26}$$

130   **131**   **132**

A = H, Ph, COOEt

$$\xrightarrow[\text{oxalic acid } 0\text{-}6]{\text{H}_2\text{O}} \quad \text{RCH—CHO}$$

A synthesis of aldehydes[1535] developed by Meyers[1536] begins with the commercially available dihydro-1,3-oxazine derivatives **130** (A = H, Ph, or COOEt).[1537] Though the ions (**131**) prepared from **130** are ambident, they are regioselectively alkylated at carbon by a wide variety of alkyl bromides and iodides. R can be primary or secondary alkyl, allylic, or benzylic and can carry another halogen or a CN group.[1538] The alkylated oxazine **132** is then reduced and hydrolyzed to give an aldehyde containing two more carbons than the starting RX. This method thus complements **0-97** 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 **131** also reacts with epoxides, to form γ-hydroxy aldehydes after reduction and hydrolysis,[1539] and with aldehydes and ketones (**6-41**). Similar aldehyde synthesis has also been carried out with thiazoles[1540] and thiazolines[1541] (five-membered rings containing N and S in the 1 and 3 positions).

The reaction has been extended to the preparation of ketones:[1542] treatment of a dihydro-1,3-oxazine (**133**) with methyl iodide forms the iminium salt **134** (**0-43**) which, when treated with a Grignard reagent or organolithium compound (**6-35**), produces **135** which can be

$$\xrightarrow{\text{MeI}} \quad \xrightarrow[6\text{-}35]{R'\text{MgX}} \quad \xrightarrow{\text{H}^+} \quad R-\overset{\text{O}}{\underset{\|}{C}}-R'$$

133   **134**   **135**

[1535]For examples of the preparation of aldehydes and ketones by the reactions in this section, see Ref. 508, pp. 729-732.

[1536]Meyers; Nabeya; Adickes; Politzer; Malone; Kovelesky; Nolen; Portnoy *J. Org. Chem.* **1973**, *38*, 36.

[1537]For reviews of the preparation and reactions of **130** see Schmidt *Synthesis* **1972**, 333-350; Collington *Chem. Ind. (London)* **1973**, 987-991.

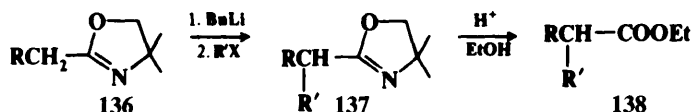[1538]Meyers; Malone; Adickes *Tetrahedron Lett.* **1970**, 3715.

[1539]Adickes; Politzer; Meyers *J. Am. Chem. Soc.* **1969**, *91*, 2155.

[1540]Altman; Richheimer *Tetrahedron Lett.* **1971**, 4709.

[1541]Meyers; Durandetta *J. Org. Chem.* **1975**, *40*, 2021.

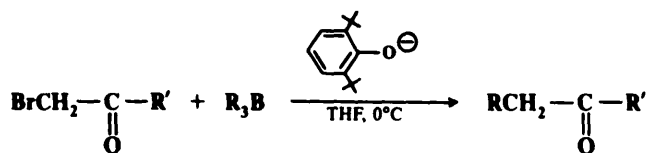[1542]Meyers; Smith *J. Am. Chem. Soc.* **1970**, 92, 1084, *J. Org. Chem.* **1972**, *37*, 4289.

hydrolyzed to a ketone. R can be alkyl, cycloalkyl, aryl, benzylic, etc., and R' can be alkyl, aryl, benzylic, or allylic. **130, 132,** and **133** themselves do not react with Grignard reagents. In another procedure, 2-oxazolines[1543] (**136**) can be alkylated to give **137,**[1544] which are easily

$$RCH_2 \xrightarrow[\substack{\text{1. BuLi} \\ \text{2. R'X}}] \quad RCH \xrightarrow[\substack{R' \ 137}] \quad \xrightarrow[\text{EtOH}]{H^+} \quad RCH-COOEt \atop R' \quad 138$$

converted directly to the esters **138** by heating in 5 to 7% ethanolic sulfuric acid. **136** and **137** are thus synthons for carboxylic acids; this is another indirect method for the α alkylation of a carboxylic acid,[1545] representing an alternative to the malonic ester synthesis (**0-94**) and to **0-96** and **0-99.** The method can be adapted to the preparation of optically active carboxylic acids by the use of a chiral reagent.[1546] Note that, unlike **130, 136** can be alkylated even if R is alkyl. However, the C=N bond of **136** and **137** cannot be effectively reduced, so that aldehyde synthesis is not feasible here.[1547]

OS **VI**, 905.

0-99   Alkylation with Trialkylboranes
Alkyl-de-halogenation

$$BrCH_2-\underset{\underset{O}{\|}}{C}-R' \ + \ R_3B \xrightarrow[\text{THF, 0°C}]{} \quad RCH_2-\underset{\underset{O}{\|}}{C}-R'$$

Trialkylboranes react rapidly and in high yields with α-halo ketones,[1548] α-halo esters,[1549] α-halo nitriles,[1550] and α-halo sulfonyl derivatives (sulfones, sulfonic esters, sulfonamides)[1551] in the presence of a base to give, respectively, alkylated ketones, esters, nitriles, and sulfonyl derivatives.[1552] Potassium *t*-butoxide is often a suitable base, but potassium 2,6-di-*t*-butyl-phenoxide at 0°C in THF gives better results in most cases, possibly because the large bulk of the two *t*-butyl groups prevents the base from coordinating with the R_3B.[1553] The tri-alkylboranes are prepared by treatment of 3 moles of an alkene with 1 mole of BH_3

[1543]For a review, see Meyers; Mihelich *Angew. Chem. Int. Ed. Engl.* **1976,** *15,* 270-281 [*Angew. Chem. 88,* 321-332].

[1544]Meyers; Temple; Nolen; Mihelich *J. Org. Chem.* **1974,** *39,* 2778; Meyers; Mihelich; Nolen *J. Org. Chem.* **1974,** *39,* 2783; Meyers; Mihelich; Kamata *J. Chem. Soc., Chem. Commun.* **1974,** 768.

[1545]For reviews, see Meyers, *Pure Appl. Chem.* **1979,** *51,* 1255-1268, *Acc. Chem. Res.* **1978,** *11,* 375-381. See also Hoobler; Bergbreiter; Newcomb *J. Am. Chem. Soc.* **1978,** *100,* 8182; Meyers; Snyder; Ackerman *J. Am. Chem. Soc.* **1978,** *100,* 8186.

[1546]For a review of asymmetric synthesis via chiral oxazolines, see Lutomski; Meyers, in Morrison, Ref. 1467, pp. 213-274.

[1547]Meyers; Temple *J. Am. Chem. Soc.* **1970,** *92,* 6644, 6646.

[1548]Brown; Rogić; Rathke *J. Am. Chem. Soc.* **1968,** *90,* 6218.

[1549]Brown; Rogić; Rathke; Kabalka *J. Am. Chem. Soc.* **1968,** *90,* 818.

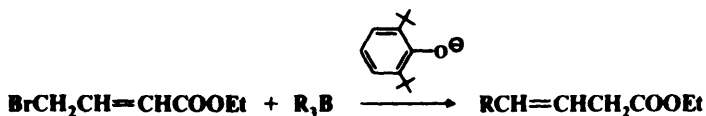[1550]Brown; Nambu; Rogić *J. Am. Chem. Soc.* **1969,** *91,* 6854.

[1551]Truce; Mura; Smith; Young *J. Org. Chem.* **1974,** *39,* 1449.

[1552]For reviews, see Negishi; Idacavage *Org. React.* **1985,** *33,* 1-246, pp. 42-43, 143-150; Weill-Raynal *Synthesis* **1976,** 633-651; Brown; Rogić *Organomet. Chem. Synth.* **1972,** *1,* 305-327; Rogić *Intra-Sci. Chem. Rep.* **1973,** *7*(2), 155-167; Brown *Boranes in Organic Chemistry*; Cornell University Press: Ithaca, NY, 1972, pp. 372-391, 404-409; Cragg, Ref. 1167, pp. 275-278, 283-287.

[1553]Brown; Nambu; Rogić *J. Am. Chem. Soc.* **1969,** *91,* 6852, 6854, 6855.

(5-12).[1554] With appropriate boranes, the R group transferred to α-halo ketones, nitriles, and esters can be vinylic,[1555] or (for α-halo ketones and esters) aryl.[1556]
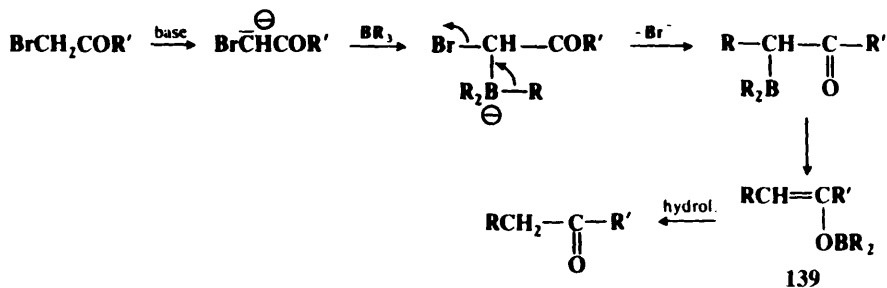
The reaction can be extended to α,α-dihalo esters[1557] and α,α-dihalo nitriles.[1558] It is possible to replace just one halogen or both. In the latter case the two alkyl groups can be the same or different. When dialkylation is applied to dihalo nitriles, the two alkyl groups can be primary or secondary, but with dihalo esters, dialkylation is limited to primary R. Another extension is the reaction of boranes with γ-halo-α,β-unsaturated esters.[1559] Alkylation takes place in the γ position, but the double bond migrates, e.g.,

$$BrCH_2CH=CHCOOEt + R_3B \longrightarrow RCH=CHCH_2COOEt$$

In this case, however, double-bond 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[1560] (see also **5-12**, **5-19**, **8-24** to **8-28**, etc.). 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 **0-95**) or a carboxylic acid (see **0-96**), and provides an additional alternative to the malonic ester and acetoacetic ester syntheses (**0-94**).

Although superficially this reaction resembles **0-87** it is likely that the mechanism is quite different, involving migration of an R group from boron to carbon (see also **8-24** to **8-28**). The mechanism is not known with certainty,[1561] but it may be tentatively shown as (illustrated for an α-halo ketone):

139

[1554]For an improved procedure, with B-R-9-BBN (see p. 785), see Brown; Rogić *J. Am. Chem. Soc.* **1969**, *91*, 2146; Brown; Rogić; Nambu; Rathke *J. Am. Chem. Soc.* **1969**, *91*, 2147; Katz; Dubois; Lion *Bull. Soc. Chim. Fr.* **1977**, 683.

[1555]Brown; Bhat; Campbell *J. Org. Chem.* **1986**, *51*, 3398.

[1556]Brown; Rogić *J. Am. Chem. Soc.* **1969**, *91*, 4304.

[1557]Brown; Rogić; Rathke; Kabalka *J. Am. Chem. Soc.* **1968**, *90*, 1911.

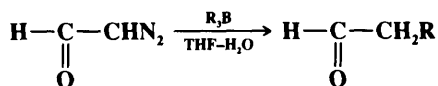[1558]Nambu; Brown *J. Am. Chem. Soc.* **1970**, *92*, 5790.

[1559]Brown; Nambu *J. Am. Chem. Soc.* **1970**, *92*, 1761.

[1560]Brown *Organic Syntheses via Boranes*; Wiley: New York, 1975, *Hydroboration*; W.A. Benjamin: New York, 1962, *Boranes in Organic Chemistry*, Ref. 1552; Pelter; Smith; Brown, Ref. 1521.

[1561]See Prager; Reece *Aust. J. Chem.* **1975**, *28*, 1775.

The first step is removal of the acidic proton by the base to give an enolate ion which combines with the borane (Lewis acid-base reaction). An R group then migrates, displacing the halogen leaving group.[1562] Another migration follows, this time of BR_2 from carbon to oxygen to give the enol borinate **139**[1563] which is hydrolyzed. Configuration at R is retained.[1564]

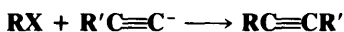The reaction has also been applied to compounds with other leaving groups. Diazo ketones, diazo esters, diazo nitriles, and diazo aldehydes[1565] react with trialkylboranes in a similar manner, e.g.,

$$H-\underset{\underset{O}{\|}}{C}-CHN_2 \xrightarrow[\text{THF-H}_2\text{O}]{\text{R}_3\text{B}} H-\underset{\underset{O}{\|}}{C}-CH_2R$$

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[1566] is especially notable, since successful reactions cannot be obtained with α-halo aldehydes.[1567]

OS **VI**, 919.

0-100 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.[1568] Only primary halides unbranched in the β position give good yields, though allylic halides can be used if CuI is present.[1569] If acetylene is the reagent, two different groups can be successively attached. Sulfates, sulfonates, and epoxides[1570] 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 **2-21**) are also frequently used, though 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.[1571] If 2 moles of a very strong base are used, alkylation can be effected at a carbon α to a terminal triple bond: $RCH_2C{\equiv}CH +$ $2BuLi \rightarrow R\overset{\ominus}{C}HC{\equiv}\bar{C}^{\ominus} + R'Br \rightarrow RR'CHC{\equiv}C^{\ominus}$.[1572] For another method of alkylating at an alkynyl carbon, see **8-28**.

OS **IV**, 117; **VI**, 273, 564, 595; **67**, 193. Also see OS **IV**, 801; **VI**, 925.

[1562]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; Zolopa; Halterman *J. Am. Chem. Soc.* **1979**, *101*, 248. See also Midland; Preston *J. Org. Chem.* **1980**, *45*, 747.
[1563]Pasto; Wojtkowski *Tetrahedron Lett.* **1970**, 215, Ref. 1490.
[1564]Brown; Rogić; Rathke; Kabalka *J. Am. Chem. Soc.* **1969**, *91*, 2150.
[1565]Hooz; Linke *J. Am. Chem. Soc.* **1968**, *90*, 5936, 6891; Hooz; Gunn; Kono *Can. J. Chem.* **1971**, *49*, 2371; Mikhailov; Gurskii *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1973**, *22*, 2588.
[1566]Hooz; Morrison *Can J. Chem.* **1970**, *48*, 868.
[1567]For an improved procedure, see Hooz; Bridson; Calzada; Brown; Midland; Levy *J. Org. Chem.* **1973**, *38*, 2574.
[1568]For reviews, see Ben-Efraim, in Patai *The Chemistry of the Carbon–Carbon Triple Bond*; Wiley: New York, 1978, pp. 790-800; Ziegenbein, in Vieh *Acetylenes*; Marcel Dekker: New York, 1969, pp. 185-206, 241-244. For a discussion of the best ways of preparing various types of alkyne, see Bernadou; Mesnard; Miginiac *J. Chem. Res. (S)* **1978**, 106, **1979**, 190.
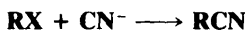[1569]Bourgain; Normant *Bull. Soc. Chim. Fr.* **1973**, 1777; Jeffery *Tetrahedron Lett.* **1989**, *30*, 2225.
[1570]For example, see Fried; Lin; Ford *Tetrahedron Lett.* **1969**, 1379; Krause; Seebach *Chem. Ber.* **1988**, *121*, 1315.
[1571]Smith; Beumel *Synthesis* **1974**, 441.
[1572]Bhanu; Scheinmann *J. Chem. Soc., Perkin Trans.1* **1979**, 1218; Quillinan; Scheinmann *Org. Synth. VI*, 595.

0-101 Preparation of Nitriles
Cyano-de-halogenation

$$RX + CN^- \longrightarrow RCN$$

The reaction between cyanide ion (isoelectronic with $HC\equiv\overline{C}^\ominus$ and of similar geometry) and alkyl halides is a convenient method for the preparation of nitriles.[1573] 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. Though a number of solvents have been used, the high yields and short reaction times observed with dimethyl sulfoxide make it a very good solvent for this reaction.[1574] Other ways to obtain high yields under mild conditions are to use a phase transfer catalyst[1575] or ultrasound.[1576] This is an important way of increasing the length of a carbon chain by one carbon, since nitriles are easily hydrolyzed to carboxylic acids (**6-5**).

The cyanide ion is an ambident nucleophile and isocyanides may be side products. If the preparation of isocyanides is desired, they can be made the main products by the use of silver or copper(I) cyanide[1577] (p. 368). Vinylic bromides can be converted to vinylic cyanides with CuCN,[1578] with KCN, a crown ether, and a Pd(0) complex,[1579] with KCN and a Ni(0) catalyst,[1580] or with $K_4Ni_2(CN)_6$.[1581] Tertiary halides can be converted to the corresponding nitriles by treatment with trimethylsilyl cyanide in the presence of catalytic amounts of $SnCl_4$: $R_3CCl + Me_3SiCN \rightarrow R_3CCN$.[1582]

The cyanide nucleophile also reacts with compounds containing other leaving groups. Esters of sulfuric and sulfonic acids behave like halides. Vinylic triflates give vinylic cyanides when treated with LiCN, a crown ether, and a palladium catalyst.[1583] Epoxides give β-hydroxy nitriles. Primary, secondary, and tertiary alcohols are converted to nitriles in good yields by treatment with NaCN, Me_3SiCl, and a catalytic amount of NaI inDMF–MeCN.[1584] One alkoxy group of acetals is replaced by CN [$R_2C(OR')_2 \rightarrow R_2C(OR')CN$] with Me_3SiCN and a catalyst[1585] or with t-BuNC and $TiCl_4$.[1586] NaCN in HMPA selectively cleaves methyl esters in the presence of ethyl esters: $RCOOMe + CN^- \rightarrow MeCN + RCOO^-$.[1587]

OS **I**, 46, 107, 156, 181, 254, 256, 536; **II**, 292, 376; **III**, 174, 372, 557; **IV**, 438, 496, 576; **V**, 578, 614.

[1573]For reviews, see, in Patai; Rappoport, Ref. 353, the articles by Fatiadi, pt. 2, pp. 1057-1303, and Friedrich, pt. 2, pp. 1343-1390; Friedrich; Wallenfels, in Rappoport *The Chemistry of the Cyano Group*; Wiley: New York, 1970, pp. 77-86.

[1574]Smiley; Arnold *J. Org. Chem.* **1960**, *25*, 257; Friedman; Shechter *J. Org. Chem.* **1960**, *25*, 877.

[1575]For reviews, see Starks; Liotta, Ref. 404, pp. 94-112; Weber; Gokel *Phase Transfer Catalysis in Organic Synthesis*, Ref. 404, pp. 96-108. See also Bram; Loupy; Pedoussaut *Tetrahedron Lett.* **1986**, *27*, 4171, *Bull. Soc. Chim. Fr.* **1986**, 124.

[1576]Ando; Kawate; Ichihara; Hanafusa *Chem. Lett.* **1984**, 725.

[1577]For an example, see Jackson; McKusick *Org. Synth. IV*, 438.

[1578]For example, see Koelsch *J. Am. Chem. Soc.* **1936**, *58*, 1328; Newman; Boden *J. Org. Chem.* **1961**, *26*, 2525; Lapouyade; Daney; Lapenue; Bouas-Laurent *Bull. Soc. Chim. Fr.* **1973**, 720.

[1579]Yamamura; Murahashi *Tetrahedron Lett.* **1977**, 4429.

[1580]Sakakibara; Yadani; Ibuki; Sakai; Uchino *Chem. Lett.* **1982**, 1565; Procházka; Široký *Collect. Czech. Chem. Commun.* **1983**, *48*, 1765.

[1581]Corey; Hegedus *J. Am. Chem. Soc.* **1969**, *91*, 1233. See also Stuhl *J. Org. Chem.* **1985**, *50*, 3934.

[1582]Reetz; Chatziiosifidis *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 1017 [*Angew. Chem. 93*, 1075].

[1583]Piers; Fleming *J. Chem. Soc., Chem. Commun.* **1989**, 756.

[1584]Davis; Untch *J. Org. Chem.* **1981**, *46*, 2985. See also Mizuno; Hamada; Shioiri *Synthesis* **1980**, 1007; Manna; Falck; Mioskowski *Synth. Commun.* **1985**, *15*, 663; Camps; Gasol; Guerrero *Synth. Commun.* **1988**, *18*, 445.

[1585]Torii; Inokuchi; Kobayashi *Chem. Lett.* **1984**, 897; Soga; Takenoshita; Yamada; Mukaiyama *Bull. Chem. Soc. Jpn.* **1990**, *63*, 3122.

[1586]Ito; Imai; Segoe; Saegusa *Chem. Lett.* **1984**, 937.

[1587]Müller; Siegfried *Helv. Chim. Acta* **1974**, *57*, 987.

0-102   Direct Conversion of Alkyl Halides to Aldehydes and Ketones
Formyl-de-halogenation

$$RX + Na_2Fe(CO)_4 \xrightarrow{Ph_3P} RCOFe(CO)_3PPh_3^- \xrightarrow{HOAc} RCHO$$
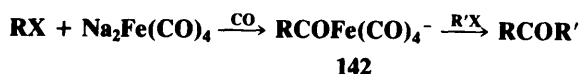$$\mathbf{140}$$

The direct conversion of alkyl bromides to aldehydes, with an increase in the chain length by one carbon, can be accomplished[1588] by treatment with sodium tetracarbonylferrate($-$II)[1589] (*Collman's reagent*) in the presence of triphenylphosphine and subsequent quenching of **140** 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 not satisfactory for benzylic bromides. The initial species produced from RX and $Na_2Fe(CO)_4$ is the ion $RFe(CO)_4^-$ (**141**) (which can be isolated[1590]); it then reacts with Ph_3P to give **140**.[1591]

The synthesis can be extended to the preparation of ketones in six distinct ways.[1592]

1. Instead of quenching **140** with acetic acid, the addition of a second alkyl halide at this point gives a ketone: **140** + R'X → RCOR'.

2. Treatment of $Na_2Fe(CO)_4$ with an alkyl halide in the absence of Ph_3P gives rise to a solution of **141**. Addition of a second alkyl halide produces a ketone: **141** + R'X → RCOR'.

3. Treatment of $Na_2Fe(CO)_4$ with an alkyl halide in the presence of CO results in an

$$RX + Na_2Fe(CO)_4 \xrightarrow{CO} RCOFe(CO)_4^- \xrightarrow{R'X} RCOR'$$
$$\mathbf{142}$$

acylated iron complex (**142**) that can be isolated.[1590] Treatment of this with a second alkyl halide gives a ketone.

4. Treatment of $Na_2Fe(CO)_4$ with an acyl halide produces **142** which, when treated with an alkyl halide, gives a ketone or, when treated with an epoxide, gives an α,β-unsaturated ketone.[1593]

5. Alkyl halides and tosylates react with $Na_2Fe(CO)_4$ in the presence of ethylene to give alkyl ethyl ketones.[1594] The reaction was not successful for higher alkenes, except that where the double bond and the tosylate group are in the same molecule, 5- and 6-membered rings can be closed.[1595]

6. If 1,4-dihalides are treated with $K_2Fe(CO)_4$, 5-membered cyclic ketones are prepared.[1596]

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.

[1588]Cooke *J. Am. Chem. Soc.* **1970**, *92*, 6080.
[1589]For a review of this reagent, see Collman *Acc. Chem. Res.* **1975**, *8*, 342-347. For a review of the related tetracarbonylhydridoferrates $MHFe(CO)_4$, see Brunet *Chem. Rev.* **1990**, *90*, 1041-1059.
[1590]Siegl; Collman *J. Am. Chem. Soc.* **1972**, *94*, 2516.
[1591]For the mechanism of the conversion **141** → **140**, see Collman; Finke; Cawse; Brauman *J. Am. Chem. Soc.* **1977**, *99*, 2515, **1978**, *100*, 4766.
[1592]For the first four of these methods, see Collman; Winter; Clark *J. Am. Chem. Soc.* **1972**, *94*, 1788; Collman; Hoffman *J. Am. Chem. Soc.* **1973**, *95*, 2689.
[1593]Yamashita; Yamamura; Kurimoto; Suemitsu *Chem. Lett.* **1979**, 1067.
[1594]Cooke; Parlman *J. Am. Chem. Soc.* **1975**, *97*, 6863.
[1595]McMurry; Andrus *Tetrahedron Lett.* **1980**, *21*, 4687, and references cited therein.
[1596]Yamashita; Uchida; Tashika; Suemitsu *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2728.
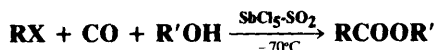
Aryl, benzylic, vinylic, and allylic halides have been converted to aldehydes by treatment with CO and Bu_3SnH, with a Pd(0) catalyst.[1597] Various other groups do not interfere. Symmetrical ketones R_2CO can be prepared by treatment of a primary alkyl or benzylic halide with $Fe(CO)_5$ and a phase transfer catalyst,[1598] or from a halide RX (R = primary alkyl, aryl, allylic, or benzylic) and CO by an electrochemical method involving a nickel complex.[1599] Several procedures for the preparation of ketones are catalyzed by palladium complexes, among them the following: 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 → RCOAr);[1600] vinylic halides react with vinylic tin reagents in the presence of CO to give unsymmetrical divinyl ketones;[1601] and aryl, vinylic, and benzylic halides can be converted to methyl ketones (RX → RCOMe) by reaction with (α-ethoxy-vinyl)tributyltin $Bu_3SnC(OEt)\!=\!CH_2$.[1602]

The conversion of alkyl halides to aldehydes and ketones can also be accomplished indirectly (**0-97**). See also **2-32**.
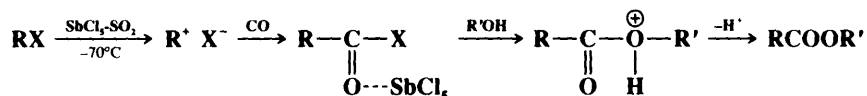
OS **VI**, 807.

0-103 Conversion of Alkyl Halides, Alcohols, or Alkanes to Carboxylic Acids and Their Derivatives
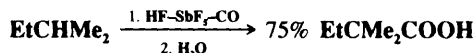**Alkoxycarbonyl-de-halogenation**

$$RX + CO + R'OH \xrightarrow[-70°C]{SbCl_5-SO_2} RCOOR'$$

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.[1603] When an alkyl halide is treated with $SbCl_5–SO_2$ at $-70°C$, it dissociates into the corresponding carbocation (p. 166). If carbon monoxide and an alcohol are present, a carboxylic ester is formed by the following route:[1604]

$$RX \xrightarrow[-70°C]{SbCl_5-SO_2} R^+ \; X^- \xrightarrow{CO} \underset{\underset{O\cdots SbCl_5}{\|}}{R-C-X} \xrightarrow{R'OH} \underset{\underset{O \quad H}{\| \quad |}}{R-C-\overset{\oplus}{O}-R'} \xrightarrow{-H^+} RCOOR'$$

This has also been accomplished with concentrated H_2SO_4 saturated with CO.[1605] Not surprisingly, only tertiary halides perform satisfactorily; secondary halides give mostly rearrangement products. An analogous reaction takes place with alkanes possessing a tertiary hydrogen, e.g.,[1606]

$$EtCHMe_2 \xrightarrow[2. H_2O]{1. HF-SbF_5-CO} 75\% \; EtCMe_2COOH$$

[1597]Baillargeon; Stille *J. Am. Chem. Soc.* **1986**, *108*, 452. See also Kasahara; Izumi; Yanai *Chem. Ind. (London)* **1983**, 898; Pri-Bar; Buchman *J. Org. Chem.* **1984**, *49*, 4009; Takeuchi; Tsuji; Watanabe *J. Chem. Soc., Chem. Commun.* **1986**, 351; Ben-David; Portnoy; Milstein *J. Chem. Soc., Chem. Commun.* **1989**, 1816.

[1598]Kimura; Tomita; Nakanishi; Otsuji *Chem. Lett.* **1979**, 321; des Abbayes; Clément; Laurent; Tanguy; Thilmont *Organometallics* **1988**, 7, 2293.

[1599]Garnier; Rollin; Périchon *J. Organomet. Chem.* **1989**, *367*, 347.

[1600]Tamaru; Ochiai; Yamada; Yoshida *Tetrahedron Lett.* **1983**, 24, 3869.

[1601]Goure; Wright; Davis; Labadie; Stille *J. Am. Chem. Soc.* **1984**, *106*, 6417. For a similar preparation of diallyl ketones, see Merrifield; Godschalx; Stille *Organometallics* **1984**, *3*, 1108.

[1602]Kosugi; Sumiya; Obara; Suzuki; Sano; Migita *Bull. Chem. Soc. Jpn.* **1987**, *60*, 767.

[1603]For discussions of most of the reactions in this section, see Colquhoun; Holton; Thompson; Twigg *New Pathways for Organic Synthesis*; Plenum: New York, 1984, pp. 199-204, 212-220, 234-235. For lists of reagents, with references, see Ref. 508, pp. 850-851, 855-856, 859-860.

[1604]Yoshimura; Nojima; Tokura *Bull. Chem. Soc. Jpn.* **1973**, *46*, 2164; Puzitskii; Pirozhkov; Ryabova; Myshenkova; Éidus *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1974**, *23*, 192.

[1605]Takahashi; Yoneda *Synth. Commun.* **1989**, *19*, 1945.

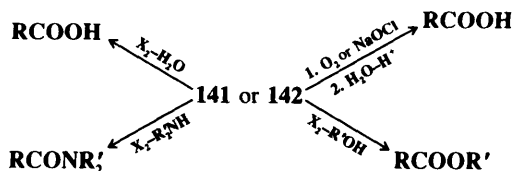[1606]Paatz; Weisgerber *Chem. Ber.* **1967**, *100*, 984.

Carboxylic acids or esters are the products, depending on whether the reaction mixture is solvolyzed with water or an alcohol. Alcohols with more than 7 carbons are cleaved into smaller fragments by this procedure.[1607] Similarly, tertiary alcohols[1608] 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 **5-23**).[1609] 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.[1610]

Another method[1611] 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

$$RX + Ni(CO)_4 \xrightarrow[R'OH]{R'O^-} RCOOR'$$

base.[1612] 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.

Still another method for the conversion of halides to acid derivatives makes use of $Na_2Fe(CO)_4$. As described in **0-102**, primary and secondary alkyl halides and tosylates react with this reagent to give the ion $RFe(CO)_4^-$ **(141)** or, if CO is present, the ion $RCOFe(CO)_4^-$ **(142)**. Treatment of **141** or **142** with oxygen or sodium hypochlorite gives, after hydrolysis, a carboxylic acid.[1613] Alternatively, **141** or **142** reacts with a halogen (for example, I_2) in the

presence of an alcohol to give a carboxylic ester,[1614] or in the presence of a secondary amine or water to give, respectively, the corresponding amide or free acid. **141** and **142** prepared from primary R give high yields. With secondary R, the best results are obtained in the solvent THF by the use of **142** prepared from secondary tosylates. Ester and keto groups may be present in R without being affected. Carboxylic esters RCO_2R' have also been

[1607]Yoneda; Takahashi; Fukuhara; Suzuki *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2819.

[1608]For reviews of other carbonylation reactions of alcohols and other saturated oxygenated compounds, see Bahrmann; Cornils, in Falbe *New Syntheses with Carbon Monoxide*; Springer: New York, 1980, pp. 226-241; Piacenti; Bianchi, in Wender; Pino *Organic Syntheses via Metal Carbonyls*, vol. 2; Wiley: New York, 1977, pp. 1-42.

[1609]For a review, see Bahrmann, in Falbe, Ref. 1608, pp. 372-413.

[1610]Booth; El-Fekky *J. Chem. Soc., Perkin Trans. 1* **1979**, 2441.

[1611]For reviews of methods involving transition metals, see Collman et al., Ref. 1266, pp. 749-768; Anderson; Davies, in Hartley; Patai, Ref. 1403, vol. 3, pp. 335-359, pp. 348-356; Heck *Adv. Catal.* **1977**, *26*, 323-349, pp. 323-336; Cassar; Chiusoli; Guerrieri *Synthesis* **1973**, 509-523.

[1612]Corey; Hegedus *J. Am. Chem. Soc.* **1969**, *91*, 1233. See also Crandall; Michaely *J. Organomet. Chem.* **1973**, *51*, 375.

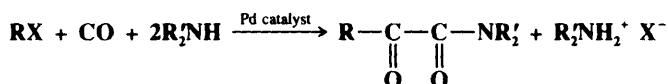[1613]Collman; Winter; Komoto *J. Am. Chem. Soc.* **1973**, *95*, 249.

[1614]Ref. 1613; Masada; Mizuno; Suga; Watanabe; Takegami *Bull. Chem. Soc. Jpn.* **1970**, *43*, 3824.

prepared by treating primary alkyl halides RX with alkoxides R'O⁻ in the presence of Fe(CO)₅.[1615] **142** is presumably an intermediate.

Palladium complexes also catalyze the carbonylation of halides.[1616] Aryl (see **3-15**), vinylic,[1617] benzylic, and allylic halides (especially iodides) can be converted to carboxylic esters with CO, an alcohol or alkoxide, and a palladium complex.[1618] Use of an amine instead of the alcohol or alkoxide leads to an amide.[1619] Benzylic and allylic halides were converted to carboxylic acids electrocatalytically, with CO and a cobalt imine complex.[1620] Vinylic halides were similarly converted with CO and nickel cyanide, under phase-transfer conditions.[1621]

Rhodium catalysts have also been used. Benzylic halides were converted to carboxylic esters with CO in the presence of a rhodium complex. In this case, the R' could come from an ether R'₂O,[1622] a borate ester B(OR')₃,[1623] or an Al, Ti, or Zr alkoxide.[1624]

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.[1625] When the catalyst is a palladium complex, best results are obtained in the formation of α-keto amides.[1626]

$$RX + CO + 2R_2'NH \xrightarrow{\text{Pd catalyst}} R-\underset{\underset{O}{\|}}{C}-\underset{\underset{O}{\|}}{C}-NR_2' + R_2'NH_2^+ \ X^-$$

R is usually aryl or vinylic.[1627] The formation of α-keto acids[1628] or esters[1629] 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.[1630] Cobalt catalysts have also been used and require lower CO pressures.[1625]

OS **V**, 20, 739.

[1615]Yamashita; Mizushima; Watanabe; Mitsudo; Takegami *Chem. Lett.* **1977**, 1355. See also Tanguy; Weinberger; des Abbayes *Tetrahedron Lett.* **1983**, *24*, 4005.

[1616]For reviews, see Gulevich; Bumagin; Beletskaya *Russ. Chem. Rev.* **1988**, *57*, 299-315, pp. 303-309; Heck *Palladium Reagents in Organic Synthesis*, Ref. 1308, pp. 348-356, 366-370.

[1617]For conversion of vinylic triflates to carboxylic esters and amides, see Cacchi; Morera; Ortar *Tetrahedron Lett.* **1985**, *26*, 1109.

[1618]Tsuji; Kishi; Imamura; Morikawa *J. Am. Chem. Soc.* **1964**, *86*, 4350; Schoenberg; Bartoletti; Heck *J. Org. Chem.* **1974**, *39*, 3318; Hidai; Hikita; Wada; Fujikura; Uchida *Bull. Chem. Soc. Jpn.* **1975**, *48*, 2075; Bumagin; Gulevich; Beletskaya *J. Organomet. Chem.* **1985**, *285*, 415; Milstein *J. Chem. Soc., Chem. Commun.* **1986**, 817; Kiji; Okano; Nishiumi; Konishi *Chem. Lett.* **1988**, 957, **1989**, 1873; Adapa; Prasad *J. Chem. Soc., Perkin Trans. 1* **1989**, 1706.

[1619]Schoenberg; Heck *J. Org. Chem.* **1974**, *39*, 3327. See also Lindsay; Widdowson *J. Chem. Soc., Perkin Trans. 1* **1988**, 569. For a review of some methods of amide formation that involve transition metals, see Screttas; Steele *Org. Prep. Proced. Int.* **1990**, *22*, 271-314, pp. 288-314.

[1620]Folest; Duprilot; Perichon; Robin; Devynck *Tetrahedron Lett.* **1985**, *26*, 2633. For other procedures involving a cobalt catalyst, see Francalanci; Gardano; Foà *J. Organomet. Chem.* **1985**, *282*, 277; Satyanarayana; Periasamy *Tetrahedron Lett.* **1987**, *28*, 2633; Miura; Okuro; Hattori; Nomura *J. Chem. Soc., Perkin Trans. 1* **1989**, 73; Urata; Goto; Fuchikami *Tetrahedron Lett.* **1991**, *32*, 3091.

[1621]Alper; Amer; Vasapollo *Tetrahedron Lett.* **1989**, *30*, 2615. See also Amer; Alper *J. Am. Chem. Soc.* **1989**, *111*, 927.

[1622]Buchan; Hamel; Woell; Alper *Tetrahedron Lett.* **1985**, 26, 5743.

[1623]Woell; Alper *Tetrahedron Lett.* **1984**, *25*, 3791; Alper; Hamel; Smith; Woell *Tetrahedron Lett.* **1985**, *26*, 2273.

[1624]Woell; Fergusson; Alper *J. Org. Chem.* **1985**, *50*, 2134.

[1625]For a review, see Collin *Bull. Soc. Chim. Fr.* **1988**, 976-981.

[1626]Kobayashi; Tanaka *J. Organomet. Chem.* **1982**, *233*, C64; Ozawa; Sugimoto; Yuasa; Santra; Yamamoto; Yamamoto *Organometallics* **1984**, *3*, 683.

[1627]Son; Yanagihara; Ozawa; Yamamoto *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1251.

[1628]Tanaka; Kobayashi; Sakakura *J. Chem. Soc., Chem. Commun.* **1985**, 837.

[1629]See Ozawa; Kawasaki; Okamoto; Yamamoto; Yamamoto *Organometallics* **1987**, *6*, 1640.

[1630]Kobayashi; Sakakura; Tanaka *Tetrahedron Lett.* **1987**, *28*, 2721.

B. Attack at an Acyl Carbon[1631]

0-104 The Conversion of Acyl Halides to Ketones with Organometallic Compounds[1632]
Alkyl-de-halogenation

$$R'-\underset{\underset{O}{\parallel}}{C}-X \;+\; R_2CuLi \;\longrightarrow\; R'-\underset{\underset{O}{\parallel}}{C}-R$$

Acyl halides react cleanly and under mild conditions with lithium dialkylcopper reagents[1633] to give high yields of ketones.[1634] R' may be primary, secondary, or tertiary alkyl or aryl and may contain iodo, keto, ester, nitro, or cyano groups. R groups that have been used successfully are methyl, primary alkyl, and vinylic. Secondary and tertiary alkyl groups can be introduced by the use of PhS(R)CuLi (p. 451) instead of R_2CuLi,[1635] or by the use of either the mixed homocuprate $(R'SO_2CH_2CuR)^-$ Li^+,[1636] or a magnesium dialkylcopper reagent "RMeCuMgX."[1637] Secondary alkyl groups can also be introduced with the copper–zinc reagents $RCu(CN)ZnI$.[1638] R may be alkynyl if a cuprous acetylide $R''C\equiv CCu$ is the reagent.[1639] Organocopper reagents generated in situ from highly reactive copper, and containing such functional groups as cyano, chloro, and ester, react with acyl halides to give ketones.[1640]

Another type of organometallic reagent[1641] that gives good yields of ketones when treated with acyl halides are organocadmiums R_2Cd (prepared from Grignard reagents, **2-21**). In this case R may be aryl or primary alkyl. In general, secondary and tertiary alkylcadmium reagents are not stable enough to be useful in this reaction.[1642] An ester group may be present in either R'COX or R_2Cd. Organozinc compounds behave similarly, but are used less often.[1643] Organomercury compounds[1644] and tetraalkylsilanes[1645] also give the reaction if an AlX_3 catalyst is present.[1646] Organotin reagents R_4Sn react with acyl halides to give high yields of ketones, if a Pd complex is present.[1647] Various other groups, for example, nitrile, ester, and aldehyde can be present in the acyl halide without interference. Still

[1631]For a discussion of many of the reactions in this section, see House, Ref. 1411, pp. 691-694, 734-765.

[1632]For a review, see Cais; Mandelbaum, in Patai, Ref. 446, vol. 1, pp. 303-330.

[1633]For examples of the use of this reaction in the synthesis of natural products, see Posner, Ref. 1352, pp. 81-85. See also Ref. 1268.

[1634]Vig; Sharma; Kapur *J. Indian Chem. Soc.* **1969**, *46*, 167; Jukes; Dua; Gilman *J. Organomet. Chem.* **1970**, *21*, 241; Posner; Whitten; McFarland *J. Am. Chem. Soc.* **1972**, *94*, 5106; Luong-Thi; Rivière *J. Organomet. Chem.* **1974**, *77*, C52.

[1635]Ref. 1276; Bennett; Nadelson; Alden; Jani *Org. Prep. Proced. Int.* **1976**, *8*, 13.

[1636]Johnson; Dhanoa *J. Org. Chem.* **1987**, *52*, 1885.

[1637]Bergbreiter; Killough *J. Org. Chem.* **1976**, *41*, 2750.

[1638]Knochel; Yeh; Berk; Talbert *J. Org. Chem.* **1988**, *53*, 2390.

[1639]Castro; Havlin; Honwad; Malte; Mojé *J. Am. Chem. Soc.* **1969**, *91*, 6464. For methods of preparing acetylenic ketones, see Verkruijsse; Heus-Kloos; Brandsma *J. Organomet. Chem.* **1988**, *338*, 289.

[1640]Wehmeyer; Rieke *Tetrahedron Lett.* **1988**, *29*, 4513.

[1641]For a list of reagents, with references, see Ref. 508, pp. 686-691.

[1642]Cason; Fessenden *J. Org. Chem.* **1960**, *25*, 477.

[1643]For examples, see Grey *J. Org. Chem.* **1984**, *49*, 2288; Tamaru; Ochiai; Nakamura; Yoshida *Org. Synth.* **67**, 98.

[1644]Kurts; Beletskaya; Savchenko; Reutov *J. Organomet. Chem.* **1969**, *17*, P21; Larock; Lu *Tetrahedron Lett.* **1988**, *29*, 6761. See also Bumagin; Kalinovskii; Beletskaya *J. Org. Chem. USSR* **1982**, *18*, 1152.

[1645]For a review, see Parnes; Bolestova *Synthesis* **1984**, 991-1008, pp. 991-996.

[1646]In the case of organomercury compounds a palladium catalyst can also be used: Bumagin; More; Beletskaya *J. Organomet. Chem.* **1989**, *365*, 379.

[1647]Kosugi; Shimizu; Migita *Chem. Lett.* **1977**, 1423; Labadie; Stille *J. Am. Chem. Soc.* **1983**, *105*, 669, 6129; Labadie; Tueting; Stille *J. Org. Chem.* **1983**, *48*, 4634. For the use of R_4Pb see Yamada; Yamamoto *J. Chem. Soc., Chem. Commun.* **1987**, 1302. See also Verlhac; Quintard *Tetrahedron Lett.* **1986**, *27*, 2361.

other reagents are organomanganese compounds[1648] (R can be primary, secondary, or tertiary alkyl, vinylic, alkynyl, or aryl), organothallium compounds (R can be primary alkyl or aryl),[1649] lithium aryltrialkylborates[1650] $ArBR_3^-$ Li^+ (which transfer an aryl group), and the alkylrhodium(I) complexes bis(triphenylphosphine)carbonylalkylrhodium(I) $Rh^IR(CO)(Ph_3P)_2$. The latter, generated in situ from $Rh^ICl(CO)(Ph_3P)_2$ (**143**) and a Grignard reagent or organolithium compound, react with acyl halides in THF at $-78°C$ to give good yields of ketones.[1651] R may be primary alkyl or aryl. An advantage of the rhodium reagents is that they do not react with aldehydes, esters, or nitriles, so that these groups may be present in R'. Another advantage is that the complex **143** is regenerated in reusable form at the end of the reaction.
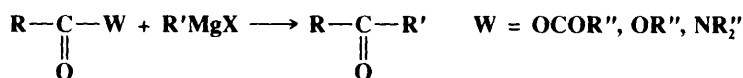
When the organometallic compound is a Grignard reagent,[1652] ketones are generally not obtained because the initially formed ketone reacts with a second molecule of RMgX to give the salt of a tertiary alcohol (**6-32**). Ketones *have* been prepared in this manner by the use of low temperatures, inverse addition (i.e., addition of the Grignard reagent to the acyl halide rather than the other way), excess acyl halide, etc., but the yields are usually low, though high yields have been reported in THF at $-78°C$.[1653] Some ketones are unreactive toward Grignard reagents for steric or other reasons; these can be prepared in this way.[1654] Other methods involve running the reaction in the presence of Me_3SiCl[1655] (which reacts with the initial adduct **67** in the tetrahedral mechanism, p. 331), and the use of a combined Grignard–lithium diethylamide reagent.[1656] Also, certain metallic halides, notably ferric and cuprous halides, are catalysts that improve the yields of ketone at the expense of tertiary alcohol.[1657] For these catalysis, both free-radical and ionic mechanisms have been proposed.[1658] The reactions with R_2CuLi, R_2Cd, and the rhodium complexes are successful because these compounds do not generally react with ketones.

Grignard reagents react with ethyl chloroformate to give carboxylic esters $EtOCOCl$ + RMgX → $EtOCOR$. Acyl halides can also be converted to ketones by treatment with $Na_2Fe(CO)_4$ followed by R'X (**0-102**, method 4).

OS **II**, 198; **III**, 601; **IV**, 708; **VI**, 248, 991; **VII**, 226, 334; **65**, 47; **66**, 87, 116; **67**, 86, 98.

0-105 The Conversion of Anhydrides, Carboxylic Esters, or Amides to Ketones with Organometallic Compounds[1659]

Alkyl-de-acyloxy-substitution

$$R\text{—}\overset{\displaystyle O}{\underset{\displaystyle \|}{C}}\text{—}W + R'MgX \longrightarrow R\text{—}\overset{\displaystyle O}{\underset{\displaystyle \|}{C}}\text{—}R' \qquad W = OCOR'', OR'', NR''_2$$

[1648]Friour; Alexakis; Cahiez; Normant *Tetrahedron* **1984**, *40*, 683; Friour; Cahiez; Normant *Synthesis* **1985**, 50; Cahiez; Laboue *Tetrahedron Lett.* **1989**, *30*, 7369.

[1649]Markó; Southern *J. Org. Chem.* **1990**, *55*, 3368.

[1650]Negishi; Abramovitch; Merrill *J. Chem. Soc., Chem. Commun.* **1975**, 138, Negishi; Chiu; Yoshida *J. Org. Chem.* **1975**, *40*, 1676. See also Miyaura; Sasaki; Itoh; Suzuki *Tetrahedron Lett.* **1977**, 173.

[1651]Hegedus; Kendall; Lo; Sheats *J. Am. Chem. Soc.* **1975**, *97*, 5448. See also Pittman; Hanes *J. Org. Chem.* **1977**, *42*, 1194.

[1652]For a review, see Kharasch; Reinmuth, Ref. 1287, pp. 712-724.

[1653]Sato; Inoue; Oguro; Sato *Tetrahedron Lett.* **1979**, 4303; Eberle; Kahle *Tetrahedron Lett.* **1980**, *21*, 2303; Föhlisch; Flogaus *Synthesis* **1984**, 734.

[1654]For example, see Lion; Dubois; Bonzougou *J. Chem. Res., (S)* **1978**, 46; Dubois; Lion; Arouisse *Bull. Soc. Chim. Belg.* **1984**, *93*, 1083.

[1655]Cooke *J. Org. Chem.* **1986**, *51*, 951.

[1656]Fehr; Galindo *Helv. Chim. Acta* **1986**, *69*, 228; Fehr; Galindo; Perret *Helv. Chim. Acta* **1987**, *70*, 1745.
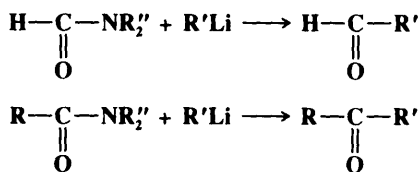
[1657]For examples, see Cason; Kraus *J. Org. Chem.* **1961**, *26*, 1768, 1772; MacPhee; Dubois *Tetrahedron Lett.* **1972**, 467; Cardellicchio; Fiandanese; Marchese; Ronzini *Tetrahedron Lett.* **1987**, *28*, 2053; Fujisawa; Sato *Org. Synth. 66*, 116; Babudri; D'Ettole; Fiandanese; Marchese; Naso *J. Organomet. Chem.* **1991**, *405*, 53.

[1658]For example, see Dubois; Boussu *Tetrahedron Lett.* **1970**, 2523, *Tetrahedron* **1973**, *29*, 3943; MacPhee; Boussu; Dubois *J. Chem. Soc., Perkin Trans. 2* **1974**, 1525.

[1659]For a review, see Kharasch; Reinmuth, Ref. 1287, pp. 561-562, 846-908.
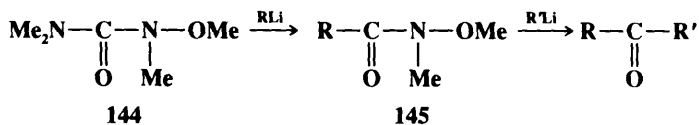
As is the case with acyl halides (**0-104**), anhydrides and carboxylic esters give tertiary alcohols (**6-32**) when treated with Grignard reagents. Low temperatures,[1660] the solvent HMPA,[1661] and inverse addition have been used to increase the yields of ketone.[1662] Amides give better yields of ketone at room temperature, but still not very high.[1663] Thiol esters RCOSR' give good yields of ketones when treated with lithium dialkylcopper reagents R''_2CuLi (R" = primary or secondary alkyl or aryl).[1664] Ketones can also be prepared by treatment of thioamides with organolithium compounds (alkyl or aryl).[1665] Organocadmium reagents are less successful with these substrates than with acyl halides (**0-104**). Esters of formic acid, dialkylformamides, and lithium or sodium formate[1666] give good yields of aldehydes, when treated with Grignard reagents.

Alkyllithium compounds have been used to give ketones from carboxylic esters. The reaction must be carried out in a high-boiling solvent such as toluene, since reaction at lower temperatures gives tertiary alcohols.[1667] Alkyllithiums also give good yields of carbonyl compounds with N,N-disubstituted amides.[1668] Dialkylformamides give aldehydes and other disubstituted amides give ketones.

$$H-\underset{\underset{O}{\|}}{C}-NR''_2 + R'Li \longrightarrow H-\underset{\underset{O}{\|}}{C}-R'$$

$$R-\underset{\underset{O}{\|}}{C}-NR''_2 + R'Li \longrightarrow R-\underset{\underset{O}{\|}}{C}-R'$$

N,N-Disubstituted amides can be converted to alkynyl ketones by treatment with alkynyl-boranes: $RCONR''_2 + (R'C{\equiv}C)_3B \rightarrow RCOC{\equiv}CR'$.[1669] Alkynyl ketones are also obtained by treatment of anhydrides with lithium alkynyltrifluoroborates $Li(RC{\equiv}C-BF_3)$.[1670] N,N-Disubstituted carbamates (X = OR") and carbamoyl chlorides (X = Cl) react with 2 moles of an alkyl- or aryllithium or Grignard reagent to give symmetrical ketones, in which both R groups are derived from the organometallic compound: $R'_2NCOX + 2RMgX \rightarrow R_2CO$.[1671] N,N-Disubstituted amides give ketones in high yields when treated with alkyl-lanthanum triflates $RLa(OTf)_2$.[1672]

By the use of the compound N-methoxy-N,N'-trimethylurea **144**, it is possible to add

$$Me_2N-\underset{\underset{O}{\|}}{C}-\underset{\underset{Me}{|}}{N}-OMe \xrightarrow{RLi} R-\underset{\underset{O}{\|}}{C}-\underset{\underset{Me}{|}}{N}-OMe \xrightarrow{R'Li} R-\underset{\underset{O}{\|}}{C}-R'$$

$$\textbf{144}\qquad\qquad\qquad\qquad \textbf{145}$$

[1660]See, for example, Newman; Smith *J. Org. Chem.* **1948**, *13*, 592; Edwards; Kammann *J. Org. Chem.* **1964**, *29*, 913; Araki; Sakata; Takei; Mukaiyama *Chem. Lett.* **1974**, 687.

[1661]Huet; Emptoz; Jubier *Tetrahedron* **1973**, *29*, 479; Huet; Pellet; Conia *Tetrahedron Lett.* **1976**, 3579.

[1662]For a list of preparations of ketones by the reaction of organometallic compounds with carboxylic esters, salts, anhydrides, or amides, with references, see Ref. 508, pp. 685-686, 693-700.

[1663]For an improved procedure with amides, see Olah; Prakash; Arvanaghi *Synthesis* **1984**, 228.

[1664]Anderson; Henrick; Rosenblum *J. Am. Chem. Soc.* **1974**, *96*, 3654. See also Kim; Lee *J. Org. Chem.* **1983**, *48*, 2608.

[1665]Tominaga; Kohra; Hosomi *Tetrahedron Lett.* **1987**, *28*, 1529.

[1666]Bogavac; Arsenijević; Pavlov; Arsenijević *Tetrahedron Lett.* **1984**, *25*, 1843.

[1667]Petrov; Kaplan; Tsir *J. Gen. Chem. USSR* **1962**, *32*, 691.

[1668]Evans *J. Chem. Soc.* **1956**, 4691. For a review, see Wakefield *Organolithium Methods*; Academic Press: New York, 1988, pp. 82-88.

[1669]Yamaguchi; Waseda; Hirao *Chem. Lett.* **1983**, 35.

[1670]Brown; Racherla; Singh *Tetrahedron Lett.* **1984**, *25*, 2411.

[1671]Michael; Hörnfeldt *Tetrahedron Lett.* **1970**, 5219; Scilly, *Synthesis* **1973**, 160.

[1672]Collins; Hong *Tetrahedron Lett.* **1987**, *28*, 4391.

two R groups, the same or different, to a CO group. Both reactions can be done in the same vessel without the isolation of **145**.[1673]

Hydrogen has been reported to be a leaving group in this reaction: Aromatic aldehydes are converted to methyl ketones (ArCHO → ArCOCH$_3$) with Al(OAr)Me$_2$ (Ar = 2,6-di-t-butyl-4-methylphenyl).[1674]
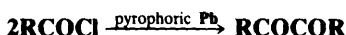
Carboxylic esters can be converted to their homologs (RCOOEt → RCH$_2$COOEt) by treatment with Br$_2$CHLi followed by BuLi at −90°C. The ynolate RC≡COLi is an intermediate.[1675] If the ynolate is treated with 1,3-cyclohexadiene, followed by NaBH$_4$, the product is the alcohol RCH$_2$CH$_2$OH.[1676]

Ketones can also be obtained by treatment of the lithium salt of a carboxylic acid with an alkyllithium reagent (**6-31**). For an indirect way to convert carboxylic esters to ketones, see **6-33**.

OS **II**, 282; **III**, 353; **IV**, 285; **VI**, 611; **VII**, 323, 451.

0-106   The Coupling of Acyl Halides
          De-halogen-coupling

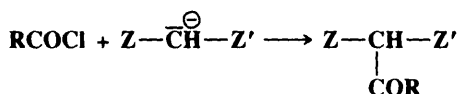$$2RCOCl \xrightarrow{\text{pyrophoric Pb}} RCOCOR$$

Acyl halides can be coupled with pyrophoric lead to give symmetrical α-diketones in a Wurtz-type reaction.[1677] The reaction has been performed with R = Me and Ph. Other reagents that give the same reaction are samarium iodide SmI$_2$[1678] and hexaethyldistannane Et$_6$Sn$_2$ (with palladium catalysts and under CO pressure).[1679] Benzoyl chloride was coupled to give benzil by subjecting it to ultrasound in the presence of Li wire: 2PhCOCl + Li → PhCOCOPh.[1247]

Unsymmetrical α-diketones RCOCOR' have been prepared by treatment of an acyl halide RCOCl with an acyltin reagent RCOSnBu$_3$, with a palladium-complex catalyst.[1680]

0-107   Acylation at a Carbon Bearing an Active Hydrogen
          Bis(ethoxycarbonyl)methyl-de-halogenation, etc.

$$RCOCl + Z-\overset{\ominus}{C}H-Z' \longrightarrow Z-\underset{\underset{COR}{|}}{C}H-Z'$$

This reaction is similar to **0-94**, though many fewer examples have been reported.[1681] Z and Z' may be any of the groups listed in **0-94**.[1682] Anhydrides react similarly but are used less often. The product contains three Z groups, since RCO is a Z group. One or two of these can be cleaved (**2-40**, **2-43**). In this way a compound ZCH$_2$Z' can be converted to ZCH$_2$Z" or an acyl halide RCOCl to a methyl ketone RCOCH$_3$. O-Acylation is sometimes a side

[1673]Hlasta; Court *Tetrahedron Lett.* **1989**, *30*, 1773. See also Nahm; Weinreb *Tetrahedron Lett.* **1981**, *22*, 3815.
[1674]Power; Barron *Tetrahedron Lett.* **1990**, *31*, 323.
[1675]Kowalski; Haque; Fields *J. Am. Chem. Soc.* **1985**, *107*, 1429; Kowalski; Haque *J. Org. Chem.* **1985**, *50*, 5140.
[1676]Kowalski; Haque *J. Am. Chem. Soc.* **1986**, *108*, 1325.
[1677]Mészáros *Tetrahedron Lett.* **1967**, 4951.
[1678]Souppe; Namy; Kagan *Tetrahedron Lett.* **1984**, *25*, 2869. See also Collin; Namy; Dallemer; Kagan *J. Org. Chem.* **1991**, *56*, 3118.
[1679]Bumagin; Gulevich; Beletskaya *J. Organomet. Chem.* **1985**, *282*, 421.
[1680]Verlhac; Chanson; Jousseaume; Quintard *Tetrahedron Lett.* **1985**, *26*, 6075. For another procedure, see Olah; Wu *J. Org. Chem.* **1991**, *56*, 902.
[1681]For examples of reactions in this section, with references, see Ref. 508, pp. 742, 764-767.
[1682]For an improved procedure, see Rathke; Cowan *J. Org. Chem.* **1985**, *50*, 2622.
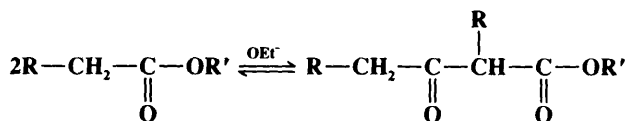
reaction.[1683] When thallium(I) salts of ZCH_2Z' are used, it is possible to achieve regiose-lective acylation at either the C or the O position. For example, treatment of the thallium(I) salt of $MeCOCH_2COMe$ with acetyl chloride at $-78°C$ gave $>90\%$ O-acylation, while acetyl fluoride at room temperature gave $>95\%$ C-acylation.[1684] The use of an alkyl chloroformate gives triesters.[1685]

The application of this reaction to simple ketones[1452] (in parallel with **0-95**) requires a strong base, such as $NaNH_2$ or Ph_3CNa, and is often complicated by O-acylation, which in many cases becomes the principal pathway because acylation at the oxygen is usually much faster. It is possible to increase the proportion of C-acylated product by employing an excess (2 to 3 equivalents) of enolate ion (and adding the substrate to this, rather than vice versa), by the use of a relatively nonpolar solvent and a metal ion (such as Mg^{2+}) which is tightly associated with the enolate oxygen atom, by the use of an acyl halide rather than an anhydride,[1686] and by working at low temperatures.[1687] In cases where the use of an excess of enolate ion results in C-acylation, it is because O-acylation takes place first, and the O-acylated product (an enol ester) is then C-acylated. Simple ketones can also be acylated by treatment of their silyl enol ethers with an acyl chloride in the presence of $ZnCl_2$ or $SbCl_3$.[1688] Ketones can be acylated by anhydrides to give β-diketones, with BF_3 as catalyst.[1689] Simple esters RCH_2COOEt can be acylated at the α carbon (at $-78°C$) if a strong base such as lithium N-isopropylcyclohexylamide is used to remove the proton.[1690]

OS **II**, 266, 268, 594, 596; **III**, 16, 390, 637; **IV**, 285, 415, 708; **V**, 384, 937; **VI**, 245; **VII**, 213, 359; **66**, 108; **69**, 44, 173. See also OS **VI**, 620; **65**, 146.

0-108 Acylation of Carboxylic Esters by Carboxylic Esters. The Claisen
and Dieckmann Condensations
Alkoxycarbonylalkyl-de-alkoxy-substitution

$$2R-CH_2-\underset{\underset{O}{\|}}{C}-OR' \xrightarrow{OEt^-} R-CH_2-\underset{\underset{O}{\|}}{C}-\overset{\overset{R}{|}}{CH}-\underset{\underset{O}{\|}}{C}-OR'$$

When carboxylic esters containing an α hydrogen are treated with a strong base such as sodium ethoxide, a condensation occurs to give a β-keto ester. This reaction is called the *Claisen condensation*. When it is carried out with a mixture of two different esters, each of which possesses an α hydrogen, a mixture of all four products is generally obtained and the reaction is seldom useful synthetically.[1691] However, if only one of the esters has an α hydrogen, the mixed reaction is frequently satisfactory. Among esters lacking α hydrogens

[1683]When phase transfer catalysts are used, O-acylation becomes the main reaction: Jones; Nokkeo; Singh *Synth. Commun.* **1977**, 7, 195.

[1684]Taylor; Hawks; McKillop *J. Am. Chem. Soc.* **1968**, 90, 2421.

[1685]See, for example, Skarżewski *Tetrahedron* **1989**, 45, 4593. For a review of triesters, see Newkome; Baker *Org. Prep. Proced. Int.* **1986**, 19, 117-144.

[1686]See House, Ref. 1411, pp. 762-765; House; Auerbach; Gall; Peet *J. Org. Chem.* **1973**, 38, 514.

[1687]Seebach; Weller; Protschuk; Beck; Hoekstra *Helv. Chim. Acta* **1981**, 64, 716.

[1688]Tirpak; Rathke *J. Org. Chem.* **1982**, 47, 5099.

[1689]For a review, see Hauser; Swamer; Adams *Org. React.* **1954**, 8, 59-196, pp. 98-106.

[1690]For example, see Rathke; Deitch *Tetrahedron Lett.* **1971**, 2953; Logue *J. Org. Chem.* **1974**, 39, 3455; Couffignal; Moreau *J. Organomet. Chem.* **1977**, 127, C65; Ohta; Shimabayashi; Hayakawa; Sumino; Okamoto *Synthesis* **1985**, 45; Hayden; Pucher; Griengl *Monatsh. Chem.* **1987**, 118, 415.

[1691]For a method of allowing certain crossed-Claisen reactions to proceed with good yields, see Tanabe *Bull. Chem. Soc. Jpn.* **1989**, 62, 1917.

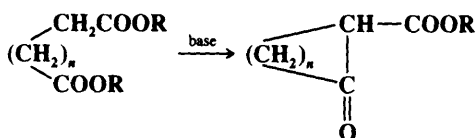(hence acting as the substrate ester) that are commonly used in this way are esters of aromatic acids, and ethyl carbonate and ethyl oxalate. Ethyl carbonate gives malonic esters.

$$EtO-\underset{\underset{O}{\|}}{C}-OEt \ + \ R-CH_2-\underset{\underset{O}{\|}}{C}-OR' \ \xrightarrow{OEt^-} \ EtO-\underset{\underset{O}{\|}}{C}-\overset{\overset{R}{|}}{C}H-\underset{\underset{O}{\|}}{C}-OR'$$

Ethyl formate serves to introduce the formyl group:

$$H-\underset{\underset{O}{\|}}{C}-OEt \ + \ R-CH_2-\underset{\underset{O}{\|}}{C}-OR' \ \xrightarrow{OEt^-} \ H-\underset{\underset{O}{\|}}{C}-\overset{\overset{R}{|}}{C}H-\underset{\underset{O}{\|}}{C}-OR'$$
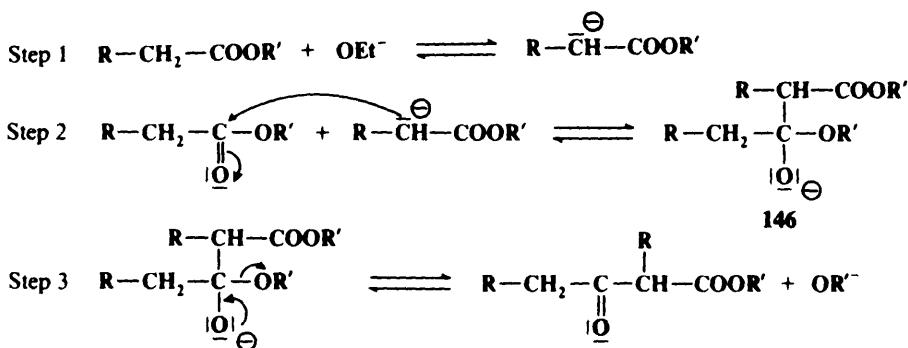
When the two ester groups involved in the condensation are in the same molecule, the product is a cyclic β-keto ester and the reaction is called the *Dieckmann condensation.*[1692]

$$(CH_2)_n \overset{CH_2COOR}{\underset{COOR}{<}} \xrightarrow{base} (CH_2)_n \overset{CH-COOR}{\underset{\underset{O}{\underset{\|}{C}}}{<}}$$

The Dieckmann condensation is most successful for the formation of 5-, 6-, and 7-membered rings. Yields for rings of 9 to 12 members are very low or nonexistent; larger rings can be closed with high-dilution techniques. Reactions in which large rings are to be closed are generally assisted by high dilution, since one end of the molecule has a better chance of finding the other end than of finding another molecule. Dieckmann condensation of unsymmetrical substrates can be made regioselective (unidirectional) by the use of solid-phase supports.[1693]

The mechanism of the Claisen and Dieckmann reactions is the ordinary tetrahedral mechanism,[1694] with one molecule of ester being converted to a nucleophile by the base and the other serving as the substrate.
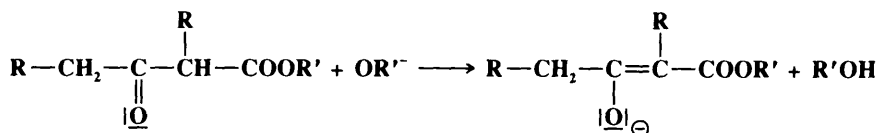
Step 1 $R-CH_2-COOR' \ + \ OEt^- \ \rightleftharpoons \ R-\overset{\ominus}{C}H-COOR'$

Step 2 $R-CH_2-\underset{\underset{|\underset{\cdot\cdot}{O}|}{\|}}{C}-OR' \ + \ R-\overset{\ominus}{C}H-COOR' \ \rightleftharpoons \ R-CH_2-\overset{\overset{R-CH-COOR'}{|}}{\underset{\underset{|\underset{\cdot\cdot}{O}|\ominus}{|}}{C}}-OR'$

146

Step 3 $R-CH_2-\overset{\overset{R-CH-COOR'}{|}}{\underset{\underset{|\underset{\cdot\cdot}{O}|\ominus}{|}}{C}}-OR' \ \rightleftharpoons \ R-CH_2-\overset{\overset{R}{|}}{\underset{\underset{|\underset{\cdot\cdot}{O}}{\|}}{C}}-CH-COOR' \ + \ OR'^-$

[1692]For a review, see Schaefer; Bloomfield *Org. React.* **1967**, *15*, 1-203.

[1693]Crowley; Rapoport *J. Org. Chem.* **1980**, *45*, 3215. For another method, see Yamada; Ishii; Kimura; Hosaka *Tetrahedron Lett.* **1981**, *22*, 1353.

[1694]There is evidence that, at least in some cases, an SET mechanism is involved: Ashby; Park *Tetrahedron Lett.* **1983**, 1667.

This reaction illustrates the striking difference in behavior between carboxylic esters on the one hand and aldehydes and ketones on the other. When a carbanion such as an enolate ion is added to the carbonyl group of an aldehyde or ketone (**6-41**), the H or R is not lost, since these groups are much poorer leaving groups than OR. Instead the intermediate similar to **146** adds a proton at the oxygen to give a hydroxy compound.
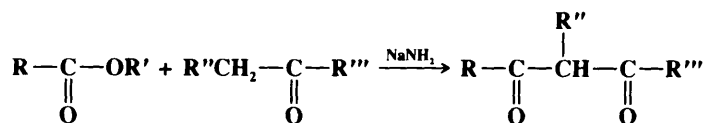
In contrast to **0-94** ordinary esters react quite well, that is, two Z groups are not needed. A lower degree of acidity is satisfactory because it is not necessary to convert the attacking ester entirely to its ion. Step 1 is an equilibrium that lies well to the left. Nevertheless, the small amount of enolate ion formed is sufficient to attack the readily approachable ester substrate. All the steps are equilibria. The reaction proceeds because the product is converted to its conjugate base by the base present (that is, a β-keto ester is a stronger acid than an alcohol):
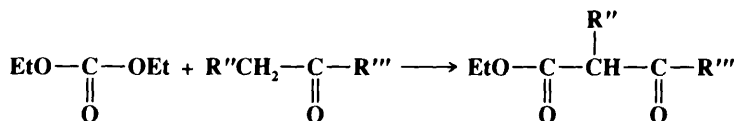
$$R-CH_2-\underset{\underset{\displaystyle |\underline{O}}{\|}}{C}-\underset{\underset{\displaystyle R}{|}}{CH}-COOR' + OR'^- \longrightarrow R-CH_2-\underset{\underset{\displaystyle |\underline{O}|_\ominus}{|}}{C}=\underset{\underset{\displaystyle R}{|}}{C}-COOR' + R'OH$$

The use of a stronger base, such as $NaNH_2$, NaH, or KH,[1695] often increases the yield. For some esters stronger bases *must* be used, since sodium ethoxide is ineffective. Among these are esters of the type $R_2CHCOOEt$, the products of which ($R_2CHCOCR_2COOEt$) lack an acidic hydrogen, so that they cannot be converted to enolate ions by sodium ethoxide.[1696]

OS **I**, 235; **II**, 116, 194, 272, 288; **III**, 231, 300, 379, 510; **IV**, 141; **V**, 288, 687, 989; **66**, 52.

0-109   Acylation of Ketones and Nitriles by Carboxylic Esters
         α-**Acylalkyl-de-alkoxy-substitution**

$$R-\underset{\underset{\displaystyle O}{\|}}{C}-OR' + R''CH_2-\underset{\underset{\displaystyle O}{\|}}{C}-R''' \xrightarrow{\text{NaNH}_2} R-\underset{\underset{\displaystyle O}{\|}}{C}-\underset{\underset{\displaystyle R''}{|}}{CH}-\underset{\underset{\displaystyle O}{\|}}{C}-R'''$$

Carboxylic esters can be treated with ketones to give β-diketones in a reaction that is essentially the same as **0-108.** The reaction is so similar that it is sometimes also called the Claisen condensation, though this usage is unfortunate. A fairly strong base, such as sodium amide or sodium hydride, is required. Yields can be increased by the catalytic addition of crown ethers.[1697] Esters of formic acid (R = H) give β-keto aldehydes. Ethyl carbonate gives β-keto esters.
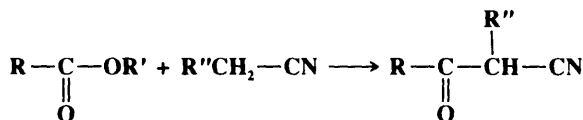
$$EtO-\underset{\underset{\displaystyle O}{\|}}{C}-OEt + R''CH_2-\underset{\underset{\displaystyle O}{\|}}{C}-R''' \longrightarrow EtO-\underset{\underset{\displaystyle O}{\|}}{C}-\underset{\underset{\displaystyle R''}{|}}{CH}-\underset{\underset{\displaystyle O}{\|}}{C}-R'''$$

[1695]Brown *Synthesis* **1975**, 326.
[1696]For a discussion, see Garst *J. Chem. Educ.* **1979**, *56*, 721.
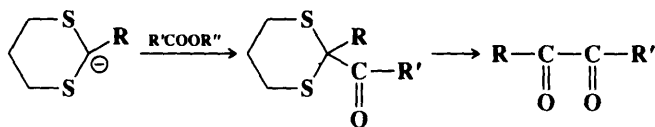[1697]Popik; Nikolaev *J. Org. Chem. USSR* **1989**, *25*, 1636.

β-Keto esters can also be obtained by treating the lithium enolates of ketones with methyl cyanoformate MeOCOCN[1698] (in this case CN is the leaving group) and by treating ketones with KH and diethyl dicarbonate $(EtOCO)_2O$.[1699]
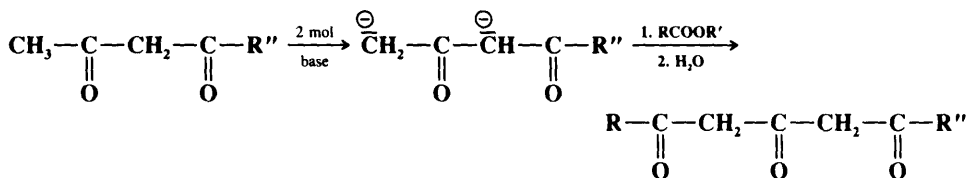
In the case of unsymmetrical ketones, the attack usually comes from the less highly substituted side, so that CH_3 is more reactive than RCH_2, and the R_2CH group rarely attacks. As in the case of **0-108**, this reaction has been used to effect cyclization, especially to prepare 5- and 6-membered rings. Nitriles are frequently used instead of ketones, the products being β-keto nitriles.

$$R-\underset{\underset{O}{\|}}{C}-OR' + R''CH_2-CN \longrightarrow R-\underset{\underset{O}{\|}}{C}-\underset{\overset{|}{R''}}{C}H-CN$$

Other carbanionic groups, such as acetylide ions, and ions derived from α-methylpyridines have also been used as nucleophiles. A particularly useful nucleophile is the methylsulfinyl carbanion $CH_3SOCH_2^-$,[1700] the conjugate base of dimethyl sulfoxide, since the β-keto sulfoxide produced can easily be reduced to a methyl ketone (p. 465). The methylsulfonyl carbanion $CH_3SO_2CH_2^-$, the conjugate base of dimethyl sulfone, behaves similarly,[1701] and the product can be similarly reduced. Certain carboxylic esters, acyl halides, and dimethylformamide acylate 1,3-dithianes[1702] (see **0-97**) to give, after oxidative hydrolysis with N-bromo- or N-chlorosuccinimide, α-keto aldehydes or α-diketones,[482] e.g.,

$$\langle\!\!\!\!\!\!\!\!\!\!\!\! \rangle \underset{S}{\overset{S}{\diagup}} R \xrightarrow{R'COOR''} \langle\!\!\!\!\!\!\!\!\!\!\!\! \rangle \underset{S}{\overset{S}{\diagup}} \underset{\underset{O}{\|}}{\overset{R}{\underset{}{C}}}-R' \longrightarrow R-\underset{\underset{O}{\|}}{C}-\underset{\underset{O}{\|}}{C}-R'$$

As in **0-94**, a ketone attacks with its second most acidic position if 2 moles of base are used. Thus, β-diketones have been converted to 1,3,5-triketones.[1703]

$$CH_3-\underset{\underset{O}{\|}}{C}-CH_2-\underset{\underset{O}{\|}}{C}-R'' \xrightarrow[\text{base}]{2 \text{ mol}} \overset{\ominus}{C}H_2-\underset{\underset{O}{\|}}{C}-\overset{\ominus}{C}H-\underset{\underset{O}{\|}}{C}-R'' \xrightarrow[\text{2. H}_2\text{O}]{\text{1. RCOOR'}}$$

$$R-\underset{\underset{O}{\|}}{C}-CH_2-\underset{\underset{O}{\|}}{C}-CH_2-\underset{\underset{O}{\|}}{C}-R''$$

Side reactions are condensation of the ketone with itself (**6-39**), of the ester with itself (**0-108**), and of the ketone with the ester but with the ester supplying the α position (**6-40**). The mechanism is the same as in **0-108**.[1704]

OS I, 238; II, 126, 200, 287, 487, 531; III, 17, 251, 291, 387, 829; IV, 174, 210, 461, 536; V, 187, 198, 439, 567, 718, 747; VI, 774; VII, 351.

[1698]Mander; Sethi *Tetrahedron Lett.* **1983**, *24*, 5425.
[1699]Hellou; Kingston; Fallis *Synthesis* **1984**, 1014.
[1700]Becker; Russell *J. Org. Chem.* **1963**, *28*, 1896; Corey; Chaykovsky *J. Am. Chem. Soc.* **1964**, *86*, 1639; Russell; Sabourin; Hamprecht *J. Org. Chem.* **1969**, *34*, 2339. For a review, see Durst *Adv. Org. Chem.* **1969**, *6*, 285-388, pp. 296-301.
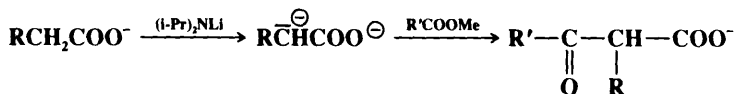[1701]Becker; Russell, Ref. 1700; Schank; Hasenfratz; Weber *Chem. Ber.* **1973**, *106*, 1107, House; Larson, Ref. 1421.
[1702]Corey; Seebach, Ref. 1501.
[1703]Miles; Harris; Hauser *J. Org. Chem.* **1965**, *30*, 1007.
[1704]Hill; Burkus; Hauser *J. Am. Chem. Soc.* **1959**, *81*, 602.

0-110 Acylation of Carboxylic Acid Salts
α-Carboxyalkyl-de-alkoxy-substitution

$$RCH_2COO^- \xrightarrow{\text{(i-Pr)}_2NLi} R\overset{\ominus}{C}HCOO^\ominus \xrightarrow{R'COOMe} R'-\underset{\underset{O}{\|}}{C}-\underset{\underset{R}{|}}{C}H-COO^-$$

We have previously seen (**0-96**) that dianions of carboxylic acids can be alkylated in the α position. These ions can also be acylated on treatment with a carboxylic ester[1705] to give salts of β-keto acids. As in **0-96**, the carboxylic acid can be of the form RCH_2COOH or $RR''CHCOOH$. Since β-keto acids are so easily converted to ketones (**2-40**), this is also a method for the preparation of ketones $R'COCH_2R$ and $R'COCHRR''$, where R' can be primary, secondary, or tertiary alkyl, or aryl. If the ester is ethyl formate, an α-formyl carboxylate salt (R' = H) is formed, which on acidification spontaneously decarboxylates into an aldehyde.[1706] This is a method, therefore, for achieving the conversion $RCH_2COOH \rightarrow RCH_2CHO$, and as such is an alternative to the reduction methods discussed in **0-83**. When the carboxylic acid is of the form $RR''CHCOOH$, better yields are obtained by acylating with acyl halides rather than esters.[1707]

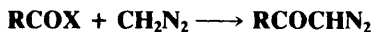**0-111** Preparation of Acyl Cyanides
Cyano-de-halogenation

$$RCOX + CuCN \longrightarrow RCOCN$$

Acyl cyanides[1708] can be prepared by treatment of acyl halides with copper cyanide. The mechanism is not known and might be free-radical or nucleophilic substitution. The reaction has also been accomplished with thallium(I) cyanide,[1709] with Me_3SiCN and an $SnCl_4$ catalyst,[1710] and with Bu_3SnCN,[1711] but these reagents are successful only when R = aryl or tertiary alkyl. KCN has also been used, along with ultrasound,[1712] as has NaCN with phase transfer catalysts.[1713]

OS **III**, 119.

0-112 Preparation of Diazo Ketones
Diazomethyl-de-halogenation

$$RCOX + CH_2N_2 \longrightarrow RCOCHN_2$$

The reaction between acyl halides and diazomethane is of wide scope and is the best way to prepare diazo ketones.[1714] Diazomethane must be present in excess or the HX produced will react with the diazo ketone (**0-71**). This reaction is the first step of the Arndt–Eistert synthesis (**8-8**). Diazo ketones can also be prepared directly from a carboxylic acid and diazomethane or diazoethane in the presence of dicyclohexylcarbodiimide.[1715]

OS **III**, 119; **VI**, 386, 613; **69**, 180.

[1705]Kuo; Yahner; Ainsworth *J. Am. Chem. Soc.* **1971**, *93*, 6321; Angelo *C.R. Seances Acad. Sci., Ser. C* **1973**, *276*, 293.

[1706]Pfeffer; Silbert *Tetrahedron Lett.* **1970**, 699; Koch; Kop *Tetrahedron Lett.* **1974**, 603.

[1707]Krapcho; Kashdan; Jahngen; Lovey *J. Org. Chem.* **1977**, *42*, 1189; Lion; Dubois *J. Chem. Res., (S)* **1980**, 44.

[1708]For a review of acyl cyanides, see Hünig; Schaller *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 36-49 [*Angew. Chem.* *94*, 1-15].

[1709]Taylor; Andrade; John; McKillop *J. Org. Chem.* **1978**, *43*, 2280.

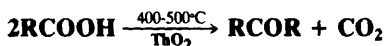[1710]Olah; Arvanaghi; Prakash *Synthesis* **1983**, 636.

[1711]Tanaka *Tetrahedron Lett.* **1980**, *21*, 2959. See also Tanaka; Koyanagi *Synthesis* **1981**, 973.

[1712]Ando; Kawate; Yamawaki; Hanafusa *Synthesis* **1983**, 637.

[1713]Koenig; Weber *Tetrahedron Lett.* **1974**, 2275. See also Sukata *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1085.

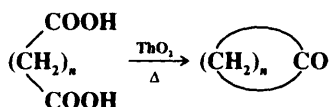[1714]For reviews, see Fridman; Ismagilova; Zalesov; Novikov *Russ. Chem. Rev.* **1972**, *41*, 371-389; Ried; Mengler *Fortshr. Chem. Forsch* **1965**, *5*, 1-88.

[1715]Hodson; Holt; Wall *J. Chem. Soc. C* **1970**, 971.

0-113   Ketonic Decarboxylation[1716]
Alkyl-de-hydroxylation

$$2RCOOH \xrightarrow[\text{ThO}_2]{\text{400-500°C}} RCOR + CO_2$$

Carboxylic acids can be converted to symmetrical ketones by pyrolysis in the presence of thorium oxide. In a mixed reaction, formic acid and another acid heated over thorium oxide give aldehydes. Mixed alkyl aryl ketones have been prepared by heating mixtures of ferrous salts.[1717] When the R group is large, the methyl ester rather than the acid can be decarbmethoxylated over thorium oxide to give the symmetrical ketone.

The reaction has been performed on dicarboxylic acids, whereupon cyclic ketones are obtained:
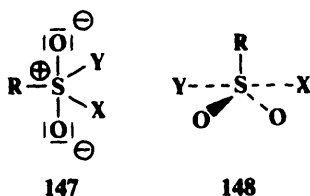

This process, called *Ruzicka cyclization*, is good for the preparation of rings of 6 and 7 members and, with lower yields, of C_8 and C_{10} to C_{30} cyclic ketones.[1718]

Not much work has been done on the mechanism of this reaction. However, a free-radical mechanism has been suggested on the basis of a thorough study of all the side products.[1719]

OS **I**, 192; **II**, 389; **IV**, 854; **V**, 589. Also see OS **IV**, 55, 560.

Nucleophilic Substitution at a Sulfonyl Sulfur Atom[1720]

Nucleophilic substitution at RSO_2X is similar to attack at RCOX. Many of the reactions are essentially the same, though sulfonyl halides are less reactive than halides of carboxylic acids.[1721] The mechanisms[1722] are not identical, because a "tetrahedral" intermediate in this case (**147**) would have five groups on the central atom. Though this is possible (since sulfur

147   **148**

can accommodate up to 12 electrons in its valence shell) it seems more likely that these mechanisms more closely resemble the SN2 mechanism, with a trigonal bipyramidal transition state (**148**). There are two major experimental results leading to this conclusion.

[1716]For a review, see Kwart; King, in Patai, Ref. 197, pp. 362-370.

[1717]Granito; Schultz *J. Org. Chem.* **1963**, *28*, 879.

[1718]See, for example, Ruzicka; Stoll; Schinz *Helv. Chim. Acta* **1926**, *9*, 249, **1928**, *11*, 1174; Ruzicka; Brugger; Seidel; Schinz *Helv. Chim. Acta* **1928**, *11*, 496.

[1719]Hites; Biemann *J. Am. Chem. Soc.* **1972**, *94*, 5772. See also Bouchoule; Blanchard; Thomassin *Bull. Soc. Chim. Fr.* **1973**, 1773.

[1720]For a review of mechanisms of nucleophilic substitutions at di-, tri-, and tetracoordinated sulfur atoms, see Ciuffarin; Fava *Prog. Phys. Org. Chem.* **1968**, *6*, 81-109.

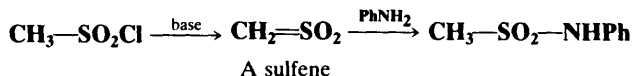[1721]For a comparative reactivity study, see Hirata; Kiyan; Miller *Bull. Soc. Chim. Fr.* **1988**, 694.

[1722]For a review of mechanisms of nucleophilic substitution at a sulfonyl sulfur, see Gordon; Maskill; Ruasse *Chem. Soc. Rev.* **1989**, *18*, 123-151.

1. The stereospecificity of this reaction is more difficult to determine than that of nucleophilic substitution at a saturated carbon, where chiral compounds are relatively easy to prepare, but it may be recalled (p. 98) that optical activity is possible in a compound of the form RSO_2X if one oxygen is ^{16}O and the other ^{18}O. When a sulfonate ester possessing this type of chirality was converted to a sulfone with a Grignard reagent (**0-119**), inversion of configuration was found.[1723] This is not incompatible with an intermediate such as **147** but it is also in good accord with an SN2-like mechanism with backside attack.

2. More direct evidence against **147** (though still not conclusive) was found in an experiment involving acidic and basic hydrolysis of aryl arenesulfonates, where it has been shown by the use of ^{18}O that an intermediate like **147** is not reversibly formed, since ester recovered when the reaction was stopped before completion contained no ^{18}O when the hydrolysis was carried out in the presence of labeled water.[1724]

Other evidence favoring the SN2-like mechanism comes from kinetics and substituent effects.[1725] However, evidence for the mechanism involving **147** is that the rates did not change much with changes in the leaving group[1726] and the ρ values were large, indicating that a negative charge builds up in the transition state.[1727]

In certain cases in which the substrate carries an α hydrogen, there is strong evidence[1728] that at least some of the reaction takes place by an elimination–addition mechanism (E1cB, similar to the one shown on p. 382), going through a *sulfene* intermediate,[1729] e.g., the reaction between methanesulfonyl chloride and aniline.

$$CH_3{-}SO_2Cl \xrightarrow{\text{base}} CH_2{=}SO_2 \xrightarrow{\text{PhNH}_2} CH_3{-}SO_2{-}NHPh$$
A sulfene

In the special case of nucleophilic substitution at a sulfonic ester RSO_2OR', where R' is alkyl, $R'{-}O$ cleavage is much more likely than $S{-}O$ cleavage because the OSO_2R group is such a good leaving group (p. 353).[1730] Many of these reactions have been considered previously (e.g., **0-4**, **0-14**, etc.), because they are nucleophilic substitutions at an alkyl carbon atom and not at a sulfur atom. However, when R' is aryl, then the $S{-}O$ bond is much more likely to cleave because of the very low tendency aryl substrates have for nucleophilic substitution.[1731]

[1723]Sabol; Andersen *J. Am. Chem. Soc.* **1969**, *91*, 3603. See also Jones; Cram *J. Am. Chem. Soc.* **1974**, *96*, 2183.

[1724]Christman; Oae *Chem. Ind. (London)* **1959**, 1251; Oae; Fukumoto; Kiritani *Bull. Chem. Soc. Jpn.* **1963**, *36*, 346; Kaiser; Zaborsky *J. Am. Chem. Soc.* **1968**, *90*, 4626.

[1725]See, for example, Robertson; Rossall *Can. J. Chem.* **1971**, *49*, 1441; Rogne *J. Chem. Soc. B* **1971**, 1855, *J. Chem. Soc., Perkin Trans 2.* **1972**, 489; Gnedin; Ivanov; Spryskov *J. Org. Chem. USSR* **1976**, *12*, 1894; Banjoko; Okwuiwe *J. Org. Chem.* **1980**, *45*, 4966; Ballistreri; Cantone; Maccarone; Tomaselli; Tripolone *J. Chem. Soc., Perkin Trans. 2* **1981**, 438; Suttle; Williams *J. Chem. Soc., Perkin Trans. 2* **1983**, 1563; D'Rozario; Smyth; Williams *J. Am. Chem. Soc.* **1984**, *106*, 5027; Lee; Kang; Lee *J. Am. Chem. Soc.* **1987**, *109*, 7472; Arcoria; Ballistreri; Spina; Tomaselli; Maccarone *J. Chem. Soc., Perkin Trans. 2* **1988**, 1793; Gnedin; Ivanov; Shchukina *J. Org. Chem. USSR* **1988**, *24*, 731.

[1726]Ciuffarin; Senatore; Isola *J. Chem. Soc., Perkin Trans. 2* **1972**, 468.

[1727]Ciuffarin; Senatore *Tetrahedron Lett.* **1974**, 1635.

[1728]For a review, see Opitz *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 107-123 [*Angew. Chem. 79*, 161-177]. See also King; Lee *J. Am. Chem. Soc.* **1969**, *91*, 6524; Skrypnik; Bezrodnyi *Doklad. Chem.* **1982**, *266*, 341; Farng; Kice *J. Am. Chem. Soc.* **1981**, *103*, 1137; Thea; Guanti; Hopkins; Williams *J. Am. Chem. Soc.* **1982**, *104*, 1128, *J. Org. Chem.* **1985**, *50*, 5592; Bezrodnyi; Skrypnik *J. Org. Chem. USSR* **1984**, *20*, 1660, 2349; King; Skonieczny *Tetrahedron Lett.* **1987**, *28*, 5001; Pregel; Buncel *J. Chem. Soc., Perkin Trans. 2* **1991**, 307.
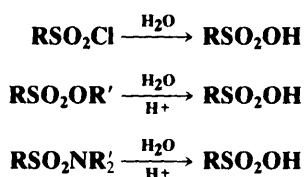
[1729]For reviews of sulfenes, see King *Acc. Chem. Res.* **1975**, *8*, 10-17; Nagai; Tokura *Int. J. Sulfur Chem., Part B* **1972**, 207-216; Truce; Liu *Mech. React. Sulfur Compd.* **1969**, *4*, 145-154; Opitz *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 107-123 [*Angew. Chem. 79*, 161-177]; Wallace *Q. Rev. Chem. Soc.* **1966**, *20*, 67-74.

[1730]A number of sulfonates in which R contains α branching, e.g., $Ph_2C(CF_3)SO_2OR'$, can be used to ensure that there will be no S—O cleavage: Netscher; Prinzbach *Synthesis* **1987**, 683.

[1731]See, for example, Oae; Fukumoto; Kiritani *Bull. Chem. Soc. Jpn.* **1963**, *36*, 346; Tagaki; Kurusu; Oae *Bull. Chem. Soc. Jpn.* **1969**, *42*, 2894.

The order of nucleophilicity toward a sulfonyl sulfur has been reported as OH⁻ > RNH₂ > N₃⁻ > F⁻ > AcO⁻ > Cl⁻ > H₂O > I⁻.[1732] This order is similar to that at a carbonyl carbon (p. 351). Both of these substrates can be regarded as relatively hard acids, compared to a saturated carbon which is considerably softer and which has a different order of nucleophilicity (p. 350).
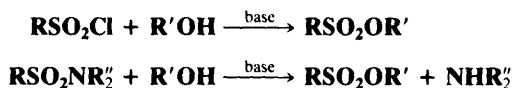
0-114 Attack by OH. Hydrolysis of Sulfonic Acid Derivatives
S-Hydroxy-de-chlorination, etc.

$$RSO_2Cl \xrightarrow{H_2O} RSO_2OH$$

$$RSO_2OR' \xrightarrow[H+]{H_2O} RSO_2OH$$

$$RSO_2NR'_2 \xrightarrow[H+]{H_2O} RSO_2OH$$

Sulfonyl chlorides as well as esters and amides of sulfonic acids can be hydrolyzed to the corresponding acids. Sulfonyl chlorides can by hydrolyzed with water or with an alcohol in the absence of acid or base. Basic catalysis is also used, though of course the salt is the product obtained. Esters are readily hydrolyzed, many with water or dilute alkali. This is the same reaction as **0-4**, and usually involves R'—O cleavage, except when R' is aryl. However, in some cases retention of configuration has been shown at alkyl R', indicating S—O cleavage in these cases.[1733] Sulfonamides are generally not hydrolyzed by alkaline treatment, not even with hot concentrated alkali. Acids, however, do hydrolyze them, though less readily than they do sulfonyl halides or sulfonic esters. Of course, ammonia or the amine appears as the salt. However, sulfonamides can be hydrolyzed with base if the solvent is HMPA.[1734]

OS **I**, 14; **II**, 471; **III**, 262;**IV**, 34; **V**, 406; **VI**, 652, 727. Also see OS **V**, 673; **VI**, 1016.

0-115 Attack by OR. Formation of Sulfonic Esters
S-Alkoxy-de-chlorination, etc.

$$RSO_2Cl + R'OH \xrightarrow{base} RSO_2OR'$$

$$RSO_2NR''_2 + R'OH \xrightarrow{base} RSO_2OR' + NHR''_2$$

Sulfonic esters are most frequently prepared by treatment of the corresponding halides with alcohols in the presence of a base. The method is much used for the conversion of alcohols to tosylates, brosylates, and similar sulfonic esters. Both R and R' may be alkyl or aryl. The base is often pyridine, which functions as a nucleophilic catalyst,[1735] as in the similar alcoholysis of carboxylic acyl halides (**0-20**). Primary alcohols react the most rapidly, and it is often possible to sulfonate selectively a primary OH group in a molecule that also contains secondary or tertiary OH groups. The reaction with sulfonamides has been much less frequently used and is limited to N,N-disubstituted sulfonamides; that is, R" may not be hydrogen. However, within these limits it is a useful reaction. The nucleophile in this case is actually R'O⁻. However, R" may be hydrogen (as well as alkyl) if the nucleophile is a phenol, so that the product is RSO₂OAr. Acidic catalysts are used in this case.[1736] Sulfonic acids have been converted directly to sulfonates by treatment with triethyl or trimethyl

[1732]Kice; Kasperek; Patterson *J. Am. Chem. Soc.* **1969**, *91*, 5516; Rogne *J. Chem. Soc. B* **1970**, 1056; Ref. 330.
[1733]Chang *Tetrahedron Lett.* **1964**, 305.
[1734]Cuvigny; Larchevêque *J. Organomet. Chem.* **1974**, *64*, 315.
[1735]Rogne *J. Chem. Soc. B* **1971**, 1334. See also Litvinenko; Shatskaya; Savelova *Doklad. Chem.* **1982**, *265*, 199.
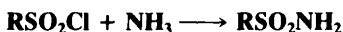[1736]Klamann; Fabienke *Chem. Ber.* **1960**, *93*, 252.

orthoformate $HC(OR)_3$, without catalyst or solvent;[1737] and with a trialkyl phosphite $P(OR)_3$.[1738]

OS **I**, 145; **III**, 366; **IV**, 753; **VI**, 56, 482, 587, 652; **VII**, 117; **66**, 1; **68**, 188. Also see OS **IV**, 529; **VI**, 324, 757; **VII**, 495; **66**, 185.

0-116   Attack by Nitrogen. Formation of Sulfonamides
S-Amino-de-chlorination

$$RSO_2Cl + NH_3 \longrightarrow RSO_2NH_2$$

The treatment of sulfonyl chlorides with ammonia or amines is the usual way of preparing sulfonamides. Primary amines give N-alkyl sulfonamides, and secondary amines give N,N-dialkyl sulfonamides. The reaction is the basis of the *Hinsberg test* for distinguishing between primary, secondary, and tertiary amines. N-Alkyl sulfonamides, having an acidic hydrogen, are soluble in alkali, while N,N-dialkyl sulfonamides are not. Since tertiary amines are usually recovered unchanged, primary, secondary, andtertiary amines can be told apart. However, the test is limited for at least two reasons.[1739] (1) Many N-alkyl sulfonamides in which the alkyl group has six or more carbons are insoluble in alkali, despite their acidic hydrogen,[1740] so that a primary amine may appear to be a secondary amine. (2) If the reaction conditions are not carefully controlled, tertiary amines may not be recovered unchanged.[1739]

A primary or a secondary amine can be protected by reaction with phenacyl-sulfonyl chloride ($PhCOCH_2SO_2Cl$) to give a sulfonamide $RNHSO_2CH_2COPh$ or $R_2NSO_2CH_2COPh$.[1741] The protecting group can be removed when desired with zinc and acetic acid. Sulfonyl chlorides react with azide ion to give sulfonyl azides RSO_2N_3.[1742]

OS **IV**, 34, 943; **V**, 39, 179, 1055; **VI**, 78, 652; **VII**, 501; **69**, 158. See also OS **VI**, 788.

0-117   Attack by Halogen. Formation of Sulfonyl Halides
S-Halo-de-hydroxylation

$$RSO_2OH + PCl_5 \longrightarrow RSO_2Cl$$

This reaction, parallel with **0-74**, is the standard method for the preparation of sulfonyl halides. Also used are PCl_3 and $SOCl_2$, and sulfonic acid salts can also serve as substrates. Sulfonyl bromides and iodides have been prepared from sulfonyl hydrazides ($ArSO_2NHNH_2$, themselves prepared by **0-116**) by treatment with bromine or iodine.[1743] Sulfonyl fluorides are generally prepared from the chlorides, by halogen exchange.[1744]

OS **I**, 84; **IV**, 571, 693, 846, 937; **V**, 196. See also OS **VII**, 495.

0-118   Attack by Hydrogen. Reduction of Sulfonyl Chlorides
S-Hydro-de-chlorination or **S-Dechlorination**

$$2RSO_2Cl + Zn \longrightarrow (RSO_2)_2Zn \xrightarrow{H^+} 2RSO_2H$$

Sulfinic acids can be prepared by reduction of sulfonyl chlorides. Though mostly done on aromatic sulfonyl chlorides, the reaction has also been applied to alkyl compounds. Besides

[1737]Padmapriya; Just; Lewis *Synth. Commun.* **1985**, *15*, 1057.
[1738]Karaman; Leader; Goldblum; Breuer *Chem. Ind. (London)* **1987**, 857.
[1739]For directions for performing and interpreting the Hinsberg test, see Gambill; Roberts; Shechter *J. Chem. Educ.* **1972**, *49*, 287.
[1740]Fanta; Wang *J. Chem. Educ.* **1964**, *41*, 280.
[1741]Hendrickson; Bergeron *Tetrahedron Lett.* **1970**, 345.
[1742]For an example, see Regitz; Hocker; Liedhegener *Org. Synth. V*, 179.
[1743]Poshkus; Herweh; Magnotta *J. Org. Chem.* **1963**, *28*, 2766; Litvinenko; Dadali; Savelova; Krichevtsova *J. Gen. Chem. USSR* **1964**, *34*, 3780.
[1744]See Bianchi; Cate *J. Org. Chem.* **1977**, *42*, 2031, and references cited therein.

zinc, sodium sulfite, hydrazine, sodium sulfide, and other reducing agents have been used. For reduction of sulfonyl chlorides to thiols, see **9-54.**

OS **I,** 7, 492; **IV,** 674.

0-119   Attack by Carbon. Preparation of Sulfones
S-Aryl-de-chlorination

$$ArSO_2Cl + Ar'MgX \longrightarrow ArSO_2Ar'$$

Grignard reagents convert aromatic sulfonyl chlorides or aromatic sulfonates to sulfones. Aromatic sulfonates have also been converted to sulfones with organolithium compounds.[1745] Vinylic and allylic sulfones have been prepared by treatment of sulfonyl chlorides with a vinylic or allylic stannane and a palladium–complex catalyst.[1746] Alkynyl sulfones can be prepared by treatment of sulfonyl chlorides with trimethylsilylalkynes, with an $AlCl_3$ catalyst.[1747]

$$ArSO_2Cl + RC\equiv CSiMe_3 \xrightarrow{\text{AlCl}_3} ArSO_2{-}C\equiv CR$$
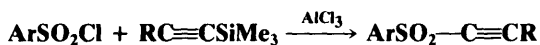
OS **67,** 149.

[1745]Baarschers *Can. J. Chem.* **1976,** *54,* 3056.
[1746]Labadie *J. Org. Chem.* **1989,** *54,* 2496.
[1747]See Waykole; Paquette *Org. Synth.* *67,* 149.