12

ALIPHATIC ELECTROPHILIC SUBSTITUTION

In Chapter 11 it was pointed out that the most important leaving groups in electrophilic substitution are those that can best exist with an outer shell that is deficient in a pair of electrons. For aromatic systems the most common leaving group is the proton. The proton is also a leaving group in aliphatic systems, but the reactivity depends on the acidity. Protons in saturated alkanes are very unreactive, but electrophilic substitutions are often easily carried out at more acidic positions, e.g., α to a carbonyl group, or at an alkynyl position (RC≡CH). Since metallic ions are easily able to bear positive charges, we might expect that organometallic compounds would be especially susceptible to electrophilic substitution, and this is indeed the case.[1] Another important type of electrophilic substitution, known as *anionic cleavage*, involves the breaking of C—C bonds; in these reactions there are carbon leaving groups (**2-40** to **2-46**). A number of electrophilic substitutions at a nitrogen atom are treated at the end of the chapter.

Since a carbanion is what remains when a positive species is removed from a carbon atom, the subject of carbanion structure and stability (Chapter 5) is inevitably related to the material in this chapter. So is the subject of very weak acids and very strong bases (Chapter 8), because the weakest acids are those in which the hydrogen is bonded to carbon.

MECHANISMS

For aliphatic electrophilic substitution, we can distinguish at least four possible major mechanisms,[2] which we call SE1, SE2 (front), SE2 (back), and SEi. The SE1 is unimolecular; the other three are bimolecular.

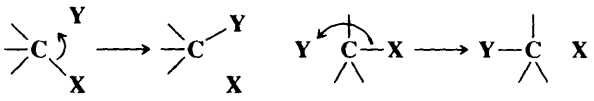
Bimolecular Mechanisms. SE2 and SEi

The bimolecular mechanisms for electrophilic aliphatic substitution are analogous to the SN2 mechanism in that the new bond forms as the old one breaks. However, in the SN2

[1]For books on the preparation and reactions of organometallic compounds, see Hartley; Patai *The Chemistry of the Metal–Carbon Bond*, 5 vols.; Wiley: New York, 1984-1990; Haiduc; Zuckerman *Basic Organometallic Chemistry*; Walter de Gruyter: New York, 1985; Negishi *Organometallics in Organic Synthesis*; Wiley: New York, 1980; Aylett *Organometallic Compounds*, 4th ed., vol. 1, pt. 2; Chapman and Hall: New York, 1979; Coates; Green; Wade *Organometallic Compounds*, 3rd ed., 2 vols.; Methuen: London, 1967-1968; Eisch *The Chemistry of Organometallic Compounds*; Macmillan: New York, 1967. For reviews, see Maslowsky *Chem. Soc. Rev.* **1980,** *9*, 25-40, and in Tsutsui *Characterization of Organometallic Compounds*; Wiley: New York, 1969-1971, the articles by Cartledge; Gilman, pt. 1, pp. 1-33, and by Reichle, pt. 2, pp. 653-826.

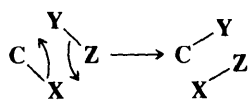
[2]For monographs, see Abraham *Comprehensive Chemical Kinetics*, Bamford; Tipper, Eds., vol. 12; Elsevier: New York, 1973; Jensen; Rickborn *Electrophilic Substitution of Organomercurials*; McGraw-Hill: New York, 1968; Reutov; Beletskaya *Reaction Mechanisms of Organometallic Compounds*; North-Holland Publishing Company: Amsterdam, 1968. For reviews, see Abraham; Grellier, in Hartley; Patai, Ref. 1, vol. 2, pp. 25-149; Beletskaya *Sov. Sci. Rev., Sect. B* **1979,** *1*, 119-204; Reutov *Pure Appl. Chem.* **1978,** *50*, 717-724, **1968,** *17*, 79-94, *Tetrahedron*, **1978,** *34*, 2827-2855, *J. Organomet. Chem.* **1975,** *100*, 219-235, *Russ. Chem. Rev.* **1967,** *36*, 163-174, *Fortschr. Chem. Forsch.* **1967,** *8*, 61-90; Matteson *Organomet. Chem. Rev., Sect. A* **1969,** *4*, 263-305; Dessy; Kitching *Adv. Organomet. Chem.* **1966,** *4*, 267-351.

mechanism the incoming group brings with it a pair of electrons, and this orbital can overlap with the central carbon only to the extent that the leaving group takes away *its* electrons; otherwise the carbon would have more than eight electrons at once in its outer shell. Since electron clouds repel, this means also that the incoming group attacks backside, at a position 180° from the leaving group, resulting in inversion of configuration. When the attacking species is an electrophile, which brings to the substrate only a vacant orbital, it is obvious that this consideration does not apply and we cannot a priori predict from which direction the attack must come. We can imagine two main possibilities: attack from the front, which we call SE2 (front), and attack from the rear, which we call SE2 (back). The possibilities can be pictured (charges not shown):



SE2 (front) SE2 (back)

Both the SE2 (front) and SE2 (back) mechanisms are designated D_EA_E in the IUPAC system. With substrates in which we can distinguish the possibility, the former mechanism should result in retention of configuration and the latter in inversion. When the electrophile attacks from the front, there is a third possibility. A portion of the electrophile may assist in the removal of the leaving group, forming a bond with it at the same time that the new C—Y bond is formed:



SEi

This mechanism, which we call the SEi mechanism[3] (IUPAC designation: cyclo-$D_EA_ED_nA_n$), also results in retention of configuration.[4] Plainly, where a second-order mechanism involves this kind of internal assistance, backside attack is impossible.

It is evident that these three mechanisms are not easy to distinguish. All three give second-order kinetics, and two result in retention of configuration.[5] In fact, although much work has been done on this question, there are few cases in which we can unequivocally say that one of these three and not another is actually taking place. Clearly, a study of the stereochemistry can distinguish between SE2 (back) on the one hand and SE2 (front) or SEi on the other. Many such investigations have been made. In the overwhelming majority of second-order electrophilic substitutions, the result has been retention of configuration or some other indication of frontside attack, indicating an SE2 (front) or SEi mechanism. For example, when *cis*-**1** was treated with labeled mercuric chloride, the **2** produced was 100% cis. The bond between the mercury and the ring must have been broken (as well as the other Hg—C bond), since each of the products contained about half of the labeled mercury.[6] Another indication of frontside attack is that second-order electrophilic substitutions proceed very easily at *bridgehead* carbons (see p. 296).[7] Still another indication is the behavior of

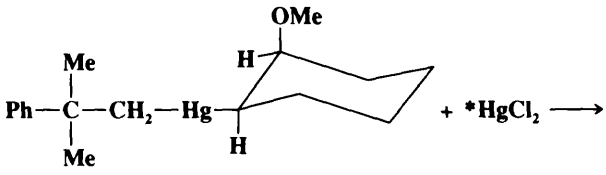
[3]The names for these mechanisms vary throughout the literature. For example, the SEi mechanism has also been called the SF2, the SE2 (closed), and the SE2 (cyclic) mechanism. The original designations, SE1, SE2, etc., were devised by the Hughes-Ingold school.

[4]It has been contended that the SEi mechanism violates the principle of conservation of orbital symmetry (p. 846), and that the SE2 (back) mechanism partially violates it: Slack; Baird *J. Am. Chem. Soc.* **1976,** *98*, 5539.

[5]For a review of the stereochemistry of reactions in which a carbon-transition metal σ bond is formed or broken, see Flood *Top. Stereochem.* **1981,** *12*, 37-117. See also Ref. 10.

[6]Winstein; Traylor; Garner *J. Am. Chem. Soc.* **1955,** *77*, 3741.

[7]Winstein; Traylor *J. Am. Chem. Soc.* **1956,** *78*, 2597; Schöllkopf *Angew. Chem.* **1960,** *72*, 147-159. For a discussion, see Fort; Schleyer *Adv. Alicyclic Chem.* **1966,** *1*, 283-370, pp. 353-370.



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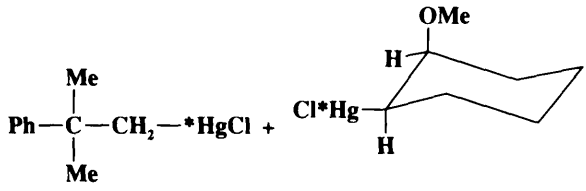


2

neopentyl as a substrate. SN2 reactions at neopentyl are extremely slow (p. 339), because attack from the rear is blocked. The fact that neopentyl systems undergo electophilic substitution only slightly more slowly than ethyl[8] is further evidence for frontside attack. One final elegant experiment may be noted. The compound di-*sec*-butylmercury was prepared with one *sec*-butyl group optically active and the other racemic.[9] This was accomplished by treatment of optically active *sec*-butylmercuric bromide with racemic *sec*-butylmagnesium bromide. The di-*sec*-butyl compound was then treated with mercuric bromide to give 2 moles of *sec*-butylmercuric bromide. The steric course of the reaction could then be predicted by the following analysis, assuming that the bonds between the mercury and each carbon have a 50% chance of breaking.

If inversion,

attack here ⟶ *S* **RHgX** + *RS* **RHgX**

R ↓ *RS*

R—Hg—R

↑

attack here ⟶ *R* **RHgX** + *RS* **RHgX**

The sum is a racemic mixture

If retention,

attack here ⟶ *R* **RHgX** + *RS* **RHgX**

R ↓ *RS*

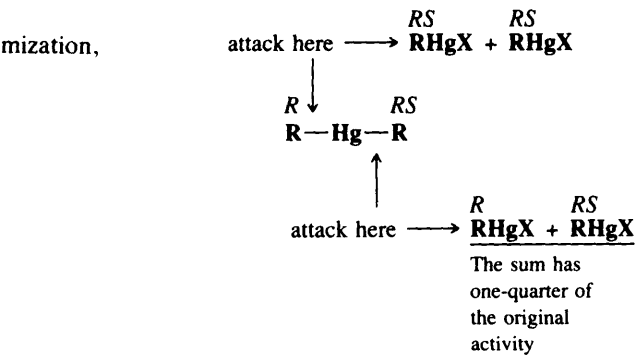
R—Hg—R

↑

attack here ⟶ *R* **RHgX** + *RS* **RHgX**

The sum has one-half of the original activity

[8]Hughes; Volger *J. Chem. Soc.* **1961,** 2359.
[9]Jensen *J. Am. Chem. Soc.* **1960,** *82,* 2469; Ingold *Helv. Chim. Acta* **1964,** *47,* 1191.



The original activity referred to is the activity of the optically active *sec*-butylmercuric bromide used to make the dialkyl compound. The actual result was that, under several different sets of conditions, the product had one-half of the original activity, demonstrating retention of configuration.

However, inversion of configuration has been found in certain cases, demonstrating that the SE2 (back) mechanism can take place. For example, the reaction of optically active *sec*-butyltrineopentyltin with bromine (**2-30**) gives inverted *sec*-butyl bromide.[10] A number of

$$\textit{sec}\text{-}\mathbf{BuSnR_3} + \mathbf{Br_3} \longrightarrow \textit{sec}\text{-}\mathbf{BuBr} \qquad \mathbf{R} = \text{neopentyl}$$

other organometallic compounds have also been shown to give inversion when treated with halogens,[11] although others do not.[12] So far, no inversion has been found with an organomercury substrate. It may be that still other examples of backside attack exist[13] but have escaped detection because of the difficulty in preparing compounds with a configurationally stable carbon–metal bond. Compounds that are chiral because of an asymmetric carbon at which a carbon–metal bond is located[13a] are often difficult to resolve and once resolved are often easily racemized. The resolution has been accomplished most often with organomercury compounds,[14] and most stereochemical investigations have therefore been made with these substrates. Only a few optically active Grignard reagents have been prepared[15] (i.e., in which the only asymmetric center is the carbon bonded to the magnesium). Because of this, the steric course of electrophilic substitutions at the C—Mg bond has not often been determined. However, in one such case, the reaction of both the exo and endo isomers of the 2-norbornyl Grignard reagent with $HgBr_2$ (to give 2-norbornylmercuric bromide) has

[10]Jensen; Davis *J. Am. Chem. Soc.* **1971,** *93*, 4048. For a review of the stereochemistry of SE2 reactions with organotin substrates, see Fukuto; Jensen *Acc. Chem. Res.* **1983,** *16*, 177-184.

[11]For example, See Applequist; Chmurny *J. Am. Chem. Soc.* **1967,** *89*, 875; Glaze; Selman; Ball; Bray *J. Org. Chem.* **1969,** *34*, 641; Brown; Lane *Chem. Commun.* **1971,** 521; Jensen; Madan; Buchanan *J. Am. Chem. Soc.* **1971,** *93*, 5283; Espenson; Williams *J. Am. Chem. Soc.* **1974,** *96*, 1008; Bock; Boschetto; Rasmussen; Demers; Whitesides *J. Am. Chem. Soc.* **1974,** *96*, 2814; Magnuson; Halpern; Levitin; Vol'pin *J. Chem. Soc., Chem. Commun.* **1978,** 44.

[12]See, for example, Rahm; Pereyre *J. Am. Chem. Soc.* **1977,** *99*, 1672; McGahey; Jensen *J. Am. Chem. Soc.* **1979,** *101*, 4397. Electrophilic bromination of certain organotin compounds was found to proceed with inversion favored for equatorial and retention for axial C—Sn bonds: Olszowy; Kitching *Organometallics* **1984,** *3*, 1676. For a similar result, see Rahm; Grimeau; Pereyre *J. Organomet. Chem.* **1985,** *286*, 305.

[13]Cases of inversion involving replacement of a metal by a metal have been reported. See Tada; Ogawa *Tetrahedron Lett.* **1973,** 2639; Fritz; Espenson; Williams; Molander *J. Am. Chem. Soc.* **1974,** *96*, 2378; Gielen; Fosty *Bull. Soc. Chim. Belg.* **1974,** *83*, 333; Bergbreiter; Rainville *J. Organomet. Chem.* **1976,** *121*, 19.

[13a]For a monograph, see Sokolov *Chirality and Optical Activity in Organometallic Compounds*; Gordon and Breach: New York, 1990.

[14]Organomercury compounds were first resolved by three groups: Jensen; Whipple; Wedegaertner; Landgrebe *J. Am. Chem. Soc.* **1959,** *81*, 1262; Charman; Hughes; Ingold *J. Chem. Soc.* **1959,** 2523, 2530; Reutov; Uglova *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1959,** 735.

[15]This was done first by Walborsky; Young *J. Am. Chem. Soc.* **1964,** *86*, 3288.

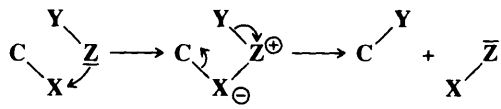
been shown to proceed with retention of configuration.[16] It is likely that inversion takes place only when steric hindrance prevents frontside attack and when the electrophile does not carry a Z group (p. 570).

The SE2 (back) mechanism can therefore be identified in certain cases (if inversion of configuration is found), but it is plain that stereochemical investigations cannot distinguish between the SE2 (front) and the SEi mechanisms and that, in the many cases where configurationally stable substrates cannot be prepared, such investigations are of no help at all in distinguishing among all three of the second-order mechanisms. Unfortunately, there are not many other methods that lead to unequivocal conclusions. One method that has been used in an attempt to distinguish between the SEi mechanism on the one hand and the SE2 pathways on the other involves the study of salt effects on the rate. It may be recalled (p. 358) that reactions in which neutral starting molecules acquire charges in the transition state are aided by an increasing concentration of added ions. Thus the SEi mechanism would be less influenced by salt effects than would either of the SE2 mechanisms. On this basis Abraham and co-workers[17] concluded that the reactions $R_4Sn + HgX_2 \rightarrow RHgX + R_3SnX$ (X = Cl or I) take place by SE2 and not by SEi mechanisms. Similar investigations involve changes in solvent polarity[18] (see also p. 580). In the case of the reaction

$$\textit{sec}\text{-}\mathbf{BuSnR_2R'} + \mathbf{Br_2} \longrightarrow \textit{sec}\text{-}\mathbf{BuBr}$$

(where R = R′ = iso-Pr and R = iso-Pr, R′ = neopentyl), the use of polar solvents gave predominant inversion, while nonpolar solvents gave predominant retention.[19]

On the basis of evidence from reactivity studies, it has been suggested[20] that a variation of the SEi mechanism is possible in which the group Z becomes attached to X before the latter becomes detached:



This process has been called the SEC[20] or SE2 (co-ord)[21] mechanism (IUPAC designation A_n + cyclo-$D_EA_ED_n$).

It has been shown that in certain cases (e.g., $Me_4Sn + I_2$) the reactants in an SE2 reaction, when mixed, give rise to an immediate charge-transfer spectrum (p. 79), showing that an electron donor–acceptor (EDA) complex has been formed.[22] In these cases it is likely that the EDA complex is an intermediate in the reaction.

The SE1 Mechanism

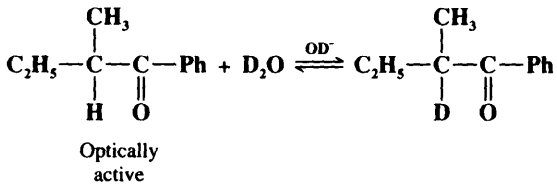
The SE1 mechanism is analogous to the SN1. It involves two steps—a slow ionization and a fast combination.

Step 1 $\mathbf{R{-}X} \xrightarrow{\text{slow}} \mathbf{\overline{R}^- + X^+}$

Step 2 $\mathbf{\overline{R}^- + Y^+} \longrightarrow \mathbf{R{-}Y}$

[16]Jensen; Nakamaye *J. Am. Chem. Soc.* **1966,** *88,* 3437.
[17]Abraham; Spalding *J. Chem. Soc. A* **1969,** 784; Abraham; Johnston *J. Chem. Soc. A* **1970,** 188.
[18]See, for example, Abraham; Dorrell *J. Chem. Soc., Perkin Trans. 2* **1973,** 444.
[19]Fukuto; Newman; Jensen *Organometallics* **1987,** *6,* 415.
[20]Abraham; Hill *J. Organomet. Chem.* **1967,** *7,* 11.
[21]Abraham, Ref. 2, p. 15.
[22]Fukuzumi; Kochi *J. Am. Chem. Soc.* **1980,** *102,* 2141, 7290.

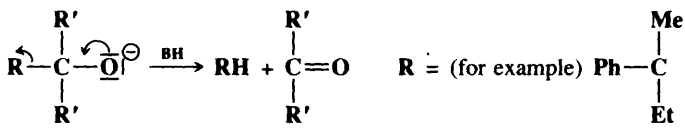
The IUPAC designation is $D_E + A_E$. First-order kinetics are predicted and many such examples have been found. Other evidence for the SEi mechanism was obtained in a study of base-catalyzed tautomerization. In the reaction



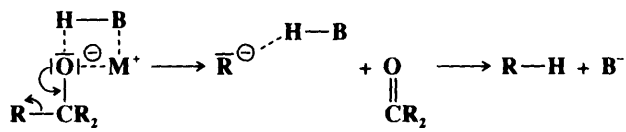
the rate of deuterium exchange was the same as the rate of racemization[23] and there was an isotope effect.[24]

SNi reactions do not proceed at bridgehead carbons in [2.2.1] bicyclic systems (p. 300) because planar carbocations cannot form at these carbons. However, carbanions not stabilized by resonance are probably not planar; SEi reactions should readily occur with this type of substrate. This is the case. Indeed, the question of carbanion structure is intimately tied into the problem of the stereochemistry of the SEi reaction. If a carbanion is planar, racemization should occur. If it is pyramidal and *can hold its structure*, the result should be retention of configuration. On the other hand, even a pyramidal carbanion will give racemization if it cannot hold its structure, i.e., if there is pyramidal inversion as with amines (p. 98). Unfortunately, the only carbanions that can be studied easily are those stabilized by resonance, which makes them planar, as expected (p. 181). For simple alkyl carbanions, the main approach to determining structure has been to study the stereochemistry of SEi reactions rather than the other way around. What is found is almost always racemization. Whether this is caused by planar carbanions or by oscillating pyramidal carbanions is not known. In either case racemization occurs whenever a carbanion is completely free or is symmetrically solvated.

However, even planar carbanions need not give racemization. Cram found that retention and even inversion can occur in the alkoxide cleavage reaction (**2-41**):

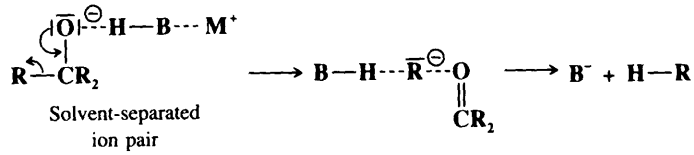


which is a first-order SEi reaction involving resonance-stabilized planar carbanions (here designated R^-).[25] By changing the solvent Cram was able to produce products ranging from 99% retention to 60% inversion and including complete racemization. These results are explained by a carbanion that is not completely free but is solvated. In nondissociating, nonpolar solvents such as benzene or dioxane, the alkoxide ion exists as an ion pair, solvated by the solvent BH:



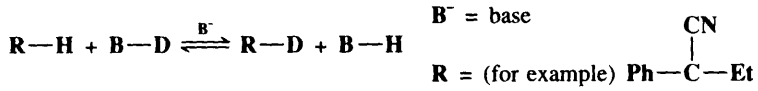
[23]Hsu; Ingold; Wilson *J. Chem. Soc.* **1938**, 78.
[24]Wilson *J. Chem. Soc.* **1936**, 1550.
[25]See Cram; Langemann; Allinger; Kopecky *J. Am. Chem. Soc.* **1959**, *81*, 5740; Hoffman; Cram *J. Am. Chem. Soc.* **1969**, *91*, 1009. For a discussion, see Cram *Fundamentals of Carbanion Chemistry*; Academic Press: New York, 1965, pp. 138-158.

In the course of the cleavage, the proton of the solvent moves in to solvate the newly forming carbanion. As is easily seen, this solvation is asymmetrical since the solvent molecule is already on the front side of the carbanion. When the carbanion actually bonds with the proton, the result is retention of the original configuration. In protic solvents, such as diethylene glycol, a good deal of inversion is found. In these solvents, the *leaving group* solvates the carbanion, so the solvent can solvate it only from the opposite side:

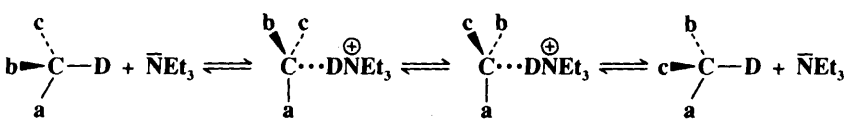


When C—H bond formation occurs, the result is inversion. Racemization results in polar aprotic solvents such as dimethyl sulfoxide. In these solvents the carbanions are relatively long-lived (because the solvent has no proton to donate) and symmetrically solvated.

Similar behavior was found for carbanions generated by base-catalyzed hydrogen exchange (reaction **2-1**):[26]



In this case information was obtained from measurement of the ratio of k_e (rate constant for isotopic exchange) to k_α (rate constant for racemization). A k_e/k_α ratio substantially greater than 1 means retention of configuration, since many individual isotopic exchanges are not producing a change in configuration. A k_e/k_α ratio of about 1 indicates racemization and a ratio of $\frac{1}{2}$ corresponds to inversion (see p. 296). All three types of steric behavior were found, depending on R, the base, and the solvent. As with the alkoxide cleavage reaction, retention was generally found in solvents of low dielectric constant, racemization in polar aprotic solvents, and inversion in protic solvents. However, in the proton exchange reactions, a fourth type of behavior was encountered. In aprotic solvents, with aprotic bases like tertiary amines, the k_e/k_α ratio was found to be *less* than 0.5, indicating that racemization took place *faster* than isotopic exchange (this process is known as *isoracemization*). Under these conditions, the conjugate acid of the amine remains associated with the carbanion as an ion pair. Occasionally, the ion pair dissociates long enough for the carbanion to turn over and recapture the proton:

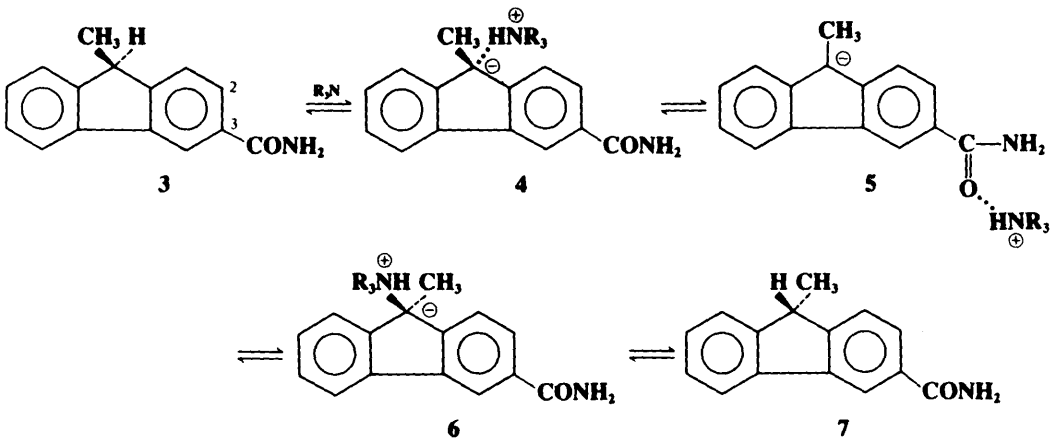


Thus, inversion (and hence racemization, which is produced by repeated acts of inversion) occurs without exchange. A single act of inversion without exchange is called *isoinversion*.

The isoinversion process can take place by a pathway in which a positive species migrates in a stepwise fashion around a molecule from one nucleophilic position to another. For example, in the exchange reaction of 3-carboxamido-9-methylfluorene (**3**) with Pr_3N in *t*-

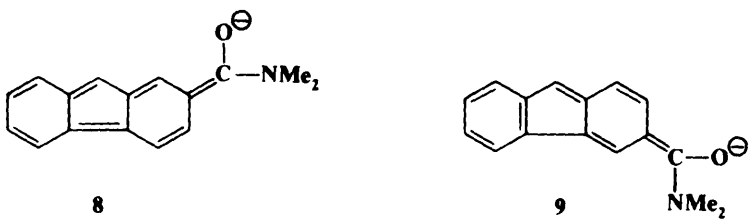
[26]See Cram; Kingsbury; Rickborn *J. Am. Chem. Soc.* **1961,** *83*, 3688; Cram; Gosser *J. Am. Chem. Soc.* **1963,** *85*, 3890, **1964,** *86*, 5445, 5457; Roitman; Cram *J. Am. Chem. Soc.* **1971,** *93*, 2225, 2231; Cram; Cram *Intra-Sci. Chem. Rep.* **1973,** *7*(3), 1-17. For a discussion, see Cram, Ref. 25, pp. 85-105.

BuOH, it has been proposed that the amine removes a proton from the 9 position of **3** and conducts the proton out to the C=O oxygen (**5**), around the molecule, and back to C-9 on



3 4 5 6 7

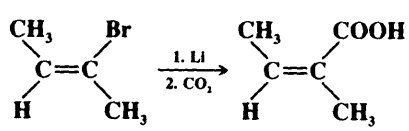
the opposite face of the anion. Collapse of **6** gives the inverted product **7.** Of course **5** could also go back to **3,** but a molecule that undergoes the total process **3** → **4** → **5** → **6** → **7** has experienced an inversion without an exchange. Evidence for this pathway, called the *conducted tour mechanism*,[27] is that the 2-carboxamido isomer of **3** does not give isoracemization. In this case the negative charge on the oxygen atom in the anion corresponding to **5** is less, because a canonical form in which oxygen acquires a full negative charge (**8**) results in



8 **9**

disruption of the aromatic sextet in both benzene rings (compare **9** where one benzene ring is intact). Whether the isoracemization process takes place by the conducted tour mechanism or a simple nonstructured contact ion-pair mechanism depends on the nature of the substrate (e.g., a proper functional group is necessary for the conducted tour mechanism) and of the base.[28]

It is known that vinylic carbanions *can* maintain configuration, so that SE1 mechanisms should produce retention there. This has been found to be the case. For example, *trans*-2-bromo-2-butene was converted to 64-74% angelic acid:[29]



[27]Cram; Ford; Gosser *J. Am. Chem. Soc.* **1968,** *90,* 2598; Ford; Cram *J. Am. Chem. Soc.* **1968,** *90,* 2606, 2612. See also Wong; Fischer; Cram *J. Am. Chem. Soc.* **1971,** *93,* 2235; Buchholz; Harms; Massa; Boche *Angew. Chem. Int. Ed. Engl.* **1989,** *28,* 73 [*Angew. Chem. 101,* 58].

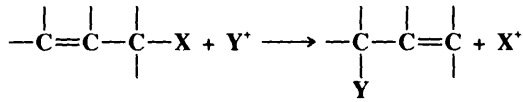
[28]Chu; Cram *J. Am. Chem. Soc.* **1972,** *94,* 3521; Almy; Hoffman; Chu; Cram *J. Am. Chem. Soc.* **1973,** *95,* 1185.

[29]Dreiding; Pratt *J. Am. Chem. Soc.* **1954,** *76,* 1902. See also Walborsky; Turner *J. Am. Chem. Soc.* **1972,** *94,* 2273.

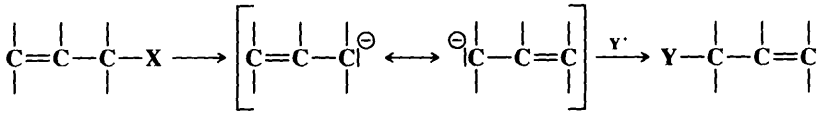
Only about 5% of the cis isomer, tiglic acid, was produced. In addition, certain carbanions in which the negative charge is stabilized by *d*-orbital overlap can maintain configuration (p. 181) and SE1 reactions involving them proceed with retention of configuration.

Electrophilic Substitution Accompanied by Double-Bond Shifts

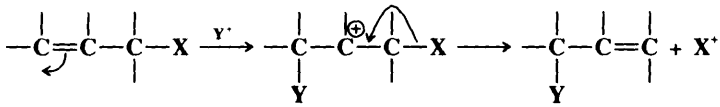
When electrophilic substitution is carried out at an allylic substrate, the product may be rearranged:



This type of process is analogous to the nucleophilic allylic rearrangements discussed in Chapter 10 (p. 327). There are two principal pathways. The first of these is analogous to the SE1 mechanism in that the leaving group is first removed, giving a resonance-stabilized allylic carbanion, and then the electrophile attacks.

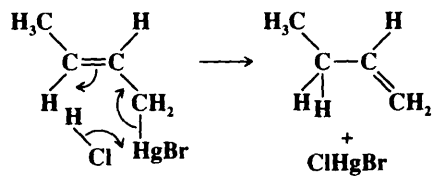


In the other pathway the Y group first attacks, giving a carbocation, which then loses X.



These mechanisms are more fully discussed under reaction **2-2.**

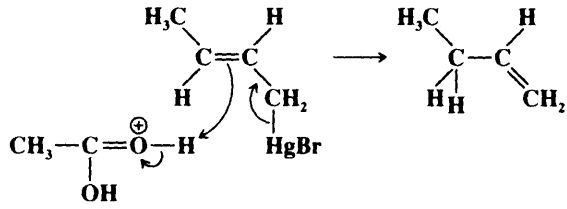
Most electrophilic allylic rearrangements involve hydrogen as the leaving group, but they have also been observed with metallic leaving groups.[30] Sleezer, Winstein, and Young found that crotylmercuric bromide reacted with HCl about 10^7 times faster than *n*-butylmercuric bromide and the product was more than 99% 1-butene.[31] These facts point to an SEi′ mechanism (IUPAC designation cyclo-1/3/$D_EA_ED_nA_n$):



The reaction of the same compound with acetic acid–perchloric acid seems to proceed by an SE2′ mechanism (IUPAC designation 1/3/D_EA_E):[31]

[30]For a review of reactions of allylic organometallic compounds, see Courtois; Miginiac *J. Organomet. Chem.* **1974,** *69*, 1-44.

[31]Sleezer; Winstein; Young *J. Am. Chem. Soc.* **1963,** *85*, 1890. See also Cunningham; Overton *J. Chem. Soc., Perkin Trans. 1* **1975,** 2140; Kashin; Bakunin; Khutoryanskii; Beletskaya; Reutov *J. Org. Chem. USSR* **1979,** *15*, 12, *J. Organomet. Chem.* **1979,** *171*, 309.



The geometry of electrophilic allylic rearrangement has not been studied very much (compare the nucleophilic case, p. 329), but in most cases the rearrangement takes place with anti stereoselectivity,[32] though syn stereoselectivity has also been demonstrated.[33] In one case, use of the electrophile H^+ and the leaving group $SnMe_3$ gave both syn and anti stereoselectivity, depending on whether the substrate was cis or trans.[34]

Other Mechanisms

Addition–elimination (**2-15**) and cyclic mechanisms (**2-40**) are also known.

Much less work has been done on electrophilic aliphatic substitution mechanisms than on nucleophilic substitutions, and the exact mechanisms of many of the reactions in this chapter are in doubt. For many of them, not enough work has been done to permit us to decide which of the mechanisms described in this chapter is operating, if indeed any is. There may be other electrophilic substitution mechanisms, and some of the reactions in this chapter may not even be electrophilic substitutions at all.

REACTIVITY

Only a small amount of work has been done in this area, compared to the vast amount done for aliphatic nucleophilic substitution and aromatic electrophilic substitution. Only a few conclusions, most of them sketchy or tentative, can be drawn.[35]

1. *Effect of substrate.* For SE1 reactions electron-donating groups decrease rates and electron-withdrawing groups increase them. This is as would be expected from a reaction in which the rate-determining step is analogous to the cleavage of a proton from an acid. For the SE2 (back) mechanism, Jensen and Davis[10] showed that the reactivity of alkyl groups is similar to that for the SN2 mechanism (i.e., Me > Et > Pr > iso-Pr > neopentyl), as would be expected, since both involve backside attack and both are equally affected by steric hindrance. In fact, this pattern of reactivity can be regarded as evidence for the occurrence of the SE2 (back) mechanism in cases where stereochemical investigation is not feasible.[36] For SE2 reactions that proceed with retention, several studies have been made with varying results, depending on the reaction.[37] One such study, which examined the

[32]Hayashi; Ito; Kumada *Tetrahedron Lett.* **1982,** *23*, 4605; Wetter; Scherer *Helv. Chim. Acta* **1983,** *66*, 118; Wickham; Kitching *J. Org. Chem.* **1983,** *48*, 612; Fleming; Kindon; Sarkar *Tetrahedron Lett.* **1987,** *28*, 5921; Hayashi; Matsumoto; Ito *Chem. Lett.* **1987,** 2037, *Organometallics* **1987,** *6*, 885; Matassa; Jenkins; Kümin; Damm; Schreiber; Felix; Zass; Eschenmoser *Isr. J. Chem.* **1989,** *29*, 321.

[33]Wetter; Scherer; Schweizer *Helv. Chim. Acta* **1979,** *62*, 1985; Young; Kitching *J. Org. Chem.* **1983,** *48*, 614, *Tetrahedron Lett.* **1983,** *24*, 5793.

[34]Kashin; Bakunin; Beletskaya; Reutov *J. Org. Chem. USSR* **1982,** *18*, 1973. See also Wickham; Young; Kitching *Organometallics* **1988,** *7*, 1187.

[35]For a discussion, see Abraham, Ref. 2, pp. 211-241.

[36]Another method involves measurement of the susceptibility of the rate to increased pressure: See Isaacs; Javaid *Tetrahedron Lett.* **1977,** 3073; Isaacs; Laila *Tetrahedron Lett.* **1984,** *25*, 2407.

TABLE 12.1 Relative rates of the reaction of RHgBr with Br_2 and Br^-[38]

R	Relative rate	R	Relative rate
Me	1	**Et**	10.8
Et	10.8	iso-**Bu**	1.24
iso-**Pr**	780	neopentyl	0.173
t-**Bu**	3370		

reaction RHgBr + $Br_2 \rightarrow$ RBr catalyzed by Br^-, gave the results shown in Table 12.1.[38] As can be seen, α branching increased the rates, while β branching decreased them. Sayre and Jensen attributed the decreased rates to steric hindrance, though attack here was definitely frontside, and the increased rates to the electron-donating effect of the alkyl groups, which stabilized the electron-deficient transition state.[39] Of course, steric hindrance should also be present with the α branched groups, so these workers concluded that if it were not, the rates would be even greater. The Br electrophile is rather a large one and it is likely that smaller steric effects are present with smaller electrophiles. The rates of certain second-order substitutions of organotin compounds have been found to increase with increasing electron withdrawal by substituents. This behavior has been ascribed[40] to an SE2 mechanism involving ion pairs, analogous to Sneen's ion-pair mechanism for nucleophilic substitution (p. 305).

2. *Effect of leaving group.* For both SE1 and second-order mechanisms, the more polar the C—X bond, the easier it is for the electrofuge to cleave. For metallic leaving groups in which the metal has a valence greater than 1, the nature of the other group or groups attached to the metal thus has an effect on the reaction. For example, consider a series of organomercurials RHgW. Because a more electronegative W decreases the polarity of the C—Hg bond and furthermore results in a less stable HgW^+, the electrofugal ability of HgW decreases with increasing electronegativity of W. Thus, HgR′ (from RHgR′) is a better leaving group than HgCl (from RHgCl). Also in accord with this is the leaving-group order Hg-*t*-Bu > Hg-iso-Pr > HgEt > HgMe, reported for acetolysis of R_2Hg,[39] since the more highly branched alkyl groups better help to spread the positive charge. It might be expected that, when metals are the leaving groups, SE1 mechanisms would be favored, while with carbon leaving groups, second-order mechanisms would be found. However, the results so far reported have been just about the reverse of this. For carbon leaving groups the mechanism is usually SE1, while for metallic leaving groups the mechanism is almost always SE2 or SEi. A number of reports of SE1 reactions with metallic leaving groups have appeared,[41] but the mechanism is not easy to prove and many of these reports have been challenged.[42] Reutov and co-workers[41] have expressed the view that in such reactions a nucleophile (which

[37]For some of these, see Abraham; Grellier *J. Chem. Soc., Perkin Trans. 2* **1973,** 1132; Dessy; Reynolds; Kim *J. Am. Chem. Soc.* **1959,** *81,* 2683; Minato; Ware; Traylor *J. Am. Chem. Soc.* **1963,** *85,* 3024; Boué; Gielen; Nasielski *J. Organomet. Chem.* **1967,** *9,* 443; Abraham; Broadhurst; Clark; Koenigsberger; Dadjour *J. Organomet. Chem.* **1981,** *209,* 37.

[38]Sayre; Jensen *J. Am. Chem. Soc.* **1979,** *101,* 6001.

[39]A similar conclusion, that steric and electronic effects are both present, was reached for a different system by Nugent; Kochi *J. Am. Chem. Soc.* **1976,** *98,* 5979.

[40]Beletskaya; Kashin; Reutov *J. Organomet. Chem.* **1978,** *155,* 31; Reutov *J. Organomet. Chem.* **1983,** *250,* 145-156. See also Butin; Magdesieva *J. Organomet. Chem.* **1985,** *292,* 47; Beletskaya, Ref. 2.

[41]For discussions, see Reutov *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1980,** *29,* 1461-1477; Beletskaya; Butin; Reutov *Organomet. Chem. Rev., Sect. A* **1971,** *7,* 51-79. See also Deacon; Smith *J. Org. Chem. USSR* **1982,** *18,* 1584; Dembech; Eaborn; Seconi *J. Chem. Soc., Chem. Commun.* **1985,** 1289.

[42]For a discussion, see Kitching *Rev. Pure Appl. Chem.* **1969,** *19,* 1-16.

may be the solvent) must assist in the removal of the electrofuge and refer to such processes as SE1(*N*) reactions.

3. *Effect of solvent.*[43] In addition to the solvent effects on certain SE1 reactions, mentioned earlier (p. 574), solvents can influence the mechanism that is preferred. As with nucleophilic substitution (p. 356), an increase in solvent polarity increases the possibility of an ionizing mechanism, in this case SE1, in comparison with the second-order mechanisms, which do not involve ions. As previously mentioned (p. 573), the solvent can also exert an influence between the SE2 (front or back) and SEi mechanisms in that the rates of SE2 mechanisms should be increased by an increase in solvent polarity, while SEi mechanisms are much less affected.

REACTIONS

The reactions in this chapter are arranged in order of leaving group: hydrogen, metals, halogen, and carbon. Electrophilic substitutions at a nitrogen atom are treated last.

Hydrogen as Leaving Group

A. Hydrogen as the Electrophile

2-1 Hydrogen Exchange
Deuterio-de-hydrogenation or **Deuteriation**

$$\mathbf{R{-}H + D^+ \rightleftharpoons R{-}D + H^+}$$

Hydrogen exchange can be accomplished by treatment with acids or bases. As with **1-1**, the exchange reaction is mostly used to study mechanistic questions such as relative acidities, but it can be used synthetically to prepare deuterated or tritiated molecules. When ordinary strong acids such as H_2SO_4 are used, only fairly acidic protons exchange, e.g., acetylenic, allylic, etc. However, primary, secondary, and tertiary hydrogens of alkanes can be exchanged by treatment with super-acids (p. 249).[44] The order of hydrogen reactivity is tertiary > secondary > primary. Where C—C bonds are present, they may be cleaved also (**2-47**). The mechanism of the exchange (illustrated for methane) has been formulated as involving attack of H^+ on the C—H bond to give the pentavalent methanonium ion which loses H_2 to give a tervalent carbocation.[45] The methanonium ion CH_5^+ has a three-center,

$$CH_3{-}H + H^+ \rightleftharpoons \left[\begin{array}{c} H \\ H_3C\cdots \\ H \end{array}\right]^+ \rightleftharpoons CH_3^+ + H_2$$

Methanonium ion

[43]For a discussion of solvent effects on organotin alkyl exchange reactions, see Petrosyan *J. Organomet. Chem.* **1983,** *250,* 157-170.

[44]Hogeveen; Bickel *Chem. Commun.* **1967,** 635; *Recl. Trav. Chim. Pays-Bas* **1969,** *88,* 371; Hogeveen; Gaasbeek *Recl. Trav. Chim. Pays-Bas* **1968,** *87,* 319; Olah; Klopman; Schlosberg *J. Am. Chem. Soc.* **1969,** *91,* 3261; Olah; Halpern; Shen; Mo *J. Am. Chem. Soc.* **1973,** *95,* 4960. For reviews, see Olah; Prakash; Sommer *Superacids*; Wiley: New York, 1985, pp. 244-249; Olah *Angew. Chem. Int. Ed. Engl.* **1973,** *12,* 173-212 [*Angew. Chem. 85,* 183-225], *CHEMTECH* **1971,** *1,* 566-573; Brouwer; Hogeveen *Prog. Phys. Org. Chem.* **1972,** *9,* 179-240, pp. 180-203.

[45]The mechanism may not be this simple in all cases. For discussions, see McMurry; Lectka *J. Am. Chem. Soc.* **1990,** *112,* 869; Culmann; Sommer *J. Am. Chem. Soc.* **1990,** *112,* 4057.

two-electron bond.[46] It is not known whether the methanonium ion is a transition state or a true intermediate, but an ion CH_5^+ has been detected in mass spectra.[47] The ir spectrum of the ethanonium ion $C_2H_7^+$ has been measured in the gas phase.[48] Note that the two electrons in the three-center, two-electron bond can move in three directions, in accord with the threefold symmetry of such a structure. The electrons can move to unite the two hydrogens, leaving the CH_3^+ free (the forward reaction), or they can unite the CH_3 with either of the two hydrogens, leaving the other hydrogen as a free H^+ ion (the reverse reaction). Actually, the methyl cation is not stable under these conditions. It can go back to CH_4 by the route shown (leading to H^+ exchange) or it can react with additional CH_4 molecules (**2-18**) to yield, eventually, the *t*-butyl cation, which is stable in these super-acid solutions. Hydride ion can also be removed from alkanes (producing tervalent carbocations) by treatment with pure SbF_5 in the absence of any source of H^+.[49] Complete or almost complete perdeuteriation of cyclic alkenes has been achieved by treatment with dilute DCl/D_2O in sealed Pyrex tubes at 165-280°C.[50]

Exchange with bases involves an SE1 mechanism.

Step 1 $\mathbf{RH + B^- \longrightarrow R^- + BH}$

Step 2 $\mathbf{R^- + BD \longrightarrow RD + B^-}$

Of course, such exchange is most successful for relatively acidic protons, such as those α to a carbonyl group, but even weakly acidic protons can exchange with bases if the bases are strong enough (see p. 176).

Alkanes and cycloalkanes, of both low and high molecular weight, can be fully perdeuteriated treatment with D_2 gas and a catalyst such as Rh, Pt, or Pd.[51]

OS **VI,** 432.

2-2 Migration of Double Bonds
3/Hydro-de-hydrogenation

$$\mathbf{C_5H_{11}—CH_2—CH{=}CH_2 \xrightarrow[Me_2SO]{KNH_2} C_5H_{11}—CH{=}CH—CH_3}$$

The double bonds of many unsaturated compounds are shifted[52] on treatment with strong bases.[53] In many cases equilibrium mixtures are obtained and the thermodynamically most stable isomer predominates.[54] Thus, if the new double bond can be in conjugation with one already present or with an aromatic ring, it goes that way.[55] If the choice is between an

[46]For a monograph on this type of species, see Olah; Prakash; Williams; Field; Wade *Hypercarbon Chemistry*; Wiley: New York, 1987.

[47]See, for example, Sefcik; Henis; Gaspar *J. Chem. Phys.* **1974,** *61,* 4321.

[48]Yeh; Price; Lee *J. Am. Chem. Soc.* **1989,** *111,* 5597.

[49]Lukas; Kramer; Kouwenhoven *Recl. Trav. Chim. Pays-Bas* **1973,** *92,* 44.

[50]Werstiuk; Timmins *Can. J. Chem.* **1985,** *63,* 530, **1986,** *64,* 1564.

[51]See, for example, Atkinson; Luke; Stuart *Can. J. Chem.* **1967,** *45,* 1511

[52]For a list of methods used to shift double and triple bonds, with references, see Larock *Comprehensive Organic Transformations*; VCH: New York, 1989, pp. 110-114, 287.

[53]For reviews of double-bond migrations, see Pines; Stalick *Base-Catalyzed Reactions of Hydrocarbons and Related Compounds*; Academic Press: New York, 1977, pp. 25-123; DeWolfe, in Bamford; Tipper *Comprehensive Chemical Kinetics*, vol. 9; Elsevier, New York, 1973, pp. 437-449; Yanovskaya; Shakhidayatov *Russ. Chem. Rev.* **1970,** *39,* 859-874; Hubert; Reimlinger *Synthesis* **1969,** 97-112, **1970,** 405-430; Mackenzie, in *The Chemistry of Alkenes*, vol. 1, Patai, Ed., pp. 416-436, vol. 2, Zabicky, Ed., pp. 132-148; Wiley: New York, 1964, 1970; Broaddus, *Acc. Chem. Res.* **1968,** *1,* 231-238; Cram, Ref. 25, pp. 175-210.

[54]For lists of which double bonds are more stable in conversions of $XCH_2CH{=}CHY$ to $XCH{=}CHCH_2Y$, see Hine; Skoglund *J. Org. Chem.* **1982,** *47,* 4766. See also Hine; Linden *J. Org. Chem.* **1983,** *48,* 584.

[55]For a review of conversions of β,γ enones to α,β enones, see Pollack; Bounds; Bevins, in Patai; Rappoport *The Chemistry of Enones*, pt. 1; Wiley: New York, 1989, pp. 559-597.

exocyclic and an endocyclic double bond (in a six-membered ring), it chooses the latter. In the absence of considerations like these, Zaitsev's rule (p. 998) applies and the double bond goes to the carbon with the fewest hydrogens. All these considerations lead us to predict that terminal olefins can be isomerized to internal ones, nonconjugated olefins to conjugated, exo six-membered-ring olefins to endo, etc., and not the other way around. This is indeed usually the case.

This reaction, for which the term *prototropic rearrangement* is sometimes used, is an example of electrophilic substitution with accompanying allylic rearrangement. The mechanism involves abstraction by the base to give a resonance-stabilized carbanion, which then combines with a proton at the position that will give the more stable olefin:[56]

Step 1 $\mathrm{R{-}CH_2{-}CH{=}CH_2 + B \longrightarrow \left[R{-}\overset{\ominus}{C}H{-}CH{=}CH_2 \longleftrightarrow R{-}CH{=}CH{-}\overset{\ominus}{C}H_2 \right] + BH^+}$

Step 2 $\mathrm{\left[R{-}\overset{\ominus}{C}H{-}CH{=}CH_2 \longleftrightarrow R{-}CH{=}CH{-}\overset{\ominus}{C}H_2 \right] \xrightarrow{BH^+} R{-}CH{=}CH{-}CH_3 + B}$

This mechanism is exactly analogous to the allylic-rearrangement mechanism for nucleophilic substitution (p. 327). Uv spectra of allylbenzene and 1-propenylbenzene in solutions containing NH_2^- are identical, which shows that the same carbanion is present in both cases, as required by this mechanism.[57] The acid BH^+ protonates the position that will give the more stable product, though the ratio of the two possible products can vary with the identity of BH^+.[58] It has been shown that base-catalyzed double-bond shifts are partially intramolecular, at least in some cases.[59] The intramolecularity has been ascribed to a conducted tour mechanism (p. 576) in which the base leads the proton from one carbanionic site to the other:[60]

$$\mathrm{RCH_2CH{=}CH_2 + B \rightleftharpoons R{-}\overset{\overset{H-B}{|}}{CH}(CH_2) \rightleftharpoons R{-}CH(\overset{\overset{H-B}{|}}{CH_2}) \rightleftharpoons RCH{=}CHCH_3 + B}$$

Triple bonds can also migrate in the presence of bases,[61] but through the allene intermediate:[62]

$$\mathrm{R{-}CH_2{-}C{\equiv}CH \rightleftharpoons R{-}CH{=}C{=}CH_2 \rightleftharpoons R{-}C{\equiv}C{-}CH_3}$$

[56]See, for example, Hassan; Nour; Satti; Kirollos *Int. J. Chem. Kinet.* **1982,** *14*, 351; Pollack; Mack; Eldin *J. Am. Chem. Soc.* **1987,** *109*, 5048.

[57]Rabinovich; Astaf'ev; Shatenshtein *J. Gen. Chem. USSR* **1962,** *32*, 746.

[58]Hünig; Klaunzer; Schlund *Angew. Chem. Int. Ed. Engl.* **1987,** *26*, 1281 [*Angew. Chem. 99*, 1322].

[59]See, for example, Cram; Uyeda *J. Am. Chem. Soc.* **1964,** *86*, 5466; Bank; Rowe; Schriesheim *J. Am. Chem. Soc.* **1963,** *85*, 2115; Doering; Gaspar *J. Am. Chem. Soc.* **1963,** *85*, 3043; Ohlsson; Wold; Bergson *Ark. Kemi.* **1968,** *29*, 351.

[60]Almy; Cram *J. Am. Chem. Soc.* **1969,** *91*, 4459; Hussénius; Matsson; Bergson *J. Chem. Soc., Perkin Trans. 2* **1989,** 851.

[61]For reviews, see Pines; Stalick, Ref. 53, pp. 124-204; Théron; Verny; Vessière, in Patai *The Chemistry of Carbon-Carbon Triple Bond*, pt. 1; Wiley: New York, 1978, pp. 381-445; Bushby *Q. Rev. Chem. Soc.* **1970,** *24*, 585-600; Iwai *Mech. Mol. Migr.* **1969,** *2*, 73-116; Wotiz, in Viehe *Acetylenes*; Marcel Dekker: New York, 1969, pp. 365-424; Vartanyan; Babanyan *Russ. Chem. Rev.* **1967,** *36*, 670.

[62]For a review of rearrangements involving allenes, see Huntsman, in Patai *The Chemistry of Ketenes, Allenes, and Related Compounds*, pt. 2; Wiley: New York, 1980, pp. 521-667.

In general, strong bases such as $NaNH_2$ convert internal alkynes to terminal alkynes (a particularly good base for this purpose is potassium 3-aminopropylamide $NH_2CH_2CH_2CH_2NHK$[63]), because the equilibrium is shifted by formation of the acetylide ion; with weaker bases such as NaOH (which are not strong enough to remove the acetylenic proton), the internal alkynes are favored because of their greater thermodynamic stability. In some cases the reaction can be stopped at the allene stage. The reaction then becomes a method for the preparation of allenes.[64]

Double-bond rearrangements can also take place on treatment with acids. Both proton and Lewis[65] acids can be used. The mechanism in the case of proton acids is the reverse of the previous one; first a proton is gained, giving a carbocation, and then another is lost:

Step 1 $CH_3—CH_2—CH=CH_2 + H^+ \longrightarrow CH_3—CH_2—\overset{\oplus}{C}H—CH_3$

Step 2 $CH_3—CH_2—\overset{\oplus}{C}H—CH_3 \longrightarrow CH_3—CH=CH—CH_3 + H^+$

As in the case of the base-catalyzed reaction, the thermodynamically most stable olefin is the one predominantly formed. However, the acid-catalyzed reaction is much less synthetically useful because carbocations give rise to many side products. If the substrate has several possible locations for a double bond, mixtures of all possible isomers are usually obtained. Isomerization of 1-decene, for example, gives a mixture that contains not only 1-decene and *cis*- and *trans*-2-decene but also the cis and trans isomers of 3-, 4-, and 5-decene as well as branched alkenes resulting from rearrangement of carbocations. It is true that the most stable olefins predominate, but many of them have stabilities that are close together. Acid-catalyzed migration of triple bonds (with allene intermediates) can be accomplished if very strong acids (e.g., $HF–PF_5$) are used.[66] If the mechanism is the same as that for double bonds, vinyl cations are intermediates.

Double-bond isomerization can also take place in other ways. Nucleophilic allylic rearrangements were discussed in Chapter 10 (p. 327). Electrocyclic and sigmatropic rearrangements are treated at **8-29** to **8-37.** Double-bond migrations have also been accomplished photochemically,[67] and by means of metallic ion (most often complex ions containing Pt, Rh, or Ru) or metal carbonyl catalysts.[68] In the latter case there are at least two possible mechanisms. One of these, which requires external hydrogen, is called the *metal hydride addition–elimination mechanism*:

$$RCH_2CH=CH_2 \overset{MH}{\rightleftharpoons} RCH_2\underset{\displaystyle M}{\underset{|}{C}}HCH_3 \overset{-MH}{\rightleftharpoons} RCH=CHCH_3$$

[63]Brown; Yamashita *J. Am. Chem. Soc.* **1975,** *97*, 891; Macaulay *J. Org. Chem.* **1980,** *45*, 734; Abrams *Can. J. Chem.* **1984,** *62*, 1333.

[64]For example, see Enomoto; Katsuki; Yamaguchi *Tetrahedron Lett.* **1986,** *27*, 4599.

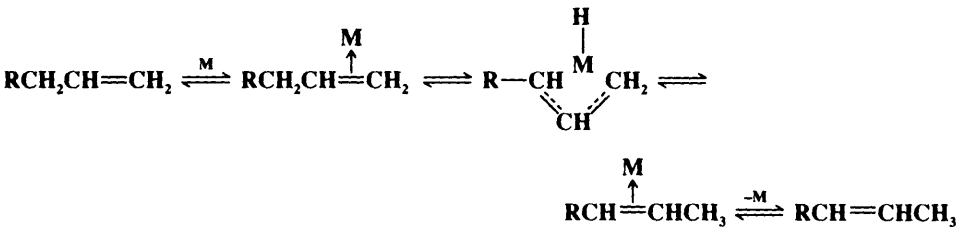
[65]For an example of a Lewis-acid catalyzed rearrangement, see Cameron; Stimson *Aust. J. Chem.* **1977,** *30*, 923.

[66]Barry; Beale; Carr; Hei; Reid *J. Chem. Soc., Chem. Commun.* **1973,** 177.

[67]Schönberg *Preparative Organic Photochemistry*; Springer: New York, 1968, pp. 22-24.

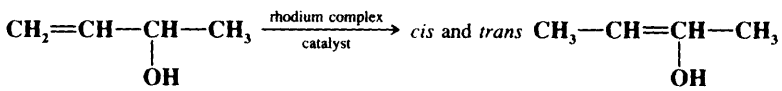
[68]For reviews, see Rodriguez; Brun; Waegell *Bull. Soc. Chim. Fr.* **1989,** 799-823; Jardine, in Harley; Patai, Ref. 1, vol. 4, pp. 733-818, pp. 736-740; Otsuka; Tani, in Morrison *Asymmetric Synthesis*, vol. 5; Academic Press: New York, 1985, pp. 171-191 (enantioselective); Colquhoun; Holton; Thompson; Twigg *New Pathways for Organic Synthesis*; Plenum: New York, 1984, pp. 173-193; Khan; Martell *Homogeneous Catalysis by Metal Complexes*; Academic Press: New York, 1974, pp. 9-37; Heck *Organotransition Metal Chemistry*; Academic Press: New York, 1974, pp. 76-82; Jira; Freiesleben, *Organomet. React.* **1972,** *3*, 1-190, pp. 133-149; Biellmann; Hemmer; Levisalles, in Zabicky, Ref. 53, vol. 2, pp. 224-230; Bird *Transition Metal Intermediates in Organic Synthesis*; Academic Press: New York, 1967, pp. 69-87; Davies *Rev. Pure Appl. Chem.* **1967,** *17*, 83-93; Orchin *Adv. Catal.* **1966,** *16*, 1-47.

The other mechanism, called the *π-allyl complex mechanism*, does not require external hydrogen:



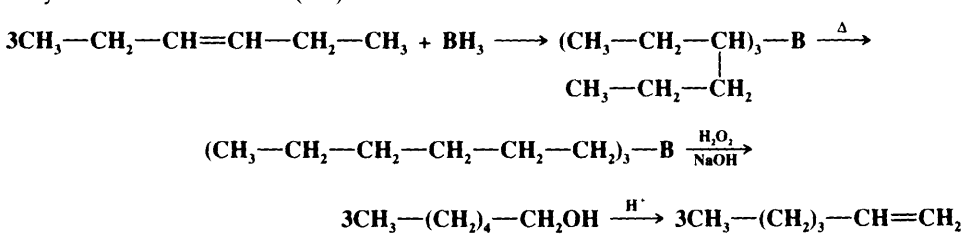
Another difference between the two mechanisms is that the former involves 1,2 and the latter 1,3 shifts. The isomerization of 1-butene by rhodium(I) is an example of a reaction that takes place by the metal hydride mechanism,[69] while an example of the π-allyl complex mechanism is found in the $Fe_3(CO)_{12}$-catalyzed isomerization of 3-ethyl-1-pentene.[70] A palladium acetate or palladium complex catalyst was used to convert alkynones $RCOC{\equiv}CCH_2CH_2R'$ to 2,4-alkadien-1-ones $RCOCH{=}CHCH{=}CHCHR'$.[71]

The metal catalysis method has been used for the preparation of simple enols, by isomerization of allylic alcohols, e.g.,[71a]



These enols are stable enough for isolation (see p. 72), but slowly tautomerize to the aldehyde or ketone, with half-lives ranging from 40-50 minutes to several days.[71a]

No matter which of the electrophilic methods of double-bond shifting is employed, the thermodynamically most stable olefin is usually formed in the largest amount in most cases, though a few anomalies are known. However, there is another, indirect, method of double-bond isomerization, by means of which migration in the other direction can often be carried out. This involves conversion of the olefin to a borane (**5-12**), rearrangement of the borane (**8-11**), oxidation and hydrolysis of the newly formed borane to the alcohol (**2-28**), and dehydration of the alcohol (**7-1**):



Since the migration reaction is always toward the end of a chain, terminal olefins can be produced from internal ones, so the migration is often opposite to that with the other methods. Alternatively, the rearranged borane can be converted directly to the olefin by heating with an alkene of molecular weight higher than that of the product (**7-15**). Photochemical isomerization can also lead to the thermodynamically less stable isomer.[72]

[69]Cramer *J. Am. Chem. Soc.* **1966,** *88,* 2272.
[70]Casey; Cyr *J. Am. Chem. Soc.* **1973,** *95,* 2248.
[71]Trost; Schmidt *J. Am. Chem. Soc.* **1988,** *110,* 2301.
[71a]Bergens; Bosnich *J. Am. Chem. Soc.* **1991,** *113,* 958.
[72]For example, see Kropp; Krauss *J. Am. Chem. Soc.* **1967,** *89,* 5199; Reardon; Krauss *J. Am. Chem. Soc.* **1971,** *93,* 5593; Duhaime; Lombardo; Skinner; Weedon *J.Org. Chem.* **1985,** *50,* 873.

If a hydroxy group is present in the chain, *it* may lose a proton, so that a ketone is the product, for example,[73]

$$R_2C{=}CHCH_2CH_2CHOHCH_3 \xrightarrow[\text{acid}]{\text{polyphosphoric}} R_2CHCH_2CH_2CH_2COCH_3$$

Similarly, α-hydroxy triple-bond compounds have given α,β-unsaturated ketones.[74]

OS **II,** 140; **III,** 207; **IV,** 189, 192, 195, 234, 398, 683; **VI,** 68, 87, 815, 925; **VII,** 249; **65,** 224; **66,** 22, 127; **68,** 162; **69,** 180.

2-3 Keto-Enol Tautomerization
3/*O*-Hydro-de-hydrogenation

$$R{-}CH_2{-}\underset{\underset{O}{\|}}{C}{-}R' \underset{OH^-}{\overset{H^+ \text{ or}}{\rightleftharpoons}} R{-}CH{=}\underset{\underset{OH}{|}}{C}{-}R'$$

The tautomeric equilibrium between enols and ketones or aldehydes is not normally a preparative reaction, though for some ketones both forms can be prepared (see p. 69 for a discussion of this and other aspects of tautomerism). For most ketones and aldehydes only the keto form is detectable under ordinary conditions, though the equilibrium must occur, since aldehydes and ketones often react through their enol forms.

Neither the forward nor the reverse reaction can take place without at least a trace of acid or base,[75] ruling out a direct shift of a hydrogen from carbon to oxygen or vice versa. The mechanisms are identical to those in **2-2**.[76]

Acid-catalyzed

$$R{-}CH_2{-}\underset{\underset{O}{\|}}{C}{-}R' \underset{\text{slow}}{\overset{H^+, \text{ fast}}{\rightleftharpoons}} R{-}CH_2{-}\overset{\oplus}{\underset{\underset{OH}{|}}{C}}{-}R' \underset{H^+, \text{ fast}}{\overset{\text{slow}}{\rightleftharpoons}} R{-}CH{=}\underset{\underset{OH}{|}}{C}{-}R'$$

Base-catalyzed[77]

$$R{-}CH_2{-}\underset{\underset{O}{\|}}{C}{-}R' \underset{\text{fast}}{\overset{B, \text{ slow}}{\rightleftharpoons}}$$

$$\left[R{-}\overset{\ominus}{\underset{\underset{\underline{O}|}{\|}}{C}}H{-}C{-}R' \longleftrightarrow R{-}CH{=}\underset{\underset{\underline{O}|^{\ominus}}{|}}{C}{-}R'\right] \underset{B, \text{ slow}}{\overset{\text{fast}}{\rightleftharpoons}} R{-}CH{=}\underset{\underset{OH}{|}}{C}{-}R'$$

10

[73]Colonge; Brunie *Bull. Soc. Chim. Fr.* **1963,** 1799. For an example with basic catalysis, see Hoffmann; Köver; Pauluth *J. Chem. Soc., Chem. Commun.* **1985,** 812. For an example with a ruthenium complex catalyst, see Trost; Kulawiec *Tetrahedron Lett.* **1991,** *32,* 3039.

[74]For example, see Chabardes *Tetrahedron Lett.* **1988,** *29,* 6253.

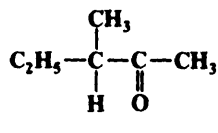
[75]In the case of the "uncatalyzed" ketonization of $CH_2{=}C(Ph)OH$, it was shown that water functions as the basic catalyst: Chiang; Kresge; Santaballa; Wirz *J. Am. Chem. Soc.* **1988,** *110,* 5506.

[76]For reviews of the mechanism, see Keeffe; Kresge, in Rappoport *The Chemistry of Enols*; Wiley: New York, 1990, pp. 399-480; Toullec *Adv. Phys. Org. Chem.* **1982,** *18,* 1-77; Lamaty *Isot. Org. Chem.* **1976,** *2,* 33-88. For discussions, see Ingold *Structure and Mechanism in Organic Chemistry*, 2nd ed.; Cornell University Press: Ithaca, NY, 1969, pp. 794-837; Bell *The Proton in Chemistry*, 2nd ed.; Cornell University Press: Ithaca, NY, 1973, pp. 171-181; Bruice; Bruice, *J. Am. Chem. Soc.* **1976,** *98,* 844; Shelly; Venimadhavan; Nagarajan; Stewart *Can. J. Chem.* **1989,** *67,* 1274. For a review of stereoelectronic control in this mechanism, see Pollack *Tetrahedron* **1989,** *45,* 4913-4938.

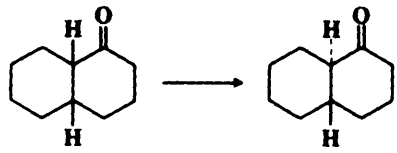
[77]Another mechanism for base-catalyzed enolization has been reported when the base is a tertiary amine: See Bruice, *J. Am. Chem. Soc.* **1983,** *105,* 4982, **1989,** *111,* 962, **1990,** *112,* 7361.

For each catalyst, the mechanism for one direction is the exact reverse of the other, by the principle of microscopic reversibility.[78] As expected from mechanisms in which the C—H bond is broken in the rate-determining step, substrates of the type RCD_2COR show deuterium isotope effects (of about 5) in both the basic-[79] and the acid[80]-catalyzed processes.

Although the conversion of an aldehyde or a ketone to its enol tautomer is not generally a preparative procedure, the reactions do have their preparative aspects. If a full mole of base per mole of ketone is used, the enolate ion (**10**) is formed and can be isolated[81] (see, for example, **0-95**).[82] When enol ethers or esters are hydrolyzed, the enols initially formed immediately tatuomerize to the aldehydes or ketones. In addition, the overall processes (forward plus reverse reactions) are often used for equilibration purposes. When an optically active compound in which the chirality is due to an asymmetric carbon α to a carbonyl group (as in **11**) is treated with acid or base, racemization results.[83] If there is another asymmetric



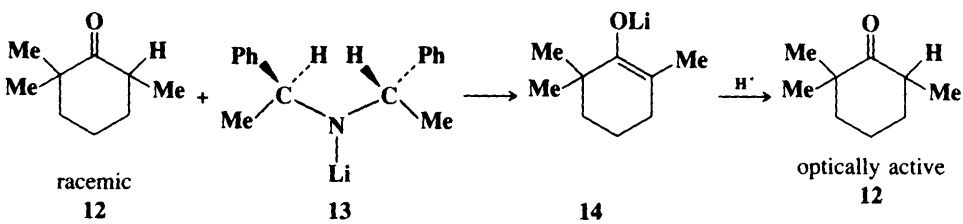
11



cis-decalone *trans*-decalone

center in the molecule, the less stable epimer can be converted to the more stable one in this manner, and this is often done. For example, *cis*-decalone can be equilibrated to the trans isomer. Isotopic exchange can also be accomplished at the α position of an aldehyde or ketone in a similar manner. For the acid-catalyzed process, exchange or equilibration is accomplished only if the carbonyl compound is completely converted to the enol and then back, but in the base-catalyzed process exchange or equilibration can take place if only the first step (conversion to the enolate ion) takes place. The difference is usually academic.

In the case of the ketone **12**, a racemic mixture was converted to an optically active mixture (optical yield 46%) by treatment with the chiral base **13**.[84] This happened because



racemic **12** **13** **14** optically active **12**

[78]It has been proposed that the acid-catalyzed ketonization of simple enols is concerted; that is, both of the processes shown in the equation take place simultaneously. This would mean that in these cases the forward reaction is also concerted. For evidence in favor of this proposal, see Capon; Siddhanta; Zucco *J. Org. Chem.* **1985,** *50*, 3580. For evidence against it, see Chiang; Kresge; Walsh *J. Am. Chem. Soc.* **1986,** *108*, 6314; Chiang; Hojatti; Keeffe; Kresge; Schepp; Wirz **1987,** *109*, 4000.

[79]Riley, Long *J. Am. Chem. Soc.* **1962,** *84*, 522; Beutelman; Xie; Saunders *J. Org. Chem.* **1989,** *54*, 1703; Xie; Saunders *J. Am. Chem. Soc.* **1991,** *113*, 3123.

[80]Swain; Stivers; Reuwer; Schaad *J. Am. Chem. Soc.* **1958,** *80*, 5885; Lienhard; Wang *J. Am. Chem. Soc.* **1969,** *91*, 1146. See also Toullec; Dubois *J. Am. Chem. Soc.* **1974,** *96*, 3524.

[81]For nmr studies of the Li enolate of acetaldehyde in solution, see Wen; Grutzner *J. Org. Chem.* **1986,** *51*, 4220.

[82]For a review of the preparation and uses of enolates, see d'Angelo *Tetrahedron* **1976,** *32*, 2979-2990.

[83]For an exception, see Guthrie; Nicolas *J. Am. Chem. Soc.* **1981,** *103*, 4637.

[84]Eleveld; Hogeveen *Tetrahedron Lett.* **1986,** *27*, 631. See also Shirai; Tanaka; Koga *J. Am. Chem. Soc.* **1986,** *108*, 543; Simpkins *J. Chem. Soc., Chem. Commun.* **1986,** 88; Cain; Cousins; Coumbarides; Simpkins *Tetrahedron* **1990,** *46*, 523.

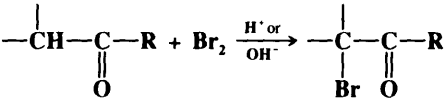
13 reacted with one enantiomer of **12** faster than with the other (an example of kinetic resolution). The enolate **14** must remain coordinated with the chiral amine, and it is the amine that reprotonates **14,** not an added proton donor.

Enolizable hydrogens can be replaced by deuterium (and ^{16}O by ^{18}O) by passage of a sample through a deuterated (or ^{18}O-containing) gas-chromatography column.[85]

There are many enol–keto interconversions and acidifications of enolate ions to the keto forms listed in *Organic Syntheses*. No attempt is made to list them here.

B. Halogen Electrophiles

2-4 Halogenation of Aldehydes and Ketones
Halogenation or Halo-de-hydrogenation



Aldehydes and ketones can be halogenated in the α position with bromine, chlorine, or iodine.[86] The reaction is not successful with fluorine,[87] but active compounds, such as β-keto esters and β-diketones, have been fluorinated with XeF_2 in the presence of a resin,[88] with an N-fluoro-N-alkylsulfonamide[89] (this can result in enantioselective fluorination, if an optically active N-fluorosulfonamide is used[90]), with cesium fluoroxysulfate,[91] with N-fluoroquinuclidium fluoride,[92] and with acetyl hypofluorite.[93] The last reagent also fluorinates simple ketones in the form of their lithium enolates.[94] In another method, enolate ions of β-keto esters are fluorinated with perchloryl fluoride $FClO_3$.[95] (However, $FClO_3$ can be a dangerous reagent. Several explosions have been reported.[96]) If the carbon attacked with $FClO_3$ has two hydrogens, the reaction cannot be stopped until two fluorines have entered. Monofluorination can be accomplished indirectly by treating an enamine, enol ether, or similar ketone derivative with $FClO_3$.[97] Fluoroxytrifluoromethane CF_3OF and similar compounds behave similarly.[98] Silyl enol ethers can also be fluorinated, with XeF_2[99] or with 5%

[85]Senn; Richter; Burlingame *J. Am. Chem. Soc.* **1965,** *87*, 680; Richter; Senn; Burlingame *Tetrahedron Lett.* **1965,** 1235.

[86]For a review, see House *Modern Synthetic Reactions*, 2nd ed.; W.A. Benjamin: New York, 1972, pp. 459-478. For lists of reagents, with references, see Ref. 52, pp. 369-372. For a monograph, see De Kimpe; Verhé *The Chemistry of α Haloketones, α Haloaldehydes, and α Haloimines;* Wiley: New York, 1988.

[87]For a review of the preparation of α-fluoro carbonyl compounds, see Rozen; Filler *Tetrahedron* **1985,** *41*, 1111-1153. For a monograph, see German; Zemskov *New Fluorinating Agents in Organic Chemistry*; Springer: New York, 1989.

[88]Zajc; Zupan *J. Chem. Soc., Chem. Commun.* **1980,** 759, *J. Org. Chem.* **1982,** *47*, 573.

[89]Barnette *J. Am. Chem. Soc.* **1984,** *106*, 452.

[90]Differding; Lang *Tetrahedron* **1988,** *29*, 6087.

[91]Stavber; Šket; Zajc; Zupan *Tetrahedron* **1989,** *45*, 6003.

[92]Banks; Du Boisson; Morton; Tsiliopoulos *J. Chem. Soc., Perkin Trans. 1* **1988,** 2805.

[93]Lerman; Rozen *J. Org. Chem.* **1983,** *48*, 724. See also Purrington; Jones *J. Org. Chem.* **1983,** *48*, 761.

[94]Rozen; Brand *Synthesis* **1985,** 665. For another reagent, see Davis; Han *Tetrahedron Lett.* **1991,** *32*, 1631.

[95]Inman; Oesterling; Tyczkowski *J. Am. Chem. Soc.* **1958,** *80*, 6533; Machleidt; Hartmann *Liebigs Ann. Chem.* **1964,** *679*, 9; Kamlet; Adolph *J. Org. Chem.* **1968,** *33*, 3073; Sheppard *Tetrahedron Lett.* **1969,** 83. For reviews of perchloryl fluoride, see Sharts; Sheppard *Org. React.* **1974,** *21*, 125-406, pp. 225-236; Sheppard; Sharts *Organic Fluorine Chemistry*; W.A. Benjamin: New York, 1969, pp. 136-148; Khutoretskii; Okhlobystina; Fainzil'berg *Russ. Chem. Rev.* **1967,** *36*, 145-155.

[96]See Peet; Rockett *J. Organomet. Chem.* **1974,** *82*, C57; Adcock; Khor *J. Organomet. Chem.* **1975,** *91*, C20.

[97]For example, see Gabbard; Jensen *J. Org. Chem.* **1958,** *23*, 1406; Nakanishi; Jensen *J. Org. Chem.* **1962,** *27*, 702.

[98]Barton; Godinho; Hesse; Pechet *Chem. Commun.* **1968,** 804; Barton *Pure Appl. Chem.* **1970,** *21*, 285-293; Hesse *Isr. J. Chem.* **1978,** *17*, 60; Middleton; Bingham *J. Am. Chem. Soc.* **1980,** *102*, 4845. See also Sharts; Sheppard, Ref. 95, pp. 243-256; Rozen; Menahem *Tetrahedron Lett.* **1979,** 725.

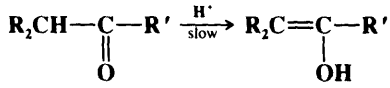
[99]Tsushima; Kawada; Tsuji *Tetrahedron Lett.* **1982,** *23*, 1165.

F_2 in N_2 at $-78°C$ in $FCCl_3$.[100] Electrochemical fluorination has also been reported.[101] Sulfuryl chloride,[102] trichloroisocyanuric acid,[103] Me_3SiCl–Me_2SO,[104] Me_3SiCl–MnO_2,[105] $TiCl_3$,[106] and cupric chloride[107] have been used as reagents for chlorination, and N-bromosuccinimide (see **4-2**), *t*-BuBr–Me_2SO,[108] Me_3SiBr–Me_2SO,[109] and tetrabutylammonium tribromide,[110] for bromination. Iodination has been accomplished with I_2–$HgCl_2$[111] and with I_2–cerium(IV) ammonium nitrate.[112]

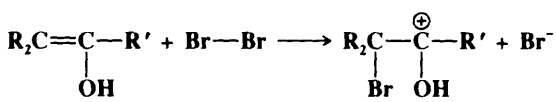
For unsymmetrical ketones the preferred position of halogenation is usually a CH group, then a CH_2 group, and then CH_3;[113] however, mixtures are frequent. With aldehydes the aldehydic hydrogen is sometimes replaced (see **4-3**). It is also possible to prepare di- and polyhalides. When basic catalysts are used, one α position of a ketone is completely halogenated before the other is attacked, and the reaction cannot be stopped until all the hydrogens of the first carbon have been replaced (see below). If one of the groups is methyl, the haloform reaction (**2-44**) takes place. With acid catalysts, it is easy to stop the reaction after only one halogen has entered, though a second halogen can be introduced by the use of excess reagent. In chlorination the second halogen generally appears on the same side as the first,[114] while in bromination the α,α′-dibromo product is found.[115] Actually, with both halogens it is the α,α-dihalo ketone that is formed first, but in the case of bromination this compound isomerizes under the reaction conditions to the α,α′ isomer.[114] Aryl methyl ketones can be dibrominated ($ArCOCH_3 \rightarrow ArCOCHBr_2$) in high yields with benzyltrimethylammonium tribromide.[116]

It is not the aldehyde or ketone itself that is halogenated, but the corresponding enol or enolate ion. The purpose of the catalyst is to provide a small amount of enol or enolate. The reaction is often done without addition of acid or base, but traces of acid or base are always present, and these are enough to catalyze formation of the enol or enolate. With acid catalysis the mechanism is

Step 1



Step 2



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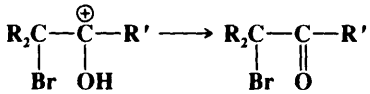


[100]Purrington; Bumgardner; Lazaridis; Singh *J. Org. Chem.* **1987,** *52*, 4307.

[101]Laurent; Marquet; Tardivel *Tetrahedron* **1989,** *45*, 4431.

[102]For a review of sulfuryl chloride, see Tabushi; Kitaguchi, in Pizey *Synthetic Reagents*, vol. 4; Wiley: New York, 1981, pp. 336-396.

[103]Hiegel; Peyton *Synth. Commun.* **1985,** *15*, 385.

[104]Bellesia; Ghelfi; Grandi; Pagnoni *J. Chem. Res. (S)* **1986,** 426; Fraser; Kong *Synth. Commun.* **1988,** *18*, 1071.

[105]Bellesia; Ghelfi; Pagnoni; Pinetti *J. Chem. Res. (S)* **1990,** 188.

[106]Glaser; Toth *J. Chem. Soc., Chem. Commun.* **1986,** 1336.

[107]For a review, see Nigh, in Trahanovsky *Oxidation in Organic Chemistry*, pt. B; Academic Press: New York, 1973, pp. 67-81. Cupric chloride has been used to chlorinate α,β-unsaturated aldehydes and ketones in the γ position: Dietl; Normark; Payne; Thweatt; Young *Tetrahedron Lett.* **1973,** 1719.

[108]Armani; Dossena; Marchelli; Casnati *Tetrahedron* **1984,** *40*, 2035.

[109]Bellesia; Ghelfi; Grandi; Pagnoni *J. Chem. Res. (S)* **1986,** 428.

[110]Kajigaeshi; Kakinami; Okamoto; Fujisaki *Bull. Chem. Soc. Jpn.* **1987,** *60*, 1159.

[111]Barluenga; Martinez-Gallo; Najera; Yus *Synthesis* **1986,** 678.

[112]Horiuchi; Kiji *Chem. Lett.* **1988,** 31. For another reagent, see Šket; Zupet; Zupan; Dolenc *Bull. Chem. Soc. Jpn.* **1989,** *62*, 3406.

[113]For chlorination this is reversed if the solvent is methanol: Gallucci; Going *J. Org. Chem.* **1981,** *46*, 2532.

[114]Rappe *Ark. Kemi.* **1965,** *24*, 321. But see also Teo; Warnhoff *J. Am. Chem. Soc.* **1973,** *95*, 2728.

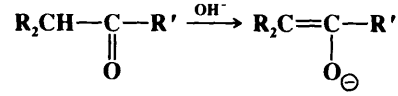
[115]Rappe; Schotte *Acta Chem. Scand.* **1962,** *16*, 2060; Rappe *Ark. Kemi* **1964,** *21*, 503; Garbisch *J. Org. Chem.* **1965,** *30*, 2109.

[116]Kajigaeshi; Kakinami; Tokiyama; Hirakawa; Okamoto *Bull. Chem. Soc. Jpn.* **1987,** *60*, 2667.

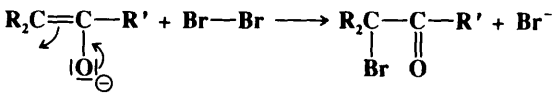
The first step, as we have already seen (**2-3**), actually consists of two steps. The second step is very similar to the first step in electrophilic addition to double bonds (p. 734). There is a great deal of evidence for this mechanism: (1) the rate is first order in substrate; (2) bromine does not appear in the rate expression at all,[117] a fact consistent with a rate-determining first step;[118] (3) the reaction rate is the same for bromination, chlorination, and iodination under the same conditions;[119] (4) the reaction shows an isotope effect; and (5) the rate of the step 2-step 3 sequence has been independently measured (by starting with the enol) and found to be very fast.[120]

With basic catalysts the mechanism may be the same as that given above (since bases also catalyze formation of the enol), or the reaction may go directly through the enolate ion without formation of the enol:

Step 1

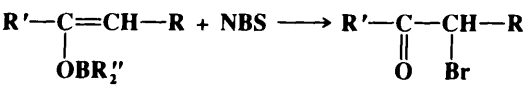


Step 2



It is difficult to distinguish the two possibilities. It was mentioned above that in the base-catalyzed reaction, if the substrate has two or three α halogens on the same side of the C=O group, it is not possible to stop the reaction after just one halogen atom has entered. The reason is that the electron-withdrawing field effect of the first halogen increases the acidity of the remaining hydrogens, i.e., a CHX group is more acidic than a CH_2 group, so that initially formed halo ketone is converted to enolate ion (and hence halogenated) more rapidly than the original substrate.

Regioselectivity in the halogenation of unsymmetrical ketones can be attained by treatment of the appropriate enol borinate of the ketone with N-bromo- or N-chlorosuccinimide.[121]



The desired halo ketone is formed in high yield. Another method for achieving the same result involves bromination of the appropriate lithium enolate at a low temperature[122] (see p. 472 for the regioselective formation of enolate ions). In a similar process, α-halo aldehydes have been prepared in good yield by treatment of silyl enol ethers $R_2C{=}CHOSiMe_3$ with Br_2 or Cl_2,[123] with sulfuryl chloride SO_2Cl_2;[124] or with I_2 and silver acetate.[125] Enol acetates have been regioselectively iodinated with I_2 and either thallium(I) acetate[126] or copper(II)

[117]When the halogenating species is at low concentration or has a low reactivity, it can appear in the rate expression. The reaction becomes first order in the halogenating species. See, for example, Tapuhi; Jencks *J. Am. Chem. Soc.* **1982,** *104*, 5758. For a case in which the reaction is first order in bromine, even at relatively high Br_2 contentration, see Pinkus; Gopalan *J. Am. Chem. Soc.* **1984,** *106*, 2630. For a study of the kinetics of iodination, see Pinkus; Gopalan *Tetrahedron* **1986,** *42*, 3411.

[118]Under some conditions it is possible for step 2 to be rate-determining: Deno; Fishbein *J. Am. Chem. Soc.* **1973,** *95*, 7445.

[119]Bell; Yates *J. Chem. Soc.* **1962,** 1927.

[120]Hochstrasser; Kresge; Schepp; Wirz *J. Am. Chem. Soc.* **1988,** *110*, 7875.

[121]Hooz; Bridson *Can. J. Chem.* **1972,** *50*, 2387.

[122]Stotter; Hill *J. Org. Chem.* **1973,** *38*, 2576.

[123]Reuss; Hassner *J. Org. Chem.* **1974,** *39*, 1785; Blanco; Amice; Conia *Synthesis* **1976,** 194.

[124]Olah; Ohannesian; Arvanaghi; Prakash *J. Org. Chem.* **1984,** *49*, 2032.

[125]Rubottom; Mott *J. Org. Chem.* **1979,** *44*, 1731.

[126]Cambie; Hayward; Jurlina; Rutledge; Woodgate *J. Chem. Soc., Perkin Trans 1.* **1978,** 126.

acetate.[127] α,β-Unsaturated ketones can be converted to α-halo-α,β-unsaturated ketones by treatment with phenylselenium bromide or chloride,[128] and to α-halo-β,γ-unsaturated ketones by two-phase treatment with HOCl.[129]

OS **I,** 127; **II,** 87, 88, 244, 480; **III,** 188, 343, 538; **IV,** 110, 162, 590; **V,** 514; **VI,** 175, 193, 368, 401, 512, 520, 711, 991; **VII,** 271; **69,** 129. See also OS **VI,** 1033; **66,** 194.

2-5 Halogenation of Carboxylic Acids and Acyl Halides
Halogenation or Halo-de-hydrogenation

$$R{-}CH_2{-}COOH + Br_2 \xrightarrow{PBr_3} R{-}\underset{\displaystyle Br}{\underset{|}{CH}}{-}COOH$$

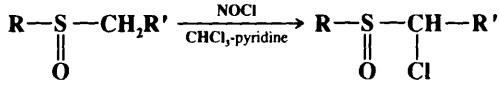
The α hydrogens of carboxylic acids can be replaced by bromine or chlorine with a phosphorus halide as catalyst.[130] The reaction, known as the *Hell–Volhard–Zelinskii reaction*, is not applicable to iodine or fluorine. When there are two α hydrogens, one or both may be replaced, though it is often hard to stop with just one. The reaction actually takes place on the acyl halide formed from the carboxylic acid and the catalyst. The acids alone are inactive, except for those with relatively high enol content, such as malonic. Less than one full mole of catalyst (per mole of substrate) is required, because of the exchange reaction between carboxylic acids and acyl halides (see **0-74**). Each molecule of acid is α halogenated while it is in the acyl halide stage. The halogen from the catalyst does not enter the α position. For example, the use of Cl_2 and PBr_3 results in α chlorination, not bromination. As expected from the foregoing, acyl halides undergo α halogenation without a catalyst. So do anhydrides and many compounds that enolize easily, e.g., malonic ester, aliphatic nitro compounds, etc. The mechanism is usually regarded as proceeding through the enol as in **2-4.**[131] If chlorosulfuric acid $ClSO_2OH$ is used as a catalyst, carboxylic acids can be α iodinated,[132] as well as chlorinated or brominated.[133]

A number of other methods exist for the α halogenation of carboxylic acids or their derivatives.[134] The acids or their chlorides or anhydrides can be α chlorinated by treatment with $CuCl_2$ in polar inert solvents (e.g., sulfolane).[135] Acyl halides can be α brominated or chlorinated by use of N-bromo- or N-chlorosuccinimide and HBr or HCl.[136] The latter is an ionic, not a free-radical halogenation (see **4-2**). Direct iodination of carboxylic acids has been achieved with I_2-Cu(II) acetate in HOAc.[137] Acyl chlorides can be α iodinated with I_2 and a trace of HI.[138] Carboxylic esters can be α halogenated by conversion to their enolate ions with lithium N-isopropylcyclohexylamide in THF and treatment of this solution at −78° with I_2[138] or with a carbon tetrahalide.[139] Carboxylic acids, esters, and amides have been α fluorinated at −78°C with F_2 diluted in N_2.[140]

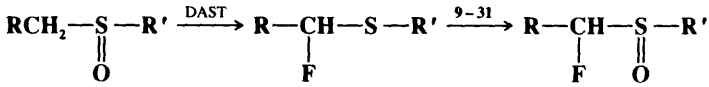
OS **I,** 115, 245; **II,** 74, 93; **III,** 347, 381, 495, 523, 623, 705, 848; **IV,** 254, 348, 398, 608, 616; **V,** 255; **VI,** 90, 190, 403. Also see OS **IV,** 877; **VI,** 427.

[127]Horiuchi; Satoh *Synthesis* **1981,** 312.
[128]Ley; Whittle *Tetrahedron Lett.* **1981,** *22,* 3301.
[129]Hegde; Wolinsky *Tetrahedron Lett.* **1981,** *22,* 5019.
[130]For a review, see Harwood, *Chem. Rev.* **1962,** *62,* 99-154, pp. 102-103.
[131]See, however, Kwart; Scalzi *J. Am. Chem. Soc.* **1964,** *86,* 5496.
[132]Ogata; Watanabe *J. Org. Chem.* **1979,** *44,* 2768, **1980,** *45,* 2831.
[133]Ogata; Sugimoto *J. Org. Chem.* **1978,** *43,* 3684; Ogata; Adachi *J. Org. Chem.* **1982,** *47,* 1182.
[134]For a list of reagents, with references, see Ref. 52, pp. 378-380.
[135]Louw *Chem. Commun.* **1966,** 544.
[136]Gleason; Harpp *Tetrahedron Lett.* **1970,** 3431; Harpp; Bao; Black; Gleason; Smith *J. Org. Chem.* **1975,** *40,* 3420.
[137]Horiuchi; Satoh *Chem. Lett.* **1984,** 1509.
[138]Rathke; Lindert *Tetrahedron Lett.* **1971,** 3995.
[139]Arnold; Kulenovic *J. Org. Chem.* **1978,** *43,* 3687.
[140]Purrington; Woodard *J. Org. Chem.* **1990,** *55,* 3423.

2-6 Halogenation of Sulfoxides and Sulfones
Halogenation or **Halo-de-hydrogenation**



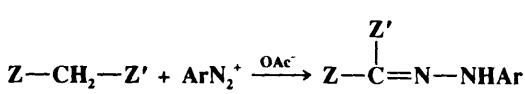
Sulfoxides can be chlorinated in the α position[141] by treatment with Cl_2,[142] TsCl,[143] N-chlorosuccinimide,[144] or $PhICl_2$,[145] all in the presence of pyridine, or with *t*-BuOCl and KOAc (or pyridine).[146] All these methods involve basic conditions. The reaction can also be accomplished in the absence of base with SO_2Cl_2 in CH_2Cl_2.[147] The bromination of sulfoxides with bromine[145] and with N-bromosuccinimide–bromine[148] have also been reported. Sulfones have been chlorinated by treatment of their conjugate bases $RSO_2\overline{C}\overset{\ominus}{H}R'$ with various reagents, among them SO_2Cl_2, CCl_4,[149] N-chlorosuccinimide,[150] and hexachloroethane.[151] The α fluorination of sulfoxides has been accomplished in a two-step pro-



cedure. Treatment with diethylaminosulfur trifluoride Et_2NSF_3 (DAST) produces an α-fluoro thioether, usually in high yield. Oxidation of this compound with *m*-chloroperbenzoic acid gives the sulfoxide.[152]

C. Nitrogen Electrophiles

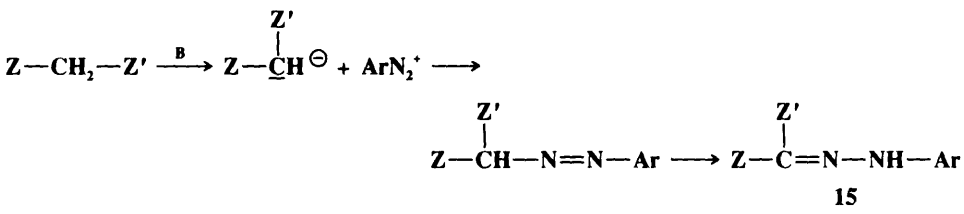
2-7 Aliphatic Diazonium Coupling
Arylhydrazono-de-dihydro-bisubstitution



If a C—H bond is acidic enough, it couples with diazonium salts in the presence of a base, most often aqueous sodium acetate.[153] The reaction is commonly carried out on compounds of the form Z—CH_2—Z′, where Z and Z′ are as defined on p. 464, e.g., β-keto esters, β-keto amides, malonic ester.

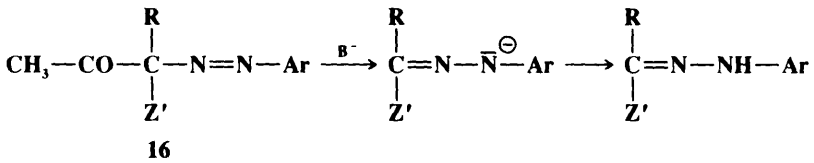
[141]For a review, see Venier; Barager *Org. Prep. Proced. Int.* **1974,** *6*, 77-102, pp. 81-84.
[142]Tsuchithashi; Iriuchijima *Bull. Chem. Soc. Jpn.* **1970,** *43*, 2271.
[143]Hojo; Yoshida *J. Am. Chem. Soc.* **1968,** *90*, 4496.
[144]Ogura; Imaizumi; Iida; Tsuchihasi *Chem. Lett.* **1980,** 1587.
[145]Cinquini; Colonna *J. Chem. Soc., Perkin Trans. I* **1972,** 1883. See also Cinquini; Colonna *Synthesis* **1972,** 259.
[146]Iriuchijima; Tsuchihashi *Tetrahedron Lett.* **1969,** 5259.
[147]Tin; Durst *Tetrahedron Lett.* **1970,** 4643.
[148]Iriuchijima; Tsuchihashi *Synthesis* **1970,** 588.
[149]Regis; Doweyko *Tetrahedron Lett.* **1982,** *23*, 2539.
[150]Paquette; Houser *J. Am. Chem. Soc.* **1969,** *91*, 3870, *J. Org. Chem.* **1971,** *36*, 1015.
[151]Kattenberg; de Waard; Huisman *Tetrahedron* **1973,** *29*, 4149, **1974,** *30*, 463.
[152]McCarthy; Peet; LeTourneau; Inbasekaran *J. Am. Chem. Soc.* **1985,** *107*, 735. See also Umemoto; Tomizawa *Bull. Chem. Soc. Jpn.* **1986,** *59*, 3625.
[153]For a review, see Parmerter *Org. React.* **1959,** *10*, 1-142.

The mechanism is probably of the simple SE1 type:

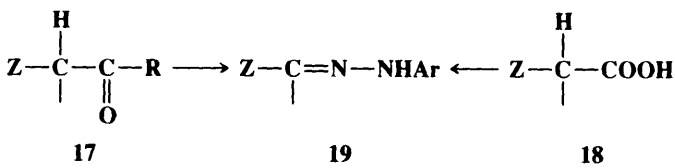


Aliphatic azo compounds in which the carbon containing the azo group is attached to a hydrogen are unstable and tautomerize to the isomeric hydrazones (**15**), which are therefore the products of the reaction.

When the reaction is carried out on a compound of the form Z—CHR—Z', so that the azo compound does not have a tautomerizable hydrogen, if at least one Z is acyl or carboxyl, this group usually cleaves:



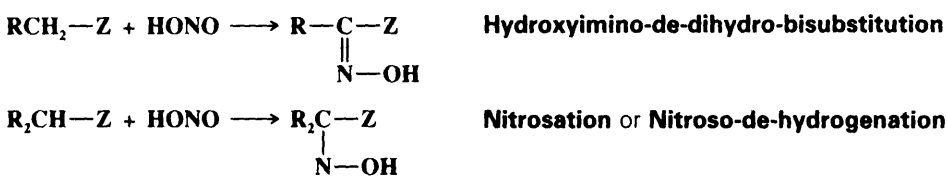
so the product in this case too is the hydrazone, and not the azo compound. In fact, compounds of the type **16** are seldom isolable from the reaction, though this has been accomplished.[154] The cleavage step shown is an example of **2-43** and, when a carbonyl group cleaves, of **2-40.** The overall process in this case is called the *Japp–Klingemann reaction*[155] and involves conversion of a ketone (**17**) or a carboxylic acid (**18**) to a hydrazone (**19**). When



an acyl and a carboxyl group are both present, the leaving group order has been reported to be MeCO > COOH > PhCO.[156] When there is no acyl or carboxyl group present, the aliphatic azo compound is stable.

OS **III,** 660; **IV,** 633.

2-8 Nitrosation at a Carbon Bearing an Active Hydrogen

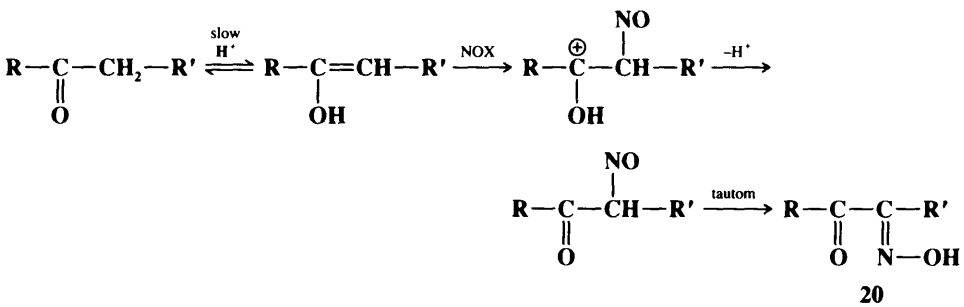


[154]See, for example, Yao; Resnick *J. Am. Chem. Soc.* **1962,** *84,* 3514.

[155]For a review, see Phillips, *Org. React.* **1959,** *10,* 143-178.

[156]Neplyuev; Bazavova; Lozinskii *J. Org. Chem. USSR* **1989,** *25,* 2011. This paper also includes a sequence of leaving group ability for other Z groups.

Carbons adjacent to a Z group (as defined on p. 464) can be nitrosated with nitrous acid or alkyl nitrites.[157] The initial product is the C-nitroso compound, but these are stable only when there is no tautomerizable hydrogen. When there is, the product is the more stable oxime. The situation is analogous to that with azo compounds and hydrazones (**2-7**). The mechanism is similar to that in **2-7**:[158] R—H → R^- + $^+N{=}O$ → R—N=O. The attacking species is either NO^+ or a carrier of it. When the substrate is a simple ketone, the mechanism goes through the enol (as in halogenation **2-4**):

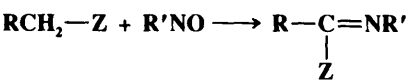


20

Evidence is that the reaction, in the presence of X^- (Br^-, Cl^-, or SCN^-) was first order in ketone and in H^+, but zero order in HNO_2 and X^-.[159] Furthermore, the rate of the nitrosation was about the same as that for enolization of the same ketones. The species NOX is formed by HONO + X^- + H^+ → HOX + H_2O. In the cases of $F_3CCOCH_2COCF_3$ and malononitrile the nitrosation went entirely through the enolate ion rather than the enol.[160]

As in the Japp–Klingemann reaction, when Z is an acyl or carboxyl group (in the case of R_2CH—Z), it can be cleaved. Since oximes and nitroso compounds can be reduced to primary amines, this reaction often provides a route to amino acids. As in the case of **2-4**, the silyl enol ether of a ketone can be used instead of the ketone itself.[161] Good yields of α-oximinoketones (**20**) can be obtained by treating ketones with *t*-butyl thionitrate.[162]

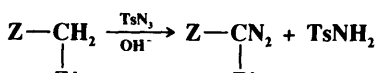
Imines can be prepared in a similar manner by treatment of an active hydrogen compound with a nitroso compound:



Alkanes can be nitrosated photochemically, by treatment with NOCl and uv light.[163] For nitration at an activated carbon, see **4-13.**

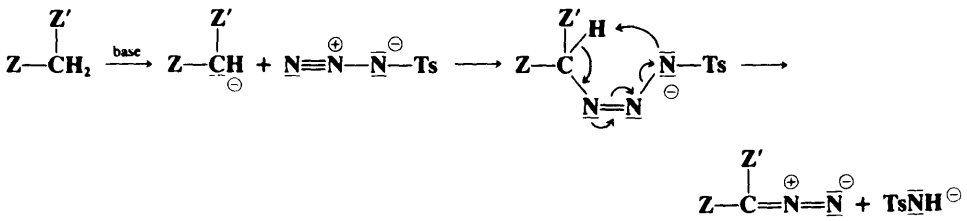
OS **II**, 202, 204, 223, 363; **III**, 191, 513; **V**, 32, 373; **VI**, 199, 840. Also see OS **V**, 650.

2-9 Direct Formation of Diazo Compounds
Diazo-de-dihydro-bisubstitution

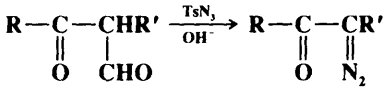


[157]For a review, see Williams *Nitrosation*; Cambridge University Press: Cambridge, 1988, pp. 1-45.
[158]For a review, see Williams *Adv. Phys. Org. Chem.* **1983,** *19*, 381-428. See also Ref. 157.
[159]Leis; Peña; Williams; Mawson *J. Chem. Soc., Perkin Trans. 2* **1988,** 157.
[160]Iglesias; Williams *J. Chem. Soc., Perkin Trans. 2* **1989,** 343; Crookes; Roy; Williams *J. Chem. Soc., Perkin Trans. 2* **1989,** 1015. See also Graham; Williams *J. Chem. Soc., Chem. Commun.* **1991,** 407.
[161]Rasmussen; Hassner *J. Org. Chem.* **1974,** *39*, 2558.
[162]Kim; Park; Kim *Tetrahedron Lett.* **1989,** *30*, 2833.
[163]For a review, see Pape *Fortschr. Chem. Forsch.* **1967,** *7*, 559-604.

Compounds containing a CH_2 bonded to two Z groups (as defined on p. 464) can be converted to diazo compounds on treatment with tosyl azide in the presence of a base.[164] The use of phase transfer catalysis increases the convenience of the method.[165] *p*-Dodecylbenzenesulfonyl azide,[166] methanesulfonyl azide,[167] and *p*-acetamidobenzenesulfonyl azide[168] also give the reaction. The reaction, which is called the *diazo transfer reaction*, can also be applied to other reactive positions, e.g., the 5 position of cyclopentadiene.[169] The mechanism is probably as follows:

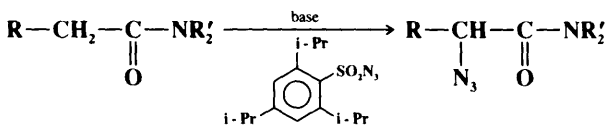


A diazo group can be introduced adjacent to a single carbonyl group indirectly by first converting the ketone to an α-formyl ketone (**0-108**) and then treating it with tosyl azide.



As in the similar cases of **2-7** and **2-8**, the formyl group is cleaved during the reaction.[170] OS **V**, 179; **VI**, 389, 414.

2-10 Conversion of Amides to α-Azido Amides
Azidation or Azido-de-hydrogenation



In reaction **2-9** treatment of Z—CH_2—Z′ with tosyl azide gives diazo transfer. When this reaction is performed on a compound with a single Z group, formation of the azide becomes a competing process.[171] Factors favoring azide formation rather than diazo transfer include

[164]For reviews, see Regitz; Maas *Diazo Compounds*; Academic Press: New York, 1986, pp. 326-435; Regitz *Synthesis* **1972**, 351-373, *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 733-749 [*Angew. Chem. 79*, 786-801], *Newer Methods Prep. Org. Chem.* **1971**, *6*, 81-126. See also Hünig *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 335-344 [*Angew. Chem. 80*, 343-352]; Koskinen; Muñoz *J. Chem. Soc., Chem. Commun.* **1990**, 652.

[165]Ledon *Synthesis* **1974**, 347, *Org. Synth. VI*, 414. For another convenient method, see Ghosh; Datta *Synth. Commun.* **1991**, *21*, 191.

[166]Hazen; Weinstock; Connell; Bollinger *Synth. Commun.* **1981**, *11*, 947.

[167]Taber; Ruckle; Hennessy *J. Org. Chem.* **1986**, *51*, 4077.

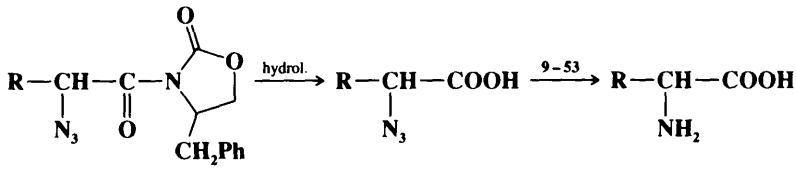
[168]Baum; Shook; Davies; Smith *Synth. Commun.* **1987**, *17*, 1709.

[169]Doering; DePuy *J. Am. Chem. Soc.* **1953**, *75*, 5955.

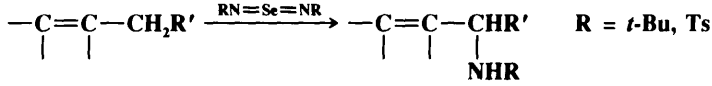
[170]For a similar approach, see Danheiser; Miller; Brisbois; Park *J. Org. Chem.* **1990**, *55*, 1959.

[171]Evans; Britton *J. Am. Chem. Soc.* **1987**, *109*, 6881, and references cited therein.

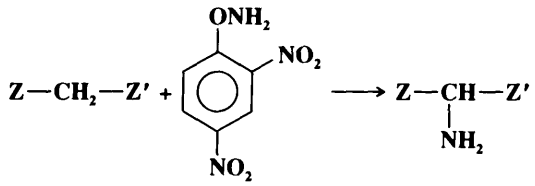
K^+ as the enolate counterion rather than Na^+ or Li^+ and the use of 2,4,6-triisopropylbenzenesulfonyl azide rather than TsN_3. When the reaction was applied to amides with a chiral R′, it was highly stereoselective, and the product could be converted to an optically active amino acid.[171]



2-11 Direct Amination at an Activated Position
Alkyamino-de-hydrogenation, etc.



Alkenes can be aminated[172] in the allylic position by treatment with solutions of imido selenium compounds R—N=Se=N—R.[173] The reaction, which is similar to the allylic oxidation of alkenes with SeO_2 (see **4-4**), has been performed with R = *t*-Bu and R = Ts. The imido sulfur compound TsN=S=NTs has also been used.[174] In another reaction, compounds containing an active hydrogen can be converted to primary amines in moderate yields by treatment with O-(2,4-dinitrophenyl)hydroxylamine.[175]



In an indirect amination process, acyl halides are enantioselectively converted to amino acids.[176] The key step involves addition to the N=N bond of a dialkyl azodicarboxylate **22.**

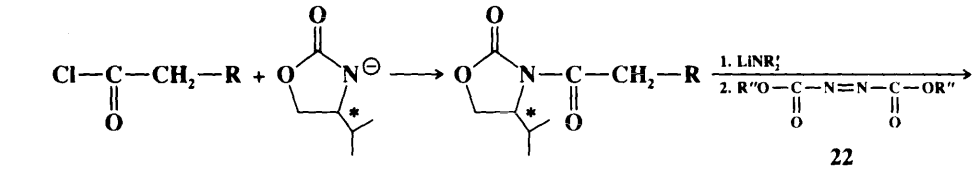
[172]For a review of direct aminations, see Sheradsky, in Patai *The Chemistry of Functional Groups, Supplement F*, pt. 1; Wiley: New York, 1982, pp. 395-416.

[173]Sharpless; Hori; Truesdale; Dietrich *J. Am. Chem. Soc.* **1976,** *98*, 269. For another method, see Kresze; Münsterer *J. Org. Chem.* **1983,** *48*, 3561. For a review, see Cheikh; Chaabouni; Laurent; Mison; Nafti *Synthesis* **1983,** 685-700, pp. 691-696.

[174]Sharpless; Hori, *J. Org. Chem.* **1979,** *41*, 176; Singer; Sharpless *J. Org. Chem.* **1978,** *43*, 1448. For other reagents, see Mahy; Bedi; Battioni; Mansuy *Tetrahedron Lett.* **1988,** *29*, 1927; Tsushima; Yamada; Onami; Oshima; Chaney; Jones; Swartzendruber *Bull. Chem. Soc. Jpn.* **1989,** *62*, 1167.

[175]Sheradsky; Salemnick; Nir *Tetrahedron* **1972,** *28* 3833; Radhakrishna; Loudon; Miller *J. Org. Chem.* **1979,** *44*, 4836.

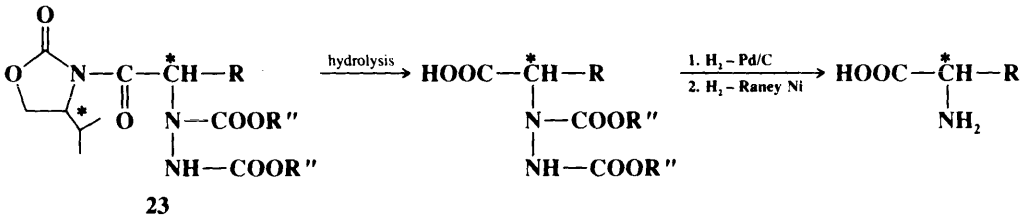
[176]Trimble; Vederas *J. Am. Chem. Soc.* **1986,** *108*, 6397; Evans; Britton; Dorow; Dellaria *J. Am. Chem. Soc.* **1986,** *108*, 6395, *Tetrahedron* **1988,** *44*, 5525; Gennari; Colombo; Bertolini *J. Am. Chem. Soc.* **1986,** *108*, 6394; Oppolzer; Moretti *Helv. Chim. Acta* **1986,** *69*, 1923, *Tetrahedron* **1988,** *44*, 5541; Guanti; Banfi; Narisano *Tetrahedron* **1988,** *44*, 5523.



(+) or (−) enantiomer

21

22



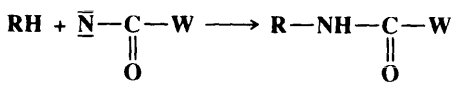
23

* = chiral carbon

In this process the presence of a chiral carbon in **21** induces chirality at the newly formed C—N bond in **23.**

See also **0-50.**

2-12 Insertion by Nitrenes
CH-[Acylimino]-insertion, etc.



Carbonylnitrenes NCOW (W = R′, Ar, or OR′) are very reactive species (p. 202) and insert into the C—H bonds of alkanes to give amides (W = R′ or Ar) or carbamates (W = OR′).[177] The nitrenes are generated as discussed on p. 202. The order of reactivity among alkane C—H bonds is tertiary > secondary > primary.[178] Indications are that in general it is only singlet and not triplet nitrenes that insert.[179] Retention of configuration is found at a chiral carbon.[180] The mechanism is presumably similar to the simple one-step mechanism for insertion of carbenes (**2-20**). Other nitrenes (e.g., cyanonitrene NCN[181] and arylnitrenes NAr[182]) can also insert into C—H bonds, but alkylnitrenes usually undergo rearrangement before they can react with the alkane. The insertion reactions are not generally useful synthetically, since they usually lead to mixtures of products, but exceptions

[177]For a review, see Lwowski, in Lwowski *Nitrenes*; Wiley: New York, 1970, pp. 199-207.

[178]For example, see Maslak *J. Am. Chem. Soc.* **1989,** *111*, 8201. Nitrenes are much more selective (and less reactive) in this reaction than carbenes (**2-20**). For a discussion, see Alewood; Kazmaier; Rauk *J. Am. Chem. Soc.* **1973,** *95*, 5466.

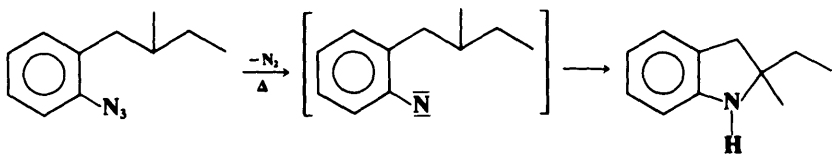
[179]For example, see Simson; Lwowski *J. Am. Chem. Soc.* **1969,** *91*, 5107; Inagaki; Shingaki; Nagai *Chem. Lett.* **1981,** 1419.

[180]Smolinsky; Feuer *J. Am. Chem. Soc.* **1964,** *86*, 3085.

[181]For a review of cyanonitrenes, see Anastassiou; Shepelavy; Simmons; Marsh, in Lwowski, Ref. 177, pp. 305-344.

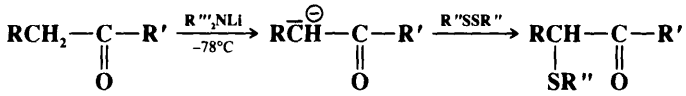
[182]For a review of arylnitrenes, see Scriven *Azides and Nitrenes*; Academic Press: New York, 1984, pp. 95-204.

are known,[183] chiefly in cyclizations.[184] For example, heating of 2-(2-methylbutyl)phenyl azide gave about 60% 2-ethyl-2-methylindoline.[180]



D. Sulfur Electrophiles

2-13 Sulfenylation and Selenylation of Ketones and Carboxylic Esters **Alkylthio-de-hydrogenation,** etc.



Ketones, carboxylic esters (including lactones),[185] and amides (including lactams)[186] can be sulfenylated in the α position by conversion to the enolate ion with a base such as lithium N-isopropylcyclohexylamide and treatment of this with a disulfide.[187] The reaction, shown above for ketones, involves nucleophilic substitution at sulfur. Analogously, α-phenylseleno ketones RCH(SePh)COR′ and α-phenylseleno esters RCH(SePh)COOR′ can be prepared[188] by treatment of the corresponding enolates with PhSeBr,[189] PhSeSePh,[190] or benzeneseleninic anhydride PhSe(O)OSe(O)Ph.[191] Another method for the introduction of a phenylseleno group into the α position of a ketone involves simple treatment of an ethyl acetate solution of the ketone with PhSeCl (but not PhSeBr) at room temperature.[192] This procedure is also successful for aldehydes but not for carboxylic esters. In another method that avoids the use of PhSeX reagents, a ketone enolate is treated with selenium to give an R′COCHRSe$^-$ ion, which is treated with MeI, producing the α-methylseleno ketone R′COCHRSeMe.[193] This method has also been applied to carboxylic esters.

The α-seleno and α-sulfenyl carbonyl compounds prepared by this reaction can be converted to α,β-unsaturated carbonyl compounds (**7-12**). The sulfenylation reaction has also

[183]For a synthetically useful noncyclization example, see Meinwald; Aue *Tetrahedron Lett.* **1967,** 2317.

[184]For a list of examples, with references, see Ref. 52, p. 564.

[185]Trost; Salzmann *J. Am. Chem. Soc.* **1973,** *95,* 6840; Seebach; Teschner *Tetrahedron Lett.* **1973,** 5113. For discussions, see Trost *Pure Apple. Chem.* **1975,** *43,* 563-585, pp. 572-578; Caine, in Augustine *Carbon–Carbon Bond Formation*, vol. 1; Marcel Dekker: New York, 1979, pp. 278-282.

[186]Zoretic; Soja *J. Org. Chem.* **1976,** *41,* 3587; Gassman; Balchunis *J. Org. Chem.* **1977,** *42,* 3236.

[187]For another reagent, see Scholz *Synthesis* **1983,** 944.

[188]For reviews of selenylations, see Back, in Liotta *Organoselenium Chemistry*; Wiley: New York, 1987, pp. 1-125; Paulmier *Selenium Reagents and Intermediates in Organic Synthesis*; Pergamon: Elmsford, NY, 1986, pp. 95-98.

[189]Reich; Reich; Renga *J. Am. Chem. Soc.* **1973,** *95,* 5813; Clive *J. Chem. Soc., Chem. Commun.* **1973,** 695; Brocksom; Petragnani; Rodrigues *J. Org. Chem.* **1974,** *39,* 2114; Schwartz; Hayasi *Tetrahedron Lett.* **1980,** *21,* 1497. See also Liotta *Acc. Chem. Res.* **1984,** *17,* 28-34.

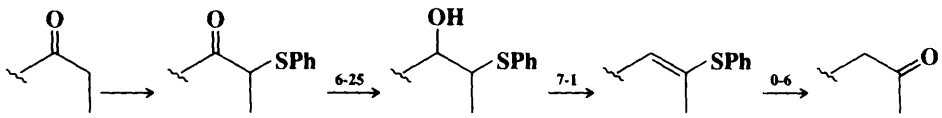
[190]Grieco; Miyashita *J. Org. Chem.* **1974,** *39,* 120. α Phenylselenation can also be accomplished with PhSeSePh, SeO_2, and an acid catalyst: Miyoshi; Yamamoto; Kambe; Murai; Sonoda *Tetrahedron Lett.* **1982,** *23,* 4813.

[191]Barton; Lester; Ley *J. Chem. Soc., Perkin Trans. 1* **1980,** 2209; Barton; Morzycki; Motherwell; Ley *J. Chem. Soc., Chem. Commun.* **1981,** 1044.

[192]Sharpless; Lauer; Teranishi *J. Am. Chem. Soc.* **1973,** *95,* 6137.

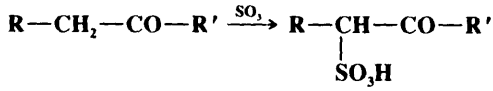
[193]Liotta; Zima; Barnum; Saindane *Tetrahedron Lett.* **1980,** *21,* 3643; Liotta; Saindane; Barnum; Ensley; Balakrishnan *Tetrahedron Lett.* **1981,** *22,* 3043; Liotta, Ref. 189.

been used[194] as a key step in a sequence for moving the position of a carbonyl group to an adjacent carbon.[195]



OS **VI,** 23, 109; **68,** 8.

2-14 Sulfonation of Aldehydes, Ketones, and Carboxylic Acids
Sulfonation or **Sulfo-de-hydrogenation**

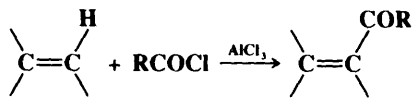


Aldehydes, ketones, and carboxylic acids containing α hydrogens can be sulfonated with sulfur trioxide.[196] The mechanism is presumably similar to that of **2-4.** Sulfonation has also been accomplished at vinylic hydrogen.

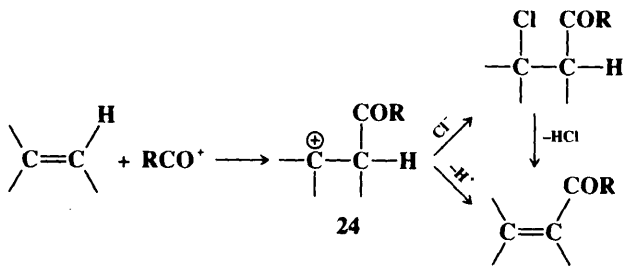
OS **IV,** 846, 862.

E. Carbon Electrophiles. With respect to the attacking molecule, these are nucleophilic substitutions.

2-15 Acylation at an Aliphatic Carbon
Acylation or **Acyl-de-hydrogenation**



Olefins can be acylated with an acyl halide and a Lewis-acid catalyst in what is essentially a Friedel–Crafts reaction at an aliphatic carbon.[197] The product can arise by two paths. The initial attack is by the acyl cation RCO^+ (or by the acyl halide free or complexed; see **1-14**) at the double bond to give a carbocation:



[194]Trost; Hiroi; Kurozumi *J. Am. Chem. Soc.* **1975,** *97,* 438.

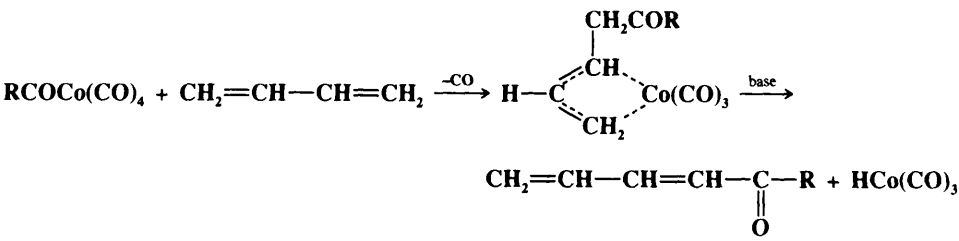
[195]There are numerous other ways of achieving this conversion. For reviews, see Morris *Chem. Soc. Rev.* **1982,** *11,* 397-434; Kane; Singh; Martin; Doyle *Tetrahedron* **1983,** *39,* 345-394.

[196]For a review, see Gilbert *Sulfonation and Related Reactions*; Wiley: New York, 1965, pp. 33-61.

[197]For reviews, see Groves *Chem. Soc. Rev.* **1972,** *1,* 73-97; Satchell; Satchell in Patai *The Chemistry of the Carbonyl Group*, vol. 1; Wiley: New York, 1966, pp. 259-266, 270-273; Nenitzescu; Balaban, in Olah *Friedel–Crafts and Related Reactions*, vol. 3; Wiley: New York, 1964, pp. 1033-1152.

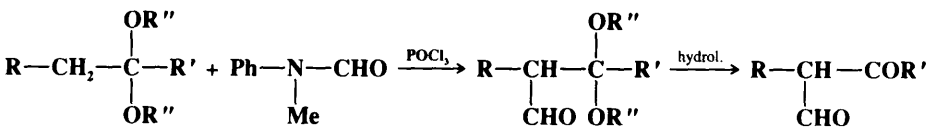
Ion **24** can either lose a proton or combine with chloride ion. If it loses a proton, the product is an unsaturated ketone; the mechanism is similar to the tetrahedral mechanism of Chapter 10, but with the charges reversed. If it combines with chloride, the product is a β-halo ketone, which can be isolated, so that the result is addition to the double bond (see **5-34**). On the other hand, the β-halo ketone may, under the conditions of the reaction, lose HCl to give the unsaturated ketone, this time by an addition–elimination mechanism. In the case of unsymmetrical olefins, the attacking ion prefers the position at which there are more hydrogens, following Markovnikov's rule (p. 750). Anhydrides and carboxylic acids (the latter with a proton acid such as anhydrous HF, H_2SO_4, or polyphosphoric acid as a catalyst) are sometimes used instead of acyl halides. With some substrates and catalysts double-bond migrations are occasionally encountered so that, for example, when 1-methylcyclohexene was acylated with acetic anhydride and zinc chloride, the major product was 6-acetyl-1-methylcyclohexene.[198]

Conjugated dienes can be acylated by treatment with acyl- or alkylcobalt tetracarbonyls, followed by base-catalyzed cleavage of the resulting π-allyl carbonyl derivatives.[199] The



reaction is very general. With unsymmetrical dienes, the acyl group generally substitutes most readily at a cis double bond, next at a terminal olefinic group, and least readily at a trans double bond. The most useful bases are strongly basic, hindered amines such as dicyclohexylethylamine. The use of an alkylcobalt tetracarbonyl $RCo(CO)_4$ gives the same product as that shown above. Acylation of vinylic ethers has been accomplished with aromatic acyl chlorides, a base, and a palladium catalyst: $ROCH{=}CH_2 \rightarrow ROCH{=}CHCOAr$.[200]

Formylation of olefins can be accomplished with N-disubstituted formamides and $POCl_3$.[201] This is an aliphatic Vilsmeier reaction (see **1-15**). Vilsmeier formylation can also be performed on the α position of acetals and ketals, so that hydrolysis of the products gives keto aldehydes or dialdehydes:[202]



Acetylation of acetals or ketals can be accomplished with acetic anhydride and BF_3–etherate.[203] The mechanism with acetals or ketals also involves attack at an olefinic carbon,

[198]Deno; Chafetz *J. Am. Chem. Soc.* **1952,** *74*, 3940. For other examples, see Beak; Berger *J. Am. Chem. Soc.* **1980,** *102*, 3848; Dubois; Saumtally; Lion *Bull. Soc. Chim. Fr.* **1984,** II-133; Grignon-Dubois; Cazaux *Bull. Soc. Chim. Fr.* **1986,** 332.

[199]For a review, see Heck, in Wender; Pino *Organic Syntheses via Metal Carbonyls*, vol. 1; Wiley: New York, 1968, pp. 388-397.

[200]Andersson; Hallberg *J. Org. Chem.* **1988,** *53*, 4257.

[201]For reviews, see Burn *Chem. Ind. (London)* **1973,** 870-873; Satchell; Satchell, Ref. 197, pp. 281-282.

[202]Youssefyeh *Tetrahedron Lett.* **1964,** 2161.

[203]Youssefyeh *J. Am. Chem. Soc.* **1963,** *85*, 3901.

since enol ethers are intermediates.[203] Ketones can be formylated in the α position by treatment with CO and a strong base.[204]

OS **IV,** 555, 560; **VI,** 744. Also see OS **VI,** 28.

2-16 Conversion of Aldehydes to β-Keto Esters or Ketones
Alkoxycarbonylalkylation or Alkoxycarbonylalkyl-de-hydrogenation

$$R{-}\underset{\underset{O}{\|}}{C}{-}H + EtOOC{-}CHN_2 \xrightarrow[CH_2Cl_2]{SnCl_2} R{-}\underset{\underset{O}{\|}}{C}{-}CH_2{-}COOEt$$

β-Keto esters have been prepared in moderate to high yields by treatment of aldehydes with diethyl diazoacetate in the presence of a catalytic amount of a Lewis acid such as $SnCl_2$, BF_3, or $GeCl_2$.[205] The reaction was successful for both aliphatic and aromatic aldehydes, but the former react more rapidly than the latter, and the difference is great enough to allow selective reactivity. In a similar process, aldehydes react with certain carbanions stabilized by boron, in the presence of $(F_3CCO)_2O$ or N-chlorosuccinimide, to give ketones.[206]

$$R{-}\underset{\underset{O}{\|}}{C}{-}H + \overset{\ominus}{\underset{\underset{BAr_2}{|}}{C}}H{-}R' \xrightarrow[\text{or NCS}]{(F_3CCO)_2O} R{-}\underset{\underset{O}{\|}}{C}{-}CH_2R' \qquad Ar = \text{mesityl}$$

2-17 Cyanation or Cyano-de-hydrogenation

$$R{-}\underset{\underset{O}{\|}}{C}{-}\underset{|}{CH} \xrightarrow[\text{2. TsCN}]{\text{1. LDA—THF}} R{-}\underset{\underset{O}{\|}}{C}{-}\underset{|}{C}{-}CN$$

Introduction of a cyano group α to the carbonyl group of a ketone can be accomplished by prior formation of the enolate with lithium diisopropylamide (LDA) in THF and addition of this solution to *p*-TsCN at −78°C.[207] The products are formed in moderate to high yields. The reaction is not applicable to methyl ketones. In a different kind of reaction, nitro compounds are α cyanated by treatment with CN^- and $K_3Fe(CN)_6$.[208] The mechanism probably involves ion radicals. In still another reaction, secondary amines are converted to α-cyanoamines by treatment with phenylseleninic anhydride and NaCN or Me_3SiCN.[209] Me_3SiCN has also been used in a reaction that cyanates benzylic positions.[210]

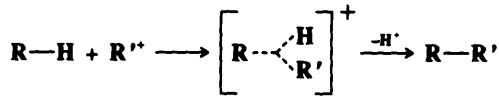
2-18 Alkylation of Alkanes
Alkylation or Alkyl-de-hydrogenation

$$RH + R'^+ \longrightarrow R{-}R' + H^+$$

Alkanes can be alkylated by treatment with solutions of stable carbocations[211] (p. 166), though the reaction is not generally useful for synthesis. Mixtures are usually obtained. In

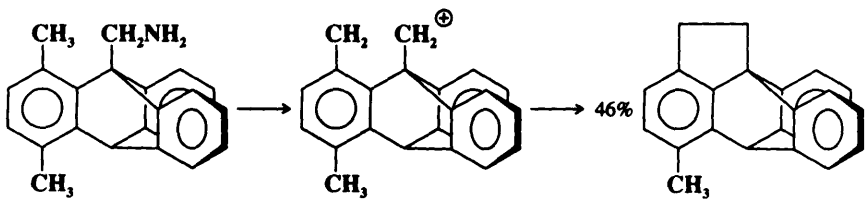
[204]See, for example, van der Zeeuw; Gersmann *Recl. Trav. Chim. Pays-Bas* **1965,** *84,* 1535.
[205]Holmquist; Roskamp *J. Org. Chem.* **1989,** *54,* 3258.
[206]Pelter; Smith; Elgendy; Rowlands *Tetrahedron Lett.* **1989,** *30,* 5643.
[207]Kahne; Collum *Tetrahedron Lett.* **1981,** *22,* 5011.
[208]Matacz; Piotrowska; Urbanski *Pol. J. Chem.* **1979,** *53,* 187; Kornblum; Singh; Kelly *J. Org. Chem.* **1983,** *48,* 332.
[209]Barton; Billion; Boivin *Tetrahedron Lett.* **1985,** *26,* 1229.
[210]Lemaire; Doussot; Guy *Chem. Lett.* **1988,** 1581. See also Hayashi; Mukaiyama *Chem. Lett.* **1987,** 1811.
[211]Olah; Mo; Olah *J. Am. Chem. Soc.* **1973,** 95, 4939. For reviews, see Olah; Farooq; Prakash, in Hill *Activation and Functionalization of Alkanes*; Wiley: New York, 1989, pp. 27-78; Olah; Prakash; Sommer, Ref. 44, pp. 270-277. For a review of the thermodynamic behavior of alkanes in super-acid media, see Fabre; Devynck; Trémillon *Chem. Rev.* **1982,** *82,* 591-614. See also Ref. 46.

a typical experiment, the treatment of propane with isopropyl fluoroantimonate (Me_2C^+ SbF_6^-) gave 26% 2,3-dimethylbutane, 28% 2-methylpentane, 14% 3-methylpentane, and 32% *n*-hexane, as well as some butanes, pentanes (formed by **2-47**), and higher alkanes. Mixtures arise in part because intermolecular hydrogen exchange ($RH + R'^+ \rightleftharpoons R^+ + R'H$) is much faster than alkylation, so that alkylation products are also derived from the new alkanes and carbocations formed in the exchange reaction. Furthermore, the carbocations present are subject to rearrangement (Chapter 18), giving rise to new carbocations. Products result from all the hydrocarbons and carbocations present in the system. As expected from their relative stabilities, secondary alkyl cations alkylate alkanes more readily than tertiary alkyl cations (the *t*-butyl cation does not alkylate methane or ethane). Stable primary alkyl cations are not available, but alkylation has been achieved with complexes formed between CH_3F or C_2H_5F and SbF_5.[212] The mechanism of alkylation can be formulated (similar to that shown in hydrogen exchange with super acids, **2-1**) as



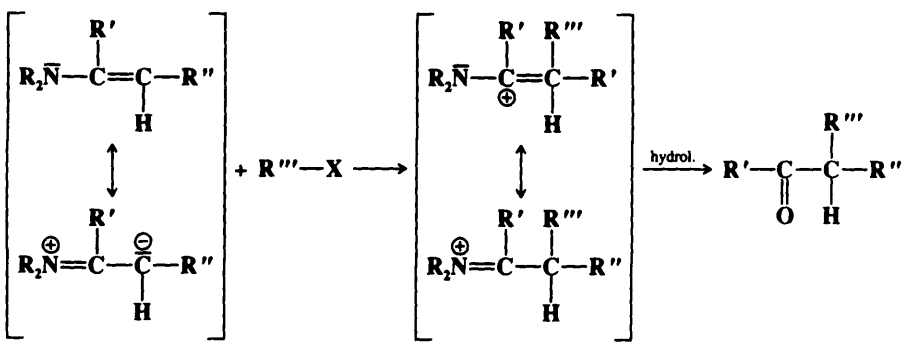
It is by means of successive reactions of this sort that simple alkanes like methane and ethane give *t*-butyl cations in super-acid solutions (p. 168).[213]

Intramolecular insertion has been reported. The positively charged carbon of the carbocation **26**, generated from the diazonium salt of the triptycene compound **25**, reacted with the CH_3 group in close proximity with it.[214]



25 **26**

2-19 The Stork Enamine Reaction
α-Acylalkyl-de-halogenation[215]



[212]Olah; DeMember; Shen *J. Am. Chem. Soc.* **1973**, *95*, 4952. See also Sommer; Muller; Laali *Nouv. J. Chem.* **1982**, *6*, 3.

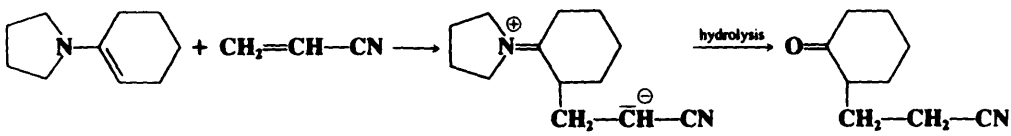
[213]For example, see Hogeveen; Roobeek *Recl. Trav. Chim. Pays-Bas* **1972**, *91*, 137.

[214]Yamamoto; Oki *Chem. Lett.* **1987**, 1163.

[215]This is the IUPAC name with respect to the halide as substrate.

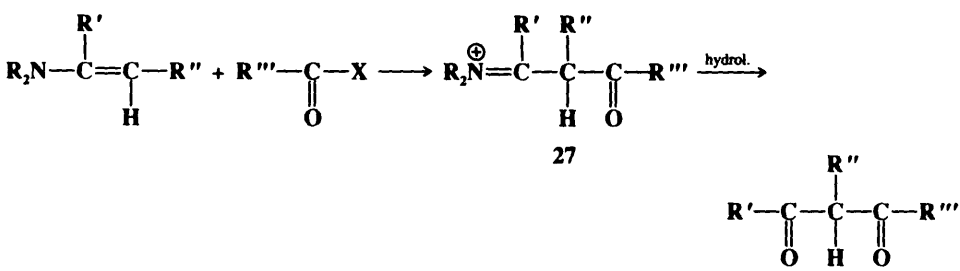
When enamines are treated with alkyl halides, an alkylation occurs that is analogous to the first step of **2-15.** Hydrolysis of the imine salt gives a ketone. Since the enamine is normally formed from a ketone (**6-14**), the net result is alkylation of the ketone at the α position. The method, known as the *Stork enamine reaction*,[216] is an alternative to the ketone alkylation considered at **0-95.** The Stork method has the advantage that it generally leads almost exclusively to monoalkylation of the ketone, while **0-95,** when applied to ketones, is difficult to stop with the introduction of just one alkyl group. Alkylation usually takes place on the less substituted side of the original ketone. The most commonly used amines are the cyclic amines piperidine, morpholine, and pyrrolidine.

The method is quite useful for particulary active alkyl halides such as allylic, benzylic, and propargylic halides, and for α-halo ethers and esters, but is not very serviceable for ordinary primary and secondary halides. Tertiary halides do not give the reaction at all since, with respect to the halide, this is nucleophilic substitution and elimination predominates. The reaction can also be applied to activated aryl halides (such as 2,4-dinitrochlorobenzene; see Chapter 13), to epoxides,[217] and to activated olefins such as acrylonitrile, e.g.,



The latter is a Michael-type reaction (p. 742) with respect to the olefin.

Acylation[218] can be accomplished with acyl halides:



or with anhydrides. A COOEt group can be introduced by treatment of the enamine with ethyl chloroformate ClCOOEt,[219] a CN group with cyanogen chloride[220] (not cyanogen bromide or iodide, which leads to halogenation of the enamine), a CHO group with the mixed anhydride of formic and acetic acids[219] or with DMF and phosgene,[221] and a

[216]Stork; Brizzolara; Landesman; Szmuszkovicz; Terrell *J. Am. Chem. Soc.* **1963,** *85*, 207. For general reviews of enamines, see Hickmott *Tetrahedron* **1984,** *40*, 2989-3051, **1982,** *38*, 1975-2050, 3363-3446; Granik *Russ. Chem. Rev.* **1984,** *53*, 383-400. For reviews of this reaction, see in Cook *Enamines*, 2nd ed.; Marcel Dekker: New York, 1988, the articles by Alt; Cook pp. 181-246, and Gadamasetti; Kuehne, pp. 531-689; Whitesell; Whitesell *Synthesis* **1983,** 517-536; Kuehne *Synthesis* **1970,** 510-537; House, Ref. 86, pp. 570-582, 766-772; Bláha; Červinka *Adv. Heterocycl. Chem.* **1966,** *6*, 147-227, pp. 186-204.

[217]Britten; Owen; Went *Tetrahedron* **1969,** *25*, 3157.

[218]For reviews, see Hickmott *Chem. Ind.* (*London*) **1974,** 731; Hünig; Hoch *Fortschr. Chem. Forsch.* **1970,** *14*, 235.

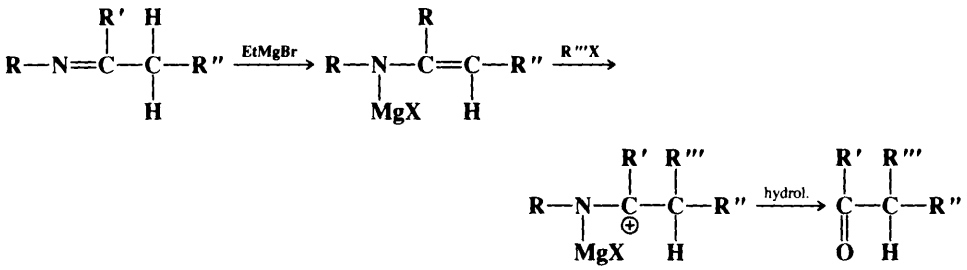
[219]Stork et al., Ref. 216.

[220]Kuehne *J. Am. Chem. Soc.* **1959,** *81*, 5400.

[221]Ziegenbein *Angew. Chem. Int. Ed. Engl.* **1965,** *4*, 358 [*Angew. Chem. 77*, 380].

C(R)=NR′ group with a nitrilium salt $RC{\equiv}\overset{\oplus}{N}R'$.[222] The acylation of the enamine can take place by the same mechanism as alkylation, but another mechanism is also possible, if the acyl halide has an α hydrogen and if a tertiary amine is present, as it often is (it is added to neutralize the HX given off). In this mechanism, the acyl halide is dehydrohalogenated by the tertiary amine, producing a ketene (**7-14**) which adds to the enamine to give a cyclobutanone (**5-49**). This compound can be cleaved in the solution to form the same acylated imine salt (**27**) that would form by the more direct mechanism, or it can be isolated (in the case of enamines derived from aldehydes), or it may cleave in other ways.[223]

Primary and secondary halides do not perform well, mostly because N-alkylation becomes important, particularly with enamines derived from aldehydes. An alternative method, which gives good yields of alkylation with primary and secondary halides, is alkylation of enamine *salts*, which are prepared by treating an imine with ethylmagnesium bromide in THF:[224]



The imines are prepared by **6-14.** The enamine salt method has also been used to give good yields of mono α alkylation of α,β-unsaturated ketones.[225] Enamines prepared from aldehydes and butylisobutylamine can be alkylated by simple primary alkyl halides in good yields.[226] N-alkylation in this case is presumably prevented by steric hindrance.

When the nitrogen of the substrate contains a chiral R group, both the Stork enamine synthesis and the enamine salt method can be used to perform enantioselective syntheses, and this has often been done.[227]

OS **V,** 533, 869; **VI,** 242, 496, 526; **VII,** 473.

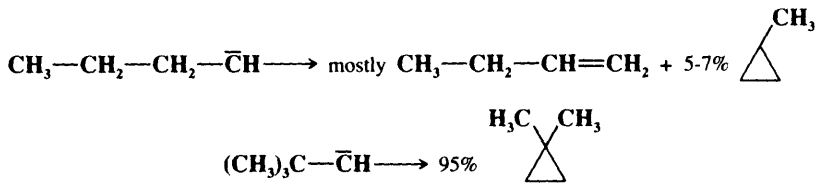
2-20 Insertion by Carbenes
CH-Methylene-insertion

$$RH + \overline{C}H_2 \longrightarrow RCH_3$$

The highly reactive species methylene inserts into C—H bonds,[228] both aliphatic and aromatic,[229] though with aromatic compounds ring expansion is also possible (see **5-50**). The reaction is useless for synthetic purposes because of its nonselectivity (see p. 199). Alkyl-

[222]Baudoux; Fuks *Bull. Soc. Chim. Belg.* **1984,** *93*, 1009.
[223]See Alt; Cook, Ref. 216, pp. 204-215.
[224]Stork; Dowd *J. Am. Chem. Soc.* **1963,** *85*, 2178.
[225]Stork; Benaim *J. Am. Chem. Soc.* **1971,** *93*, 5938.
[226]Curphey; Hung; Chu *J. Org. Chem.* **1975,** *40*, 607. See also Ho; Wong *Synth. Commun.* **1974,** *4*, 147.
[227]For reviews, see Nóagrádi *Stereoselective Synthesis*; VCH: New York, 1986, pp. 248-255; Whitesell *Acc. Chem. Res.* **1985,** *18*, 280-284; Bergbreiter; Newcomb, in Morrison, Ref. 68, vol. 2, 1983, pp. 243-273.
[228]First reported by Meerwein; Rathjen; Werner *Ber.* **1942,** *75*, 1610. For reviews, see Bethell, in McManus *Organic Reactive Intermediates*; Academic Press: New York, 1973, pp. 92-101; Kirmse *Carbene Chemistry*, 2nd ed.; Academic Press: New York, 1971, pp. 209-266.
[229]Terao; Shida *Bull. Chem. Soc. Jpn.* **1964,** *37*, 687.

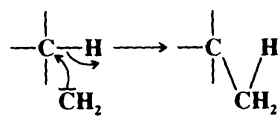
carbenes usually rearrange rather than give insertion (p. 201), but, when this is impossible, *intramolecular* insertion[230] is found rather than intermolecular.[231]



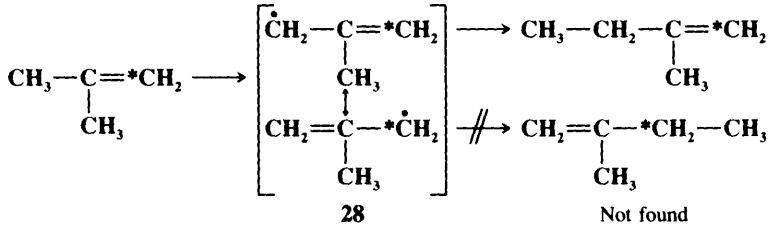
CH_2 generated by photolysis of CH_2N_2 in the liquid phase is indiscriminate—totally nonselective—in its reactivity (p. 199). CH_2 generated in other ways and other carbenes are less reactive and insert in the order tertiary > secondary > primary.[232] Halocarbenes insert much less readily, though a number of instances have been reported.[233] Nevertheless, even for less reactive carbenes, the insertion reaction has seldom been used for synthetic purposes.[234] The carbenes can be generated in any of the ways mentioned in Chapter 5 (p. 198). For the similar insertion of nitrenes, see **2-12.**

The mechanism[235] of the insertion reaction is not known with certainty, but there seem to be at least two possible pathways.

1. A simple one-step process involving a three-center cyclic transition state:



The most convincing evidence for this mechanism is that in the reaction between isobutene-1-^{14}C and carbene the product 2-methyl-1-butene was labeled only in the 1 position.[236] This rules out a free radical or other free intermediate such as a carbocation or carbanion. If **28** (or a corresponding ion) were an intermediate, resonance would ensure that some carbene attacked at the 1 position:



28 Not found

[230]Kirmse; Doering *Tetrahedron* **1960,** *11*, 266; Friedman; Berger *J. Am. Chem. Soc.* **1961,** *83*, 492, 500.

[231]For a review of the intramolecular insertions of carbenes or carbenoids generated from diazocarbonyl compounds, see Burke; Grieco *Org. React.* **1979,** *26*, 361-475.

[232]Doering; Knox *J. Am. Chem. Soc.* **1961,** *83*, 1989.

[233]For example, see Parham; Koncos *J. Am. Chem. Soc.* **1961,** *83*, 4034; Fields *J. Am. Chem. Soc.* **1962,** *82*, 1744; Anderson; Lindsay; Reese *J. Chem. Soc.* **1964,** 4874; Seyferth; Cheng *J. Am. Chem. Soc.* **1973,** *95*, 6763, *Synthesis* **1974,** 114; Steinbeck *Tetrahedron Lett.* **1978,** 1103; Boev *J. Org. Chem. USSR* **1981,** *17*, 1190.

[234]For some examples of intramolecular carbene insertions used synthetically, see Gilbert; Giamalva; Weerasooriya *J. Org. Chem.* **1983,** *48*, 5251; Taber; Ruckle *J. Am. Chem. Soc.* **1986,** *108*, 7686; Paquette; Kobayashi; Gallucci *J. Am. Chem. Soc.* **1988,** *110*, 1305; Adams; Poupart; Grenier; Schaller; Ouimet; Frenette *TetrahedronLett.* **1989,** *30*, 1749; Doyle; Bagheri; Pearson; Edwards *Tetrahedron Lett.* **1989,** *30*, 7001.

[235]For a discussion, see Bethell, *Adv. Phys. Org. Chem.* **1969,** 7, 153-209, pp. 190-194.

[236]Doering; Prinzbach *Tetrahedron* **1959,** 6, 24.

Other evidence is that retention of configuration, which is predicted by this mechanism, has been found in a number of instances.[237]

2. A free-radical process in which the carbene directly abstracts a hydrogen from the substrate to generate a pair of free radicals:

$$RH + CH_2 \longrightarrow R\cdot + CH_3\cdot$$

$$R\cdot + CH_3\cdot \longrightarrow RCH_3$$

One fact supporting this mechanism is that among the products obtained (beside butane and isobutane) on treatment of propane with CH_2 (generated by photolysis of diazomethane and ketene) were propene and ethane,[238] which could arise, respectively, by

$$2CH_3CH_2CH_2\cdot \longrightarrow CH_3CH{=}CH_2 + CH_3CH_2CH_3 \quad \text{(disproportionation)}$$

and

$$CH_3CH_2CH_3 + \bar{C}H_2 \longrightarrow CH_3CH_2CH_2\cdot + CH_3\cdot$$

$$2CH_3\cdot \longrightarrow CH_3CH_3$$

That this mechanism can take place under suitable conditions has been demonstrated by isotopic labeling[239] and by other means.[240] However, the obtention of disproportionation and dimerization products does not always mean that the free-radical abstraction process takes place. In some cases these products arise in a different manner.[241] We have seen that the product of the reaction between a carbene and a molecule may have excess energy (p. 197). Therefore it is possible for the substrate and the carbene to react by mechanism 1 (the direct-insertion process) and for the excess energy to cause the compound thus formed to cleave to free radicals. When this pathway is in operation, the free radicals are formed *after* the actual insertion reaction.

It has been suggested[242] that singlet carbenes insert by the one-step direct-insertion process and triplets (which, being free radicals, are more likely to abstract hydrogen) by the free-radical process. In support of this suggestion is that CIDNP signals[243] (p. 187) were observed in the ethylbenzene produced from toluene and triplet CH_2, but not from the same reaction with singlet CH_2.[244] Carbenoids (e.g., compounds of the form R_2CMCl—see **2-39**) can insert into a C—H bond by a different mechanism, similar to pathway 2, but involving abstraction of a hydride ion rather than a hydrogen atom.[245]

The reaction in which aldehydes are converted to methyl ketones, $RCHO + CH_2N_2 \rightarrow RCOCH_3$, while apparently similar, does not involve a free carbene intermediate. It is considered in Chapter 18 (**8-9**).

OS **VII**, 200.

[237]See, for example, Kirmse; Buschhoff *Chem. Ber.* **1969**, *102*, 1098; Seyferth; Cheng *J. Am. Chem. Soc.* **1971**, *93*, 4072.

[238]Frey *Proc. Chem. Soc.* **1959**, 318.

[239]Halberstadt; McNesby *J. Chem. Phys.* **1966**, *45*, 1666; McNesby; Kelly *Int. J. Chem. Kinet.* **1971**, *3*, 293.

[240]Ring; Rabinovitch *J. Am. Chem. Soc.* **1966**, *88*, 4285, *Can J. Chem.* **1968**, *46*, 2435.

[241]Bell *Prog. Phys. Org. Chem.* **1964**, *2*, 1-61, pp. 30-43.

[242]Richardson; Simmons; Dvoretzky *J. Am. Chem. Soc.* **1961**, *83*, 1934.

[243]For a review of the use of CIDNP to study carbene mechanisms, see Roth *Acc. Chem. Res.* **1977**, *10*, 85-91.

[244]Roth *J. Am. Chem. Soc.* **1972**, *94*, 1761. See also Closs; Closs *J. Am. Chem. Soc.* **1969**, *91*, 4549; Bethell; McDonald *J. Chem. Soc., Perkin Trans. 2* **1977**, 671.

[245]See Harada; Nozaki; Yamaura; Oku *J. Am. Chem. Soc.* **1985**, *107*, 2189; Oku; Yamaura; Harada *J. Org. Chem.* **1986**, *51*, 3730; Ritter; Cohen *J. Am. Chem. Soc.* **1986**, *108*, 3718.

F. Metal Electrophiles

2-21 Metallation with Organometallic Compounds **Metallation** or **Metallo-de-hydrogenation**

$$\mathbf{RH + R'M \longrightarrow RM + R'H}$$

Many organic compounds can be metallated by treatment with an organometallic compound.[246] Since the reaction involves a proton transfer, the equilibrium lies on the side of the weaker acid. For example, fluorene reacts with butyllithium to give butane and 9-fluoryllithium. Since aromatic hydrocarbons are usually stronger acids than aliphatic ones, R is most often aryl. The most common reagent is butyllithium.[247] Normally, only active aromatic rings react with butyllithium. Benzene itself is not reactive enough, though benzene can be metallated by butyllithium either in the presence of *t*-BuOK[248] or coordinated with various diamines.[249] Metallation of aliphatic RH is most successful when the carbanions are stabilized by resonance (allylic, benzylic, propargylic,[250] etc.) or when the negative charge is at an *sp* carbon (at triple bonds). Very good reagents for allylic metallation are trimethylsilylmethyl potassium Me_3SiCH_2K[251] and a combination of an organolithium compound with a bulky alkoxide (LICKOR superbase).[252] The former is also useful for benzylic positions. A combination of BuLi, *t*-BuOK, and tetramethylethylenediamine has been used to convert ethylene to vinylpotassium.[253] In certain cases *gem*-dialkali metal or 1,1,1-trialkali metal compounds can be prepared.[254] Examples are the conversion of phenylacetonitrile to 1,1-dilithiophenylacetonitrile $PhCLi_2CN$[255] and propyne to tetralithiopropyne $Li_3CC{\equiv}CLi$[256] in each case by treatment with excess butyllithium. The reaction can be used to determine relative acidities of very weak acids by allowing two R—H compounds to compete for the same R'M and to determine which proton in a molecule is the most acidic.[257]

In general, the reaction can be performed only with organometallics of active metals such as lithium, sodium, and potassium, but Grignard reagents abstract protons from a sufficiently acidic C—H bond, as in R—C≡C—H → R—C≡C—MgX. This is the best method for the preparation of alkynyl Grignard reagents.[258]

[246]For reviews, see Wardell, in Zuckerman *Inorganic Reactions and Methods*, vol. 11; VCH: New York, 1988, pp. 44-107; Wardell, in Hartley, Patai, Ref. 1, vol. 4, pp. 1-157, pp. 27-71; Narasimhan; Mali *Synthesis* **1983,** 957-986; Biellmann; Ducep *Org. React.* **1982,** *27*, 1-344; Gschwend; Rodriguez *Org. React.* **1979,** *26*, 1-360; Mallan; Bebb *Chem. Rev.* **1969,** *69*, 693-755.

[247]For a review, see Durst, in Buncel; Durst *Comprehensive Carbanion Chemistry*, vol. 5, pt. B; Elsevier: New York, 1984, pp. 239-291, pp. 265-279. For an article on the safe handling of RLi compounds, see Anderson *Chem. Ind. (London)* **1984,** 205.

[248]Schlosser *J. Organomet. Chem.* **1967,** *8*, 9. See also Schlosser; Katsoulos; Takagishi *Synlett* **1990,** 747.

[249]Eberhardt; Butte *J. Org. Chem.* **1964,** *29*, 2928; Langer *Trans. N.Y. Acad. Sci.* **1965,** *27*, 741; Eastham; Screttas *J. Am. Chem. Soc.* **1965,** *87*, 3276; Rausch; Ciappenelli *J. Organomet. Chem.* **1967,** *10*, 127.

[250]For a review of directive effects in allylic and benzylic metallation, see Klein *Tetrahedron* **1983,** *39*, 2733-2759. For a review of propargylic metallation, see Klein, in Patai *The Chemistry of the Carbon–Carbon Triple Bond*, pt. 1; Wiley: New York, 1978, pp. 343-379.

[251]Hartmann; Schlosser *Helv. Chim. Acta* **1976,** *59*, 453.

[252]Schlosser *Pure Appl. Chem.* **1988,** *60*, 1627. For sodium analogs, see Schlosser; Hartmann; Stähle; Kramař; Walde; Mordini *Chimia* **1986,** *40*, 306.

[253]Brandsma; Verkruijsse; Schade; Schleyer *J. Chem. Soc., Chem. Commun.* **1986,** 260.

[254]For a review of di and polylithium compounds, see Maercker; Theis *Top. Curr. Chem.* **1987,** *138*, 1-61.

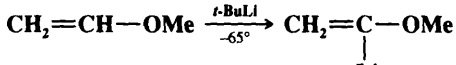
[255]Kaiser; Solter; Schwartz; Beard; Hauser *J. Am. Chem. Soc.* **1971,** *93*, 4237. See also Kowalski; O'Dowd; Burke; Fields *J. Am. Chem. Soc.* **1980,** *102*, 5411.

[256]Priester; West *J. Am. Chem. Soc.* **1976,** *98*, 8421, 8426 and references cited therein.

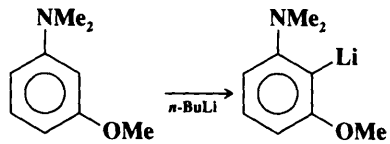
[257]For examples, see Broaddus; Logan; Flautt *J. Org. Chem.* **1963,** *28*, 1174; Finnegan; McNees *J. Org. Chem.* **1964,** *29*, 3234; Shirley; Hendrix *J. Organomet. Chem.* **1968,** *11*, 217.

[258]For a review of the synthetic applications of metallation by Grignard reagents at positions other than at triple bonds, see Blagoev; Ivanov *Synthesis* **1970,** 615-628.

When a hetero atom, such as N, O, S,[259] or a halogen,[260] is present in a molecule containing an aromatic ring or a double bond, lithiation is usually quite regioselective.[261] The lithium usually bonds with the sp^2 carbon closest to the hetero atom, probably because the attacking species coordinates with the hetero atom.[262] In the case of aromatic rings this means attack at the ortho position.[263] Two examples are

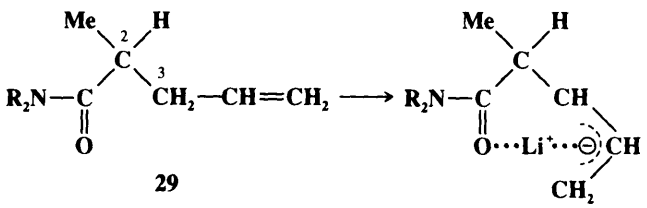


Ref. 264



Ref. 265

In the second example, the lithium goes into the 2 position so as to be ortho to both substituents.[266] This regioselectivity can be quite valuable synthetically. In the case of γ,δ-unsaturated disubstituted amides (**29**),the lithium does not go to the closest position, but in



this case too the regiochemistry is controlled by coordination to the oxygen.[267] The 2 position is much more acidic than the 3 position (Table 8.1), but a negative charge at C-3 is in a more favorable position to be stabilized by the Li^+. Ortho magnesiation has been accomplished with bases of the form $(R_2N)_2Mg$.[268]

The mechanism involves a nucleophilic attack by R'^- (or a polar R') on the *hydrogen*.[269] Evidence is that resonance effects of substituents in R seem to make little difference. When

[259]For example, see Figuly; Loop; Martin *J. Am. Chem. Soc.* **1989,** *111*, 654; Block; Eswarakrishnan; Gernon; Ofori-Okai; Saha; Tang; Zubieta *J. Am. Chem. Soc.* **1989,** *111*, 658; Smith; Lindsay; Pritchard *J. Am. Chem. Soc.* **1989,** *111*, 665.

[260]Fluorine is an especially powerful ortho director in lithiation of aromatic systems: Gilday; Negri; Widdowson *Tetrahedron* **1989,** *45*, 4605.

[261]For a review of regioselective lithiation of heterocycles, see Katritzky; Lam; Sengupta *Prog. Heterocycl. Chem.* **1989,** *1*, 1-29.

[262]For many examples with references, see Ref. 246; Beak; Meyers *Acc. Chem. Res.* **1986,** *19*, 356-363; Beak; Snieckus *Acc. Chem. Res.* **1982,** *15*, 306-312; Snieckus *Bull. Soc. Chim. Fr.* **1988,** 67-78; Narasimhan; Mali *Top. Curr. Chem.* **1987,** *138*, 63-147; Reuman; Meyers *Tetrahedron* **1985,** *41*, 837-860; and the papers in *Tetrahedron* **1983,** *39*, 1955-2091.

[263]For reviews of ortho metallation, see Snieckus *Chem. Rev.* **1990,** *90*, 879-933, *Pure Appl. Chem.* **1990,** *62*, 2047-2056. For a discussion of the mechanism, see Bauer; Schleyer *J. Am. Chem. Soc.* **1989,** *111*, 7191.

[264]Baldwin; Höfle; Lever *J. Am. Chem. Soc.* **1974,** *96*, 7125.

[265]Slocum; Jennings *J. Org. Chem.* **1976,** *41*, 3653.

[266]However, the regioselectivity can depend on reaction conditions: See Meyers; Avila *Tetrahedron Lett.* **1980,** 3335.

[267]Beak; Hunter; Jun; Wallin *J. Am. Chem. Soc.* **1987,** *109*, 5403. See also Stork; Polt; Li; Houk *J. Am. Chem. Soc.* **1988,** *110*, 8360; Barluenga; Foubelo; Fañanas; Yus *J. Chem. Res. (S)* **1989,** 200.

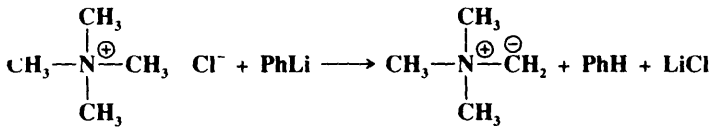
[268]Eaton; Lee; Xiong *J. Am. Chem. Soc.* **1989,** *111*, 8016.

[269]Benkeser; Trevillyan; Hooz *J. Am. Chem. Soc.* **1962,** *84*, 4971.

R is aryl, OMe and CF_3 *both* direct ortho, while isopropyl directs meta and para (mostly meta).[270] These results are exactly what would be expected from pure field effects, with no contribution from resonance effects, which implies that attack occurs at the hydrogen and not at R. Other evidence for the involvement of H in the rate-determining step is that there are large isotope effects.[271] The nature of R′ also has an effect on the rate. In the reaction between triphenylmethane and R′Li, the rate decreased in the order R′ = allyl > Bu > Ph > vinyl > Me, though this order changed with changing concentration of R′Li, because of varying degrees of aggregation of the R′Li.[272]

With respect to the reagent, this reaction is a special case of **2-24.**

A closely related reaction is formation of nitrogen ylides from quaternary ammonium salts (see **7-7**):



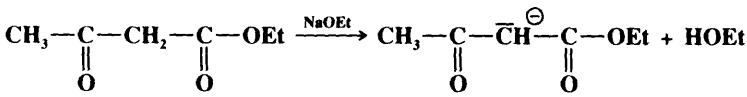
Phosphonium salts undergo a similar reaction (see **6-47**).

OS **II,** 198; **III,** 413, 757; **IV,** 792; **V,** 751; **VI,** 436, 478, 737, 979; **VII,** 172, 334, 456, 524; **65,** 61; **68,** 14, 25, 162.

2-22 Metallation with Metals and Strong Bases
Metallation or Metallo-de-hydrogenation

$$2RH + M \longrightarrow 2RM + H_2$$

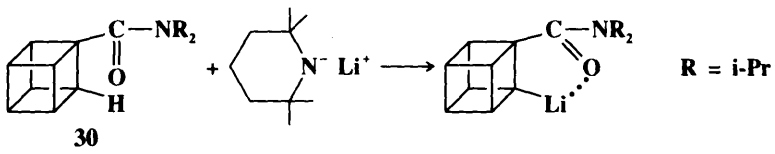
Organic compounds can be metallated at suitably acidic positions by active metals and by strong bases.[273] The reaction has been used to study the acidities of very weak acids (see p. 176). Synthetically, the most important use of the method is to convert ketones, carboxylic esters, and similar compounds to their enolate forms,[274] e.g.,



for use in nucleophilic substitutions (**0-94, 0-95,** and **3-14**) and in additions to multiple bonds (**5-17** and **6-41**). Another important use is the conversion of terminal alkynes to acetylide ions.[275] For very weak acids, the most common reagents for synthetic purposes are lithium amides, especially lithium diisopropylamide (LDA) $(i\text{-}Pr)_2NLi$.[276]

It has been shown that lithiation with lithium amides can also be regioselective (see **2-21**).[277] In the case of the cubane derivative **30,** a saturated unactivated position was regioselectively lithiated.[278]

[270]Bryce-Smith *J. Chem. Soc.* **1963,** 5983; Benkeser; Hooz; Liston; Trevillyan *J. Am. Chem. Soc.* **1963,** *85,* 3984.
[271]Bryce-Smith; Gold; Satchell *J. Chem. Soc.* **1954,** 2743; Pocker; Exner *J. Am. Chem. Soc.* **1968,** *90,* 6764.
[272]West; Waack; Purmort *J. Am. Chem. Soc.* **1970,** *92,* 840.
[273]For a review, see Durst, Ref. 247, pp. 239-291. For reviews with respect to lithium, see Wardell, Ref. 246; Wakefield *Organolithium Methods*; Academic Press: New York, 1988, pp. 32-44.
[274]For a review, see Caine, Ref. 185, vol. 1, pp. 95-145, 284-291.
[275]For a review, see Ziegenbein, in Viehe *Acetylenes*; Marcel Dekker: New York, 1969, pp. 170-185. For an improved method, see Fisch; Coisne; Figeys *Synthesis* **1982,** 211.
[276]The alkali metal hydrides, LiH, NaH, and KH, when prepared in a special way, are very rapid metallation agents: Klusener; Brandsma; Verkruijsse; Schleyer; Friedl; Pi *Angew. Chem. Int. Ed. Engl.* **1986,** *25,* 465 [*Angew. Chem. 98,* 458].
[277]For example, see Comins; Killpack *J. Org. Chem.* **1987,** *52,* 104.
[278]Eaton; Castaldi *J. Am. Chem. Soc.* **1985,** *107,* 724; Jayasuriya; Alster; Politzer *J. Org. Chem.* **1987,** *52,* 2306.

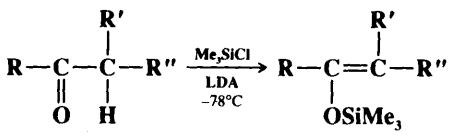


30

Mercuration of aromatic compounds[279] can be accomplished with mercuric salts, most often $Hg(OAc)_2$[280] or $Hg(ClO_4)_2$ (to give ArHgOAc or $ArHgClO_4$, respectively). This is ordinary electrophilic aromatic substitution and takes place by the arenium ion mechanism (p. 501).[281] Aromatic compounds can also be converted to arylthallium bis(trifluoroacetates) $ArTl(OOCCF_3)_2$ by treatment with thallium (III) trifluoroacetate[282] in trifluoroacetic acid.[283] These arylthallium compounds can be converted to phenols (**2-26**), aryl iodides or fluorides (**2-30**), aryl cyanides (**2-33**), aryl nitro compounds,[284] or aryl esters (**2-32**). The mechanism of thallation appears to be complex, with electrophilic and electron-transfer mechanisms both taking place.[285]

OS **I,** 70, 161, 490; **IV,** 473; **VI,** 468, 542, 611, 683, 709; **VII,** 229, 339. Conversions of ketones or esters to enolates are not listed.

2-23 Conversion of Enolates to Silyl Enol Ethers
3/*O*-Trimethylsilyl-de-hydrogenation



Silyl enol ethers,[286] important reagents with a number of synthetic uses (see, for example, **0-95, 2-4, 5-17, 5-50, 6-40**), can be prepared by base treatment of a ketone (converting it to its enolate) followed by addition of a trialkylchlorosilane. Other silylating agents have also been used.[287] Both strong bases, e.g., lithium diisopropylamide (LDA), and weaker bases, e.g. Et_3N, have been used for this purpose. In some cases, the base and the silylating agent can be present at the same time.[288] Enolates prepared in other ways (e.g., as shown

[279]For reviews, see Larock *Organomercury Compounds in Organic Synthesis*; Springer: New York, 1985, pp. 60-97; Wardell, in Zuckerman, Ref. 246, pp. 308-318.

[280]For a review of mercuric acetate, see Butler, in Pizey, Ref. 102, vol. 4, 1981, pp. 1-145.

[281]For a review, see Taylor, in Bamford; Tipper, Ref. 53, vol. 13, 1972, pp. 186-194. An alternative mechanism, involving radial cations, has been reported: Courtneidge; Davies; McGuchan; Yazdi *J. Organomet. Chem.* **1988,** *341*, 63.

[282]For a review of this reagent, see Uemura, in Pizey, Ref. 102, vol. 5, 1983, pp. 165-241.

[283]McKillop; Hunt; Zelesko; Fowler; Taylor; McGillivray; Kienzle *J. Am. Chem. Soc.* **1971,** *93*, 4841; Taylor; Kienzle; McKillop *Org. Synth. VI*, 709; Al-Azzawi; Roberts *J. Chem. Soc., Perkin Trans. 2* **1982,** 677; Taylor; Katz; Alvarado; McKillop *J. Organomet. Chem.* **1985,** *285*, C9. For reviews, see Usyatinskii; Bregadze *Russ. Chem. Rev.* **1988,** *57*, 1054-1068; Uemura, in Hartley; Patai, Ref. 1, vol. 4, pp. 473-538.

[284]Uemura; Toshimitsu; Okano *Bull. Chem. Soc. Jpn.* **1976,** *49*, 2582.

[285]Lau; Kochi *J. Am. Chem. Soc.* **1984,** *106*, 7100, **1986,** *108*, 6720.

[286]For reviews of these compounds, see Poirier *Org. Prep. Proced. Int.* **1988,** *20*, 319-369; Brownbridge *Synthesis* **1983,** 1-28, 85-104; Rasmussen *Synthesis* **1977,** 91-110. See also references given in Rubottom; Mott; Krueger *Synth. Commun* **1977,** *7*, 327. For monographs on silicon reagents in organic synthesis, see Colvin *Silicon Reagents in Organic Synthesis*; Academic Press: New York, 1988; Weber *Silicon Reagents for Organic Synthesis*; Springer: New York, 1983; Colvin *Silicon in Organic Synthesis*; Butterworth: London, 1981 [reprinted, with revisions: Krieger: Melbourne, FL, 1985]. For reviews, see Colvin, in Hartley; Patai, Ref. 1, vol. 4, pp. 539-621; Ager *Chem. Soc. Rev.* **1982,** *11*, 493-522; Colvin *Chem. Soc. Rev.* **1978,** *7*, 15-64, pp. 43-50.

[287]For a review of silylating agents, see Mizhiritskii; Yuzhelevskii *Russ. Chem. Rev.* **1987,** *56*, 355-365. For a list, with references, see Ref. 52, pp. 746-748.

[288]Corey; Gross *Tetrahedron Lett.* **1984,** *25*, 495.

for **112** on p. 452) also give the reaction. The reaction can be applied to aldehydes by the use of the base KH in 1,2-dimethoxyethane.[289] A particularly mild method for conversion of ketones or aldehydes to silyl enol ethers uses Me_3SiI and the base hexamethyldisilazane $(Me_3Si)_2NH$.[290] Cyclic ketones can be converted to silyl enol ethers in the presence of acyclic ketones, by treatment with Me_3SiBr, tetraphenylstibonium bromide Ph_4SbBr, and an aziridine.[291]

OS **VI,** 327, 445; **VII,** 282, 312, 424, 512; **65,** 1; **67,** 141; **69,** 129. See also OS **VII,** 66, 266. For the conversion of ketones to vinylic triflates, see OS **68,** 116, 138.

Metals as Leaving Groups

A. Hydrogen as the Electrophile

2-24 Replacement of Metals by Hydrogen
Hydro-de-metallation or **Demetallation**

$$\mathbf{RM + HA \longrightarrow RH + MA}$$

Organometallic compounds react with acids in reactions in which the metal is replaced by hydrogen.[292] R may be aryl (see **1-44**). The reaction is often used to introduce deuterium or tritium into susceptible positions. For Grignard reagents, water is usually a strong enough acid, but stronger acids are also used. An important method for the reduction of alkyl halides consists of the process $RX \rightarrow RMgX \rightarrow RH$.

Other organometallic compounds that are hydrolyzed by water are those of sodium, potassium, lithium, zinc, etc.—the ones high in the electromotive series. When the metal is less active, stronger acids are required. For example, R_2Zn compounds react explosively with water, R_2Cd slowly, and R_2Hg not at all, though the latter can be cleaved with concentrated HCl. However, this general statement has many exceptions, some hard to explain. For example, BR_3 compounds are completely inert to water, and GaR_3 at room temperature cleave just one R group, but AlR_3 react violently with water. However, BR_3 can be converted to RH with carboxylic acids.[293] For less active metals it is often possible to cleave just one R group from a multivalent metal. For example,

$$\mathbf{R_2Hg + HCl \longrightarrow RH + RHgCl}$$

Organometallic compounds of less active metals and metalloids, such as silicon,[294] antimony, bismuth, etc., are quite inert to water. Organomercury compounds (RHgX or R_2Hg) can be reduced to RH by H_2, $NaBH_4$, or other reducing agents.[295] The reduction with $NaBH_4$

[289]Ladjama; Riehl *Synthesis* **1979,** 504. This base has also been used for ketones: See Orban; Turner; Twitchin *Tetrahedron Lett.* **1984,** *25,* 5099.

[290]Miller; McKean *Synthesis* **1979,** 730, *Synth. Commun.* **1982,** *12,* 319. See also Cazeau; Duboudin; Moulines; Babot; Dunogues *Tetrahedron* **1987,** *43,* 2075, 2089; Ahmad; Khan; Iqbal *Synth. Commun.* **1988,** *18,* 1679.

[291]Fujiwara; Baba; Matsuda *Chem. Lett.* **1989,** 1247.

[292]For reviews, see Abraham; Grellier, in Hartley; Patai, Ref. 1, vol. 2, pp. 25-149, pp. 105-136; Abraham, Ref. 2, pp. 107-134; Jensen; Rickborn, Ref. 2. pp. 45-74; Schlosser *Angew. Chem. Int. Ed. Engl.* **1964,** *3,* 287-306, 362-373 [*Angew. Chem. 76,* 124-143, 258-269], *Newer Methods Prep. Org. Chem.* **1968,** *5,* 238-311.

[293]Brown; Hébert *J. Organomet. Chem.* **1983,** *255,* 135; Brown; Murray *Tetrahedron* **1986,** *42,* 5497; Pelter; Smith; Brown *Borane Reagents*; Academic Press: New York, 1988, pp. 242-244.

[294]For a review of hydro-de-silylation of allylic and vinylic silanes, see Fleming; Dunoguès; Smithers *Org. React.* **1989,** *37,* 57-575, pp. 89-97, 194-243.

[295]For a review, see Makarova *Organomet. React.* **1970,** *1,* 119-348, pp. 251-270, 275-300.

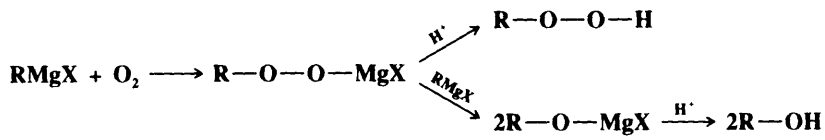
takes place by a free-radical mechanism.[296] Alkyl–silicon bonds can be cleaved by H_2SO_4, e.g., $HOOCCH_2CH_2SiMe_3 \rightarrow 2CH_4 + (HOOCCH_2CH_2SiMe_2)_2O$.[297]

When the hydrogen of the HA is attached to carbon, this reaction is the same as **2-21.**

We do not list the many hydrolyses of sodium or potassium enolates, etc. found in *Organic Syntheses.* The hydrolysis of a Grignard reagent to give an alkane is found at OS **II,** 478; the reduction of a vinylic tin compound at OS **66,** 75; and the reduction of an alkynylsilane at OS **67,** 149.

B. Oxygen Electrophiles

2-25 The Reaction between Organometallic Reagents and Oxygen[298] Hydroperoxy-de-metallation; Hydroxy-de-metallation



Oxygen reacts with Grignard reagents to give either hydroperoxides or alcohols. The reaction can be used to convert alkyl halides to alcohols without side reactions. With aryl Grignard reagents yields are lower and only phenols are obtained, not hydroperoxides. It is because of the possibility of this reaction that oxygen should be excluded when Grignard reagents are desired for other purposes. A better procedure for the conversion of aryl Grignard reagents to phenols involves the use of trimethyl borate followed by oxidation with H_2O_2 in acetic acid[299] (see **2-28**).

Most other organometallic compounds also react with oxygen. Aryllithiums have been converted to phenols by treatment with oxygen.[300] Trialkylboranes and alkyldichloroboranes $RBCl_2$ can be conveniently converted to hydroperoxides by treatment with oxygen followed by hydrolysis.[301] Dilithiated carboxylic acids (see **0-96**) react with oxygen to give (after hydrolysis) α-hydroxy carboxylic acids.[302] There is evidence that the reaction between Grignard reagents and oxygen involves a free-radical mechanism.[303]

The 1,1-dimetallic compounds $R_2C(SnMe_3)ZnBr$ were oxidized by dry air at −10 to 0°C in the presence of Me_3SiCl to give aldehydes or ketones $R_2C{=}O$.[304]

OS **V,** 918. See also OS **69,** 96.

[296]For a review of this and other free radical reactions of organomercury compounds, see Barluenga; Yus *Chem. Rev.* **1988,** *88,* 487-509.

[297]Sommer; Marans; Goldberg; Rockett; Pioch *J. Am. Chem. Soc.* **1951,** *73,* 882. See also Abraham; Grellier, Ref. 292, p. 117.

[298]For a monograph, see Brilkina; Shushunov *Reactions of Organometallic Compounds with Oxygen and Peroxides*; CRC Press: Boca Raton, FL, 1969. For a review, see Wardell; Paterson, in Hartley; Patai, Ref. 1, vol. 2, 1985, pp. 219-338, pp. 311-316.

[299]Hawthorne *J. Org. Chem.* **1957,** *22,* 1001. For other procedures, see Lewis; Gabbe *Aust. J. Chem.* **1978,** *31,* 2091; Hoffmann; Ditrich *Synthesis* **1983,** 107.

[300]Parker; Koziski *J. Org. Chem.* **1987,** *52,* 674. For other reagents, see Taddei; Ricci *Synthesis* **1986,** 633; Einhorn; Luche; Demerseman *J. Chem. Soc., Chem. Commun.* **1988,** 1350.

[301]Brown; Midland *Tetrahedron* **1987,** *43,* 4059.

[302]Moersch; Zwiesler *Synthesis* **1971,** 647; Adam; Cueto *J. Org. Chem.* **1977,** *42,* 38.

[303]Lamb; Ayers; Toney; Garst *J. Am. Chem. Soc.* **1966,** *88,* 4261; Davies; Roberts *J. Chem. Soc. B* **1969,** 317; Walling; Cioffari *J. Am. Chem. Soc.* **1970,** *92,* 6609; Garst; Smith; Farrar *J. Am. Chem. Soc.* **1972,** *94,* 7707. For a review, see Davies *J. Organomet. Chem.* **1980,** *200,* 87-99.

[304]Knochel; Xiao; Yeh *Tetrahedron Lett.* **1988,** *29,* 6697.

2-26 Conversion of Arylthallium Compounds to Phenols
Hydroxy-de-(bistrifluoroacetoxy)thallation

$$ArTl(OOCCF_3)_2 \xrightarrow[3.\ dil.\ NaOH]{1.\ Pb(OAc)_4,\ 2.\ PPh_3} ArOH$$

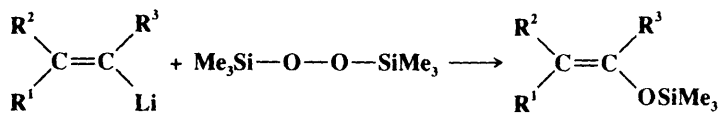
Arythallium bis(trifluoroacetates) (prepared by **2-22**) can be converted to phenols by treatment with lead tetraacetate followed by triphenylphosphine and then dilute NaOH.[305] The entire process, including the thallation reaction, can be carried out in a single reaction vessel without isolation of any of the intermediate products, so that this is a method of accomplishing the conversion ArH → ArOH. Diarylthallium trifluoroacetates undergo the same reaction.[306]

2-27 Reaction Between Organometallic Reagents and Peroxides
t-Butoxy-de-metallation

$$RMgX + t\text{-}Bu{-}O{-}O{-}\underset{\underset{O}{\|}}{C}{-}R' \longrightarrow R{-}O{-}t\text{-}Bu + R'COOMgX$$

A convenient method of preparation of *t*-butyl ethers consists of treating Grignard reagents with *t*-butyl acyl peroxides.[307] Both alkyl and aryl Grignard reagents can be used. The application of this reaction to Grignard reagents prepared from cyclopropyl halides permits cyclopropyl halides to be converted to *t*-butyl ethers of cyclopropanols,[308] which can then be easily hydrolyzed to the cyclopropanols. The direct conversion of cyclopropyl halides to cyclopropanols by **0-1** is not generally feasible, because cyclopropyl halides do not generally undergo nucleophilic substitutions without ring opening.

Vinyllic lithium reagents (**31**) react with silyl peroxides to give high yields of silyl enol ethers with retention of configuration.[309] Since the preparation of **31** from vinylic halides



31

(**2-39**) also proceeds with retention, the overall procedure is a method for the stereospecific conversion of a vinylic halide to a silyl enol ether. In a related reaction, alkynyl esters can be prepared from lithium acetylides and phenyliodine(III) dicarboxylates.[310]

$$RC{\equiv}CLi + PhI(O_2CR')_2 \longrightarrow RC{\equiv}C{-}O{-}\underset{\underset{O}{\|}}{C}{-}R'$$

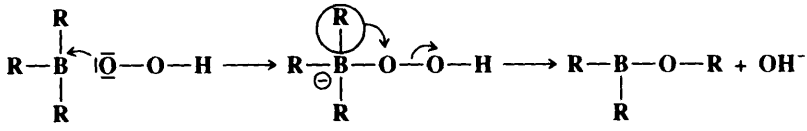
OS **V**, 642, 924.

[305]Taylor; Altland; Danforth; McGillivray; McKillop *J. Am. Chem. Soc.* **1970**, *92*, 3520.
[306]Taylor; Altland; McKillop *J. Org. Chem.* **1975**, *40*, 2351.
[307]Lawesson; Yang *J. Am. Chem. Soc.* **1959**, *81*, 4230; Lawesson; Frisell; Denney; Denney *Tetrahedron* **1963**, *19*, 1229. For a monograph on the reactions of organometallic compounds with peroxides, see Ref. 298. For a review, see Razuvaev; Shushunov; Dodonov; Brilkina, in Swern *Organic Peroxides*, vol. 3; Wiley: New York, 1972, pp. 141-270.
[308]Longone; Miller *Tetrahedron Lett.* **1967**, 4941.
[309]Davis; Lal; Wei *Tetrahedron Lett.* **1988**, *29*, 4269.
[310]Stang; Boehshar; Wingert; Kitamura *J. Am. Chem. Soc.* **1988**, *110*, 3272.

2-28 Oxidation of Trialkylboranes to Borates

$$R_3B \xrightarrow[NaOH]{H_2O_2} (RO)_3B \longrightarrow 3ROH + B(OH)_3$$

Treatment with alkaline H_2O_2 oxidizes trialkylboranes to esters of boric acid.[311] This reaction does not affect double or triple bonds, aldehydes, ketones, halides, or nitriles. The R group does not rearrange, and this reaction is a step in the hydroboration method of converting olefins to alcohols (**5-12**). The mechanism has been formulated as involving a rearrangement from boron to oxygen:[311]

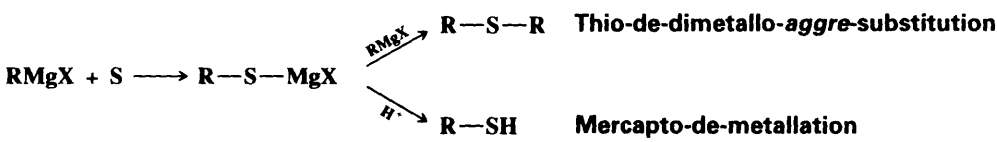


The other two R groups then similarly migrate. Retention of configuration is observed in R. Boranes can also be oxidized to borates in good yields with oxygen,[312] with sodium perborate $NaBO_3$,[313] with sodium percarbonate ($Na_2CO_3 \cdot \frac{3}{2}H_2O_2$),[314] and with trimethylamine oxide, either anhydrous[315] or in the form of the dihydrate.[316] The reaction with oxygen is free radical in nature.[317]

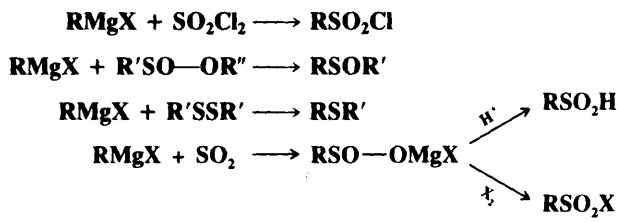
OS **V**, 918; **VI**, 719, 852, 919.

C. Sulfur Electrophiles

2-29 Conversion of Grignard Reagents to Sulfur Compounds



Thiols and sulfides are occasionally prepared by treatment of Grignard reagents with sulfur.[318] Analogous reactions are known for selenium and tellurium compounds. Grignard reagents



[311]For reviews, see Pelter; Smith; Brown, Ref. 293, pp. 244-249; Brown *Boranes in Organic Chemistry*; Cornell University Press: Ithaca, NY, 1972, pp. 321-325; Matteson in Hartley; Patai, Ref. 1, vol. 4, pp. 307-409, pp. 337-340. See also Brown; Snyder; Subba Rao; Zweifel *Tetrahedron* **1986**, *42*, 5505.

[312]Brown; Midland; Kabalka *J. Am. Chem. Soc.* **1971**, *93*, 1024, *Tetrahedron* **1986**, *42*, 5523.

[313]Kabalka; Shoup; Goudgaon *J. Org. Chem.* **1989**, *54*, 5930.

[314]Kabalka; Wadgaonkar; Shoup *Organometallics* **1990**, *9*, 1316.

[315]Köster; Morita *Justus Liebigs Ann. Chem.* **1967**, *704*, 70; Köster; Arora; Binger *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 205 [*Angew. Chem. 81*, 185].

[316]Kalbalka; Hedgecock *J. Org. Chem.* **1975**, *40*, 1776, *J. Chem. Educ.* **1975**, *52*, 745; Kabalka; Slayden *J. Organomet. Chem.* **1977**, *125*, 273.

[317]Mirviss *J. Am. Chem. Soc.* **1961**, *83*, 3051, *J. Org. Chem.* **1967**, *32*, 1713; Davies; Roberts *Chem. Commun.* **1966**, 298; Midland; Brown *J. Am. Chem. Soc.* **1971**, *93*, 1506.

[318]For reviews of the reactions in this section, see Wardell; Paterson, Ref. 298, pp. 316-323; Wardell, in Patai *The Chemistry of the Thiol Group*, pt. 1; Wiley: New York, 1974, pp. 211-215; Wakefield, Ref. 273, pp. 135-142.

and other organometallic compounds[319] react with sulfuryl chloride to give sulfonyl chlorides,[320] with esters of sulfinic acids to give (stereospecifically) sulfoxides,[321] with disulfides to give sulfides,[322] and with SO_2 to give sulfinic acid salts[323] which can be hydrolyzed to sulfinic acids or treated with halogens to give sulfonyl halides.[324]

OS **III,** 771; **IV,** 667; **VI,** 533, 979.

D. Halogen Electrophiles

2-30 Halo-de-metallation

$$\mathbf{RMgX + I_2 \longrightarrow RI + MgIX}$$

Grignard reagents react with halogens to give alkyl halides. The reaction is useful for the preparation of iodo compounds from the corresponding chloro or bromo compounds. The reaction is not useful for preparing chlorides, since the reagents RMgBr and RMgI react with Cl_2 to give mostly RBr and RI, respectively.[325] Alkyl, aryl, and vinylic Grignard reagents and lithium compounds can be converted to fluorides in moderate to high yields with perchloryl fluoride $FClO_3$[326] (but see **2-4** for the explosive nature of this reagent).

Most organometallic compounds, both alkyl and aryl, also react with halogens to give alkyl or aryl halides.[327] The reaction can be used to convert acetylide ions to 1-haloalkynes.[328] Since acetylide ions are easily prepared from alkynes (**2-22**), this provides a means of making the conversion RC≡CH → RC≡CX. Trialkylboranes react rapidly with I_2[329] or Br_2[330] in the presence of NaOMe in methanol, or with $FeCl_3$ or other reagents[331] to give alkyl iodides, bromides, or chlorides, respectively. Combined with the hydroboration reaction (**5-12**), this is an indirect way of adding HBr, HI, or HCl to a double bond to give products with an anti-Markovnikov orientation (see **5-1**). Trialkylboranes can also be converted to alkyl iodides by treatment with allyl iodide and air in a free radical process.[332]

trans-1-Alkenylboronic acids **33,** prepared by hydroboration of terminal alkynes with catecholborane[333] (**5-12**) followed by hydrolysis, react with I_2 in the presence of NaOH at 0°C in ethereal solvents to give trans vinylic iodides.[334] This is an indirect way of accom-

[319]For a discussion of conversions of organomercury compounds to sulfur-containing compounds, see Larock, Ref. 279, pp. 210-216.

[320]Bhattacharya; Eaborn; Walton *J. Chem. Soc. C* **1968,** 1265. For similar reactions with organolithiums, see Quast; Kees *Synthesis* **1974,** 489; Hamada; Yonemitsu *Synthesis*, **1986,** 852.

[321]Harpp; Vines; Montillier; Chan *J. Org. Chem.* **1976,** *41*, 3987.

[322]For a discussion, see Negishi, Ref. 1, pp. 243-247.

[323]For a review of the reactions of organometallic compounds with SO_2, see Kitching; Fong *Organomet. Chem. Rev., Sect. A* **1970,** *5*, 281-321.

[324]Asinger; Laue; Fell; Gubelt *Chem. Ber.* **1967,** *100*, 1696.

[325]Zakharkin; Gavrilenko; Paley *J. Organomet. Chem.* **1970,** *21*, 269.

[326]Schlosser; Heinz *Chem. Ber.* **1969,** *102*, 1944. See also Satyamurthy; Bida; Phelps; Barrio *J. Org. Chem.* **1990,** 55, 3373.

[327]For a review, see Abraham; Grellier, Ref. 292, pp. 72-105. For reviews with respect to organomercury compounds, see Larock, Ref. 279, pp. 158-178; Makarova, Ref. 295, pp. 325-348.

[328]For a review, see Delavarenne; Viehe, in Viehe, Ref. 275, pp. 665-688. For a list of reagents, with references, see Ref. 52, pp. 333-334. For an improved procedure, see Brandsma; Verkruijsse *Synthesis* **1990,** 984.

[329]Brown; Rathke; Rogić; De Lue *Tetrahedron* **1988,** *44*, 2751.

[330]Brown; Lane *Tetrahedron* **1988,** *44*, 2763; Brown; Lane; De Lue *Tetrahedron* **1988,** *44*, 2273. For another reagent, see Nelson; Soundararajan *J. Org. Chem.* **1989,** *54*, 340.

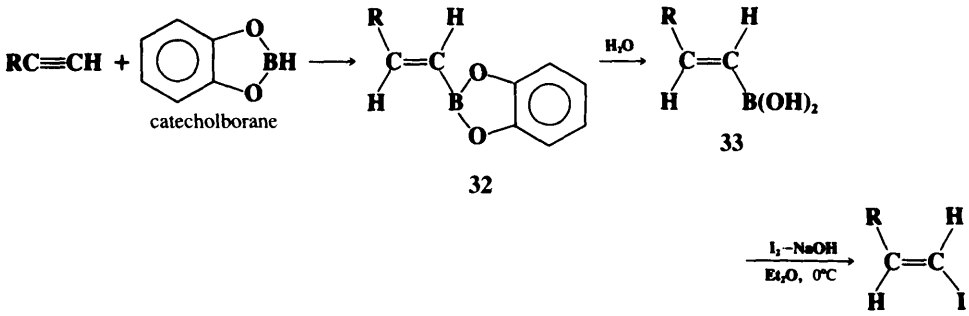
[331]Nelson; Soundararajan *J. Org. Chem.* **1988,** *53*, 5664. For other reagents, see Jigajinni; Paget; Smith *J. Chem. Res., (S)* **1981,** 376; Brown; De Lue *Tetrahedron* **1988,** *44*, 2785.

[332]Suzuki; Nozawa; Harada; Itoh; Brown; Midland *J. Am. Chem. Soc.* **1971,** *93*, 1508. For reviews, see Brown; Midland *Angew. Chem. Int. Ed. Engl.* **1972,** *11*, 692-700, pp. 699-700 [*Angew. Chem. 84*, 702-710]; Brown, Ref. 311, pp. 442-446.

[333]For a review of this reagent, see Kabalka *Org. Prep. Proced. Int.* **1977,** *9*, 131-147.

[334]Brown; Hamaoka; Ravindran; Subrahmanyam; Somayaji; Bhat *J. Org. Chem.* **1989,** *54*, 6075. See also Kabalka; Gooch; Hsu *Synth. Commun.* **1981,** *11*, 247.

plishing the anti-Markovnikov addition of HI to a terminal triple bond. The reaction cannot be applied to alkenylboronic acids prepared from internal alkynes. However, alkenylboronic



acids prepared from both internal and terminal alkynes react with Br_2 (2 moles of Br_2 must be used) followed by base to give the corresponding vinylic bromide, but in this case with *inversion* of configuration; so the product is the cis vinylic bromide.[335] Alkenylboronic acids also give vinylic bromides and iodides when treated with a mild oxidizing agent and NaBr or NaI, respectively.[336] Treatment of **33** (prepared from terminal alkynes) with Cl_2 gave vinylic chlorides with inversion.[337] Vinylic halides can also be prepared from vinylic silanes[338] and from vinylic aluminum[339] or vinylic copper reagents. The latter react with I_2 to give iodides,[340] and with N-chloro- or N-bromosuccinimide at −45°C to give chlorides or bromides.[341]

Aryl iodides[342] and fluorides can be prepared from arylthallium bis(trifluoroacetates) (see **2-22**), indirectly achieving the conversions ArH → ArI and ArH → ArF. The bis(trifluoroacetates) react with KI to give ArI in high yields.[343] The reaction with KF gives arylthallium(III) difluorides $ArTlF_2$, but these react with BF_3 to give ArF in moderate overall yields.[344] Aryllead triacetates $ArPb(OAc)_3$ can be converted to aryl fluorides by treatment with BF_3–etherate.[345] Aryl fluorides have also been prepared in low-to-moderate yields by treatment of arylmetal compounds such as Ph_4Sn and Ph_2Hg with F_2[346] and with fluoroxytrifluoromethane CF_3OF or cesium fluoroxy sulfate $CsSO_4F$.[347]

For the reaction of lithium enolates of esters with I_2 or CX_4 see **2-5.**

It is unlikely that a single mechanism suffices to cover all conversions of organometallic compounds to alkyl halides.[348] In a number of cases the reaction has been shown to involve

[335]Brown; Hamaoka; Ravindran *J. Am. Chem. Soc.* **1973,** *95*, 6456. See also Brown; Bhat; Rajagopalan *Synthesis* **1986,** 480; Brown; Bhat *Tetrahedron Lett.* **1988,** *29*, 21.

[336]See Kabalka; Sastry; Knapp; Srivastava *Synth. Commun.* **1983,** *13*, 1027.

[337]Kunda; Smith; Hylarides; Kabalka *Tetrahedron Lett.* **1985,** *26*, 279.

[338]See, for example Chou; Kuo; Wang; Tsai; Sun *J. Org. Chem.* **1989,** *54*, 868.

[339]Zweifel; Whitney *J. Am. Chem. Soc.* **1967,** *89*, 2753.

[340]Normant; Chaiez; Chuit; Villieras *J. Organomet. Chem.* **1974,** *77*, 269, *Synthesis* **1974,** 803.

[341]Westmijze; Meijer; Vermeer *Recl. Trav. Chim. Pays-Bas* **1977,** *96*, 168; Levy; Talley; Dunford *Tetrahedron Lett.* **1977,** 3545.

[342]For reviews of the synthesis of aryl iodides, see Merkushev *Synthesis* **1988,** 923-937, *Russ. Chem. Rev.* **1984,** *53*, 343-350.

[343]Ref. 283. See also Ishikawa; Sekiya *Bull. Chem. Soc. Jpn.* **1974,** *47*, 1680 and Ref. 306.

[344]Taylor; Bigham; Johnson; McKillop *J. Org. Chem.* **1977,** *42*, 362.

[345]De Meio; Pinhey *J. Chem. Soc., Chem. Commun.* **1990,** 1065.

[346]Adam; Berry; Hall; Pate; Ruth *Can. J. Chem.* **1983,** *61*, 658. See also Adam; Ruth; Jivan; Pate *J. Fluorine Chem.* **1984,** *25*, 329; Speranza; Shiue; Wolf; Wilbur; Angelini *J. Fluorine Chem.* **1985,** *30*, 97.

[347]Bryce; Chambers; Mullins; Parkin *Bull. Soc. Chim. Fr.* **1986,** 930. See also Clough; Diorazio; Widdowson *Synlett* **1990,** 761.

[348]For reviews of the mechanisms, see Abraham; Grellier, Ref. 327; Abraham, Ref. 2, pp. 135-177; Jensen; Rickborn, Ref. 2, pp. 75-97.

inversion of configuration (see p. 572), indicating an SE2 (back) mechanism, while in other cases retention of configuration has been shown,[349] implicating an SE2 (front) or SEi mechanism. In still other cases complete loss of configuration as well as other evidence have demonstrated the presence of a free-radical mechanism.[350]

OS **I,** 125, 325, 326; **III,** 774, 813; **V,** 921; **VI,** 709; **VII,** 290; **65,** 108. Also see OS **II,** 150.

E. Nitrogen Electrophiles

2-31 The Conversion of Organometallic Compounds to Amines
Amino-de-metallation

$$\mathbf{RLi} \xrightarrow[\mathbf{MeLi}]{\mathbf{CH_3ONH_2}} \mathbf{RNH_2}$$

There are several methods for conversion of alkyl- or aryllithium compounds to primary amines.[351] The two most important are treatment with hydroxylamine derivatives and with certain azides.[352] In the first of these methods, treatment of RLi with methoxyamine and MeLi in ether at −78°C gives RNH_2.[353] Grignard reagents give lower yields. The reaction can be extended to give secondary amines by the use of N-substituted methoxyamines CH_3ONHR'.[354] There is evidence[355] that the mechanism involves the direct displacement of OCH_3 by R on an intermediate $CH_2O\bar{N}R'^-$ ($CH_3O\bar{N}R'^-$ Li^+ + RLi → CH_3OLi + $R\bar{N}R'^-$ Li^+). The most useful azide is tosyl azide TsN_3.[356] The initial product is usually RN_3, but this is easily reducible to the amine (**9-53**). With some azides, such as azidomethyl phenyl sulfide $PhSCH_2N_3$, the group attached to the N_3 is a poor leaving group, so the inital product is a triazene (in this case $ArNH{=}NHCH_2SPh$ from ArMgX), which can be hydrolyzed to the amine.[357]

Organoboranes react with a mixture of aqueous NH_3 and NaOCl to produce primary amines.[358] It is likely that the actual reagent is chloramine NH_2Cl. Chloramine itself,[359]

$$\mathbf{R_3B} \xrightarrow{\mathbf{NH_3\text{-}NaOCl}} \mathbf{2RNH_2 + RB(OH)_2}$$

[349]For example, see Jensen; Gale *J. Am. Chem. Soc.* **1960,** *82*, 148.

[350]See, for example, Ref. 349; Beletskaya; Reutov; Gur'yanova *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1961,** 1483; Beletskaya; Ermanson; Reutov *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1965,** 218; de Ryck; Verdonck; Van der Kelen *Bull. Soc. Chim. Belg.* **1985,** *94*, 621.

[351]For a review of methods for achieving the conversion RM → RNH_2, see Erdik; Ay *Chem. Rev.* **1989,** *89*, 1947-1980.

[352]For some other methods of converting organolithium or Grignard reagents to primary amines, see Alvernhe; Laurent *Tetrahedron Lett.* **1972,** 1007; Hagopian; Therien; Murdoch *J. Am. Chem. Soc.* **1984,** *106*, 5753; Genet; Mallart; Greck; Piveteau *Tetrahedron Lett.* **1991,** *32*, 2359.

[353]Beak; Kokko *J. Org. Chem.* **1982,** *47*, 2822. For other hydroxylamine derivatives, see Colvin; Kirby; Wilson *Tetrahedron Lett.* **1982,** *23*, 3835; Boche; Bernheim; Schrott *Tetrahedron Lett.* **1982,** *23*, 5399; Boche; Schrott *Tetrahedron Lett.* **1982,** *23*, 5403.

[354]Kokko; Beak *Tetrahedron Lett.* **1983,** *24*, 561.

[355]Beak; Basha; Kokko; Loo *J. Am. Chem. Soc.* **1986,** *108*, 6016.

[356]See, for example, Spagnolo; Zanirato; Gronowitz *J. Org. Chem.* **1982,** *47*, 3177; Reed; Snieckus *Tetrahedron Lett.* **1983,** *24*, 3795. For other azides, see Hassner; Munger; Belinka *Tetrahedron Lett.* **1982,** *23*, 699; Mori; Aoyama; Shioiri *Tetrahedron Lett.* **1984,** *25*, 429.

[357]Trost; Pearson *J. Am. Chem. Soc.* **1981,** *103*, 2483; **1983,** *105*, 1054.

[358]Kabalka; Sastry; McCollum; Yoshioka *J. Org. Chem.* **1981,** *46*, 4296; Kabalka; Wang; Goudgaon *Synth. Commun.* **1989,** *19*, 2409. For the extension of this reaction to the preparation of secondary amines, see Kabalka; Wang *Organometallics* **1989,** *8*, 1093, *Synth. Commun.* **1990,** *20*, 231.

[359]Brown; Heydkamp; Breuer; Murphy *J. Am. Chem. Soc.* **1964,** *86*, 3565.

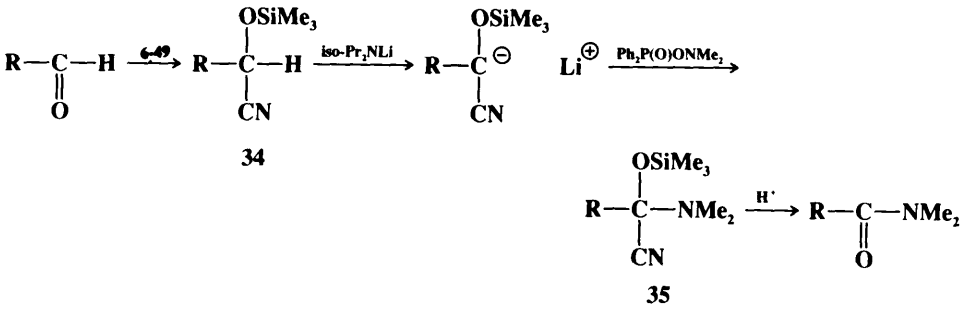
hydroxylamine-O-sulfonic acid in diglyme,[360] and trimethylsilyl azide[361] also give the reaction. Since the boranes can be prepared by the hydroboration of alkenes (**5-12**), this is an indirect method for the addition of NH_3 to a double bond with anti-Markovnikov orientation. Secondary amines can be prepared[362] by the treatment of alkyl- or aryldichloroboranes or dialkylchloroboranes with alkyl or aryl azides.

$$RBCl_2 + R'N_3 \longrightarrow RR'NBCl_2 \xrightarrow[OH^-]{H_2O} RNHR'$$

$$R_2BCl + R'N_3 \xrightarrow[2.H_2O]{1.Et_2O} RNHR'$$

The use of an optically active $RBCl_2$ gave secondary amines of essentially 100% optical purity.[363] In other methods, trialkylboranes R_3B gave secondary amines RR'NH upon treatment with N-chloroamines R'NHCl,[364] and aryllead triacetates $ArPb(OAc)_3$ give secondary amines ArNHAr' when treated with primary aromatic amines $Ar'NH_2$ and $Cu(OAc)_2$.[365]

An indirect method for the conversion of aldehydes to N,N-disubstituted amides is based on the conversion of an O-(trimethylsilyl)aldehyde cyanohydrin **34** to the amine **35**.[366]



Secondary amines have been converted to tertiary amines by treatment with dialkylcopperlithium reagents: $R_2CuLi + NHR \rightarrow RNR'_2$.[367] The reaction was also used to convert primary amines to secondary, but yields were lower.[367] However, primary aromatic amines $ArNH_2$ were converted to diaryl amines ArNHPh by treatment with $Ph_3Bi(OAc)_2$[368] and a copper powder catalyst.[369]

Molecular nitrogen (N_2) reacts with aryllithium compounds in the presence of compounds of such transition metals as titanium, chromium, molybdenum, or vanadium (e.g., $TiCl_4$) to give (after hydrolysis) primary aromatic amines.[370]

$$ArLi + N_2 \xrightarrow[2.H_2O]{1.MX_n} ArNH_2 + NH_3$$

OS **VI**, 943.

[360]Rathke; Inoue; Varma; Brown *J. Am. Chem. Soc.* **1966,** *88*, 2870; Brown; Kim; Srebnik; Singaram *Tetrahedron* **1987,** *43*, 4071. For a method of using this reaction to prepare optically pure chiral amines, see Brown; Kim; Cole; Singaram *J. Am. Chem. Soc.* **1986,** *106*, 6761.

[361]Kabalka; Goudgaon; Liang *Synth. Commun.* **1988,** *18*, 1363.

[362]Brown; Midland; Levy; Suzuki; Sono; Itoh *Tetrahedron* **1987,** *43*, 4079; Carboni; Vaultier; Courgeon; Carrié *Bull. Soc. Chim. Fr.* **1989,** 844.

[363]Brown; Salunkhe; Singaram *J. Org. Chem.* **1991,** *56*, 1170.

[364]Kabalka; McCollum; Kunda *J. Org. Chem.* **1984,** *49*, 1656.

[365]Barton; Donnelly; Finet; Guiry *Tetrahedron Lett.* **1989,** *30*, 1377.

[366]Boche; Bosold; Niessner *Tetrahedron Lett.* **1982,** *23*, 3255.

[367]Yamamoto; Maruoka *J. Org. Chem.* **1980,** *45*, 2739.

[368]For a review of arylations with bismuth reagents, see Finet *Chem. Rev.* **1989,** *89*, 1487-1501.

[369]Dodonov; Gushchin; Brilkina *Zh. Obshch. Khim.* **1985,** *55*, 466 [*Chem. Abstr. 103*, 22218z]; Barton; Finet; Khamsi *Tetrahedron Lett.* **1986,** *27*, 3615; Barton; Yadav-Bhatnagar; Finet; Khamsi *Tetrahedron Lett.* **1987,** *28*, 3111.

[370]Vol'pin *Pure Appl. Chem.* **1972,** *30*, 607.

F. Carbon Electrophiles

2-32 The Conversion of Organometallic Compounds to Ketones, Aldehydes, Carboxylic Esters, or Amides

Acyl-de-metallation, etc.

$$RHgX + Co_2(CO)_8 \xrightarrow{THF} R{-}\overset{\overset{O}{\|}}{C}{-}R$$

Symmetrical ketones[371] can be prepared in good yields by the reaction of organomercuric halides[372] with dicobalt octacarbonyl in THF,[373] or with nickel carbonyl in DMF or certain other solvents.[374] R may be aryl or alkyl. However, when R is alkyl, rearrangements may intervene in the $Co_2(CO)_8$ reaction, though the $Ni(CO)_4$ reaction seems to be free from such rearrangements.[374] Divinylic ketones have been prepared in high yields by treatment of vinylic mercuric halides with CO and a rhodium catalyst.[375] When arylmercuric halides are treated with nickel carbonyl in the presence of Ar'I, unsymmetrical diaryl ketones can be obtained.[374] In a more general synthesis of unsymmetrical ketones, tetraalkyltin compounds R_4Sn are treated with a halide R'X (R' = aryl, vinylic, benzylic), CO, and a Pd complex catalyst.[376] Similar reactions use Grignard reagents, $Fe(CO)_5$, and an alkyl halide;[377] and an organoaluminum compound, an aryl halide, CO, and a palladium catalyst.[378] Aryl ketones can be prepared from aryltrimethylsilanes $ArSiMe_3$ and acyl chlorides in the presence of $AlCl_3$.[379]

Grignard reagents react with formic acid to give good yields of aldehydes. Two moles of RMgX are used; the first converts HCOOH to $HCOO^-$, which reacts with the second mole to give RCHO.[380] Aryllithiums and Grignard reagents react with iron pentacarbonyl to give aldehydes ArCHO,[381] while alkyllithium reagents react with CO to give symmetrical ketones.[382] α,β-Unsaturated aldehydes can be prepared by treatment of vinylic silanes with dichloromethyl methyl ether and $TiCl_4$ at −90°C.[383] Vinylic aluminum compounds react with methyl chloroformate ClCOOMe to give α,β-unsaturated esters directly.[384] The latter compounds can also be prepared by treating boronic esters **32** with CO, $PdCl_2$, and NaOAc in MeOH.[385] The synthesis of α,β-unsaturated esters has also been accomplished by treat-

[371]For reviews of the reactions in this section, and related reactions, see Narayana; Periasamy *Synthesis* **1985,** 253-268; Gulevich; Bumagin; Beletskaya *Russ. Chem. Rev.* **1988,** *57,* 299-315.

[372]For a monograph on the synthetic uses of organomercury compounds, see Larock, Ref. 279. For reviews, see Larock *Tetrahedron* **1982,** *38,* 1713-1754, *Angew. Chem. Int. Ed. Engl.* **1978,** *17,* 27-37 [*Angew. Chem. 90,* 28-38].

[373]Seyferth; Spohn *J. Am. Chem. Soc.* **1969,** *91,* 3037.

[374]Hirota; Ryang; Tsutsumi *Tetrahedron Lett.* **1971,** 1531; Ryu; Ryang; Rhee; Omura; Murai; Sonoda *Synth. Commun.* **1984,** *14,* 1175. For another method, see Hatanaka; Hiyama *Chem. Lett.* **1989,** 2049.

[375]Larock; Hershberger *J. Org. Chem.* **1980,** *45,* 3840.

[376]Tanaka *Tetrahedron Lett.* **1979,** 2601.

[377]Yamashita; Suemitsu *Tetrahedron Lett.* **1978,** 761. See also Vitale; Doctorovich; Nudelman *J. Organomet. Chem.* **1987,** *332,* 9.

[378]Bumagin; Ponomarev; Beletskaya *Doklad. Chem.* **1986,** *291,* 471.

[379]Dey; Eaborn; Walton *Organomet. Chem. Synth.* **1971,** *1,* 151-160.

[380]Sato; Oguro; Watanabe; Sato *Tetrahedron Lett.* **1980,** *21,* 2869. For another method of converting RMgX to RCHO, see Meyers; Comins *Tetrahedron Lett.* **1978,** 5179; Comins; Meyers *Synthesis* **1978,** 403; Amaratunga; Fréchet *Tetrahedron Lett.* **1983,** *24,* 1143.

[381]Ryang; Rhee; Tsutsumi *Bull. Chem. Soc. Jpn.* **1964,** *37,* 341; Giam; Ueno *J. Am. Chem. Soc.* **1977,** *99,* 3166; Yamashita; Miyoshi; Nakazono; Suemitsu *Bull. Chem. Soc. Jpn.* **1982,** *55,* 1663. For another method, see Gupton; Polk *Synth. Commun.* **1981,** *11,* 571.

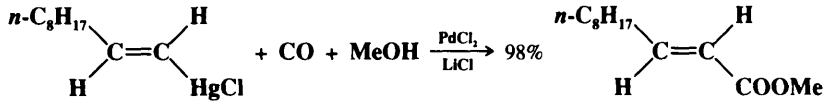
[382]Ryang; Tsutsumi *Bull. Chem. Soc. Jpn.* **1962,** *35,* 1121; Ryang; Sawa; Hasimoto; Tsutsumi *Bull. Chem. Soc. Jpn.* **1964,** *37,* 1704; Trzupek; Newirth; Kelly; Sbarbati; Whitesides *J. Am. Chem. Soc.* **1973,** *95,* 8118.

[383]Yamamoto; Nunokawa; Tsuji *Synthesis* **1977,** 721; Yamamoto; Yohitake; Qui; Tsuji *Chem. Lett.* **1978,** 859.

[384]Zweifel; Lynd *Synthesis* **1976,** 625.

[385]Miyaura; Suzuki *Chem. Lett.* **1981,** 879. See also Yamashina; Hyuga; Hara; Suzuki *Tetrahedron Lett.* **1989,** *30,* 6555.

ment of vinylic mercuric chlorides with CO at atmospheric pressure and a Pd catalyst in an alcohol as solvent, e.g.,[386]

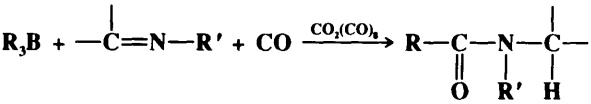


Arylthallium bis(trifluoroacetates) (see **2-22**) can be carbonylated with CO, an alcohol, and a $PdCl_2$ catalyst to give esters:[387]

$$\mathbf{ArTl(OOCCF_3)_2 + ROH + CO \xrightarrow{PdCl_2} ArCOOR}$$

Organomercury compounds undergo a similar reaction.[388] Alkyl and aryl Grignard reagents can be converted to carboxylic esters with $Fe(CO)_5$ instead of CO.[389]

Amides have been prepared by the treatment of trialkyl or triarylboranes with CO and an imine, in the presence of catalytic amounts of cobalt carbonyl:[390]



In another method for the conversion RM → $RCONR'_2$, Grignard reagents and organolithium compounds are treated with a formamide $HCONR'_2$ to give the intermediate $RCH(OM)NR'_2$, which is not isolated, but treated with PhCHO or Ph_2CO to give the product $RCONR'_2$.[391]

See also reactions **0-102, 5-21, 6-70,** and **8-24** to **8-26.**

OS **68,** 116.

2-33 Cyano-de-metallation

$$\mathbf{ArTl(OOCCF_3)_2 + CuCN \longrightarrow ArCN}$$

Arylthallium bis(trifluoroacetates) (see **2-22**) can be converted to aryl nitriles by treatment with copper(I) cyanide in acetonitrile.[392] Another procedure uses excess aqueous KCN followed by photolysis of the resulting complex ion $ArTl(CN)_3^-$ in the presence of excess KCN.[305] Alternatively, arylthallium acetates react with $Cu(CN)_2$ or CuCN to give aryl nitriles, e.g.[393]

$$\mathbf{PhTl(OAc)(ClO_4) + Cu(CN)_2 \xrightarrow[pyridine]{115°C,\ 5\ hr} 75\%\ PhCN}$$

Yields from this procedure are variable, ranging from almost nothing to 90 or 100%.

Vinylic copper reagents react with ClCN to give vinyl cyanides, though BrCN and ICN give the vinylic halide instead.[394] Vinylic cyanides have also been prepared by the reaction

[386]Larock *J. Org. Chem.* **1975,** *40,* 3237.
[387]Larock; Fellows *J. Am. Chem. Soc.* **1982,** *104,* 1900.
[388]Baird; Hartgerink; Surridge *J. Org. Chem.* **1985,** *50,* 4601.
[389]Yamashita; Suemitsu *Tetrahedron Lett.* **1978,** 1477.
[390]Alper; Amaratunga *J. Org. Chem.* **1982,** *47,* 3593.
[391]Screttas; Steele *J. Org. Chem.* **1988,** *53,* 5151.
[392]Taylor; Katz; McKillop *Tetrahedron Lett.* **1984,** *25,* 5473.
[393]Uemura; Ikeda; Ichikawa *Tetrahedron* **1972,** *28,* 3025.
[394]Westmijze; Vermeer *Synthesis* **1977,** 784.

between vinylic lithium compounds and phenyl cyanate PhOCN.[395] Alkyl cyanides RCN have been prepared, in varying yields, by treatment of sodium trialkylcyanoborates with NaCN and lead tetraacetate.[396]

For other electrophilic substitutions of the type RM → RC, see **0-86** to **0-107,** which are discussed under nucleophilic substitutions in Chapter 10. See also **6-69.**

G. Metal Electrophiles

2-34 Transmetallation with a Metal
Metallo-de-metallation

$$\mathbf{RM + M' \rightleftharpoons RM' + M}$$

Many organometallic compounds are best prepared by this reaction, which involves replacement of a metal in an organometallic compound by another metal. RM′ can be successfully prepared only when M′ is above M in the electromotive series, unless some other way is found to shift the equilibrium. That is, RM is usually an unreactive compound and M′ is a metal more active than M. Most often, RM is R_2Hg, since mercury alkyls[372] are easy to prepare and mercury is far down in the electromotive series.[397] Alkyls of Li, Na, K, Be, Mg, Al, Ga, Zn, Cd, Te, Sn, etc. have been prepared this way. An important advantage of this method over **2-38** is that it ensures that the organometallic compound will be prepared free of any possible halide. This method can be used for the isolation of solid sodium and potassium alkyls.[398] If the metals lie too close together in the series, it may not be possible to shift the equilibrium. For example, alkylbismuth compounds cannot be prepared in this way from alkylmercury compounds.

OS **V,** 1116.

2-35 Transmetallation with a Metal Halide
Metallo-de-metallation

$$\mathbf{RM + M'X \rightleftharpoons RM' + MX}$$

In contrast to **2-34** the reaction between an organometallic compound and a metal *halide* is successful only when M′ is *below* M in the electromotive series.[399] The two reactions considered together therefore constitute a powerful tool for preparing all kinds of organometallic compounds. In this reaction the most common substrates are Grignard reagents and organolithium compounds.[400] Among others, alkyls of Be, Zn,[401] Cd, Hg, Al, Sn, Pb, Co, Pt, and Au have been prepared by treatment of Grignard reagents with the appropriate halide.[402] The reaction has been used to prepare alkyls of almost all nontransition metals and even of some transition metals. Alkyls of metalloids and of nonmetals, including Si, B,[403] Ge, P,

[395]Murray; Zweifel *Synthesis* **1980,** 150.

[396]Masuda; Hoshi; Yamada; Arase *J. Chem. Soc., Chem. Commun.* **1984,** 398.

[397]For a review of the reaction when M is Hg, see Makarova, Ref. 295, pp. 190-226. For a review where M′ is Li, see Wardell, in Zuckerman, Ref. 246, pp. 31-44.

[398]BuNa and BuK have also been prepared by exchange of BuLi with *t*-BuONa or *t*-AmOK: Pi; Bauer; Brix; Schade; Schleyer *J. Organomet. Chem.* **1986,** *306,* C1.

[399]For reviews of the mechanism, see Abraham; Grellier, Ref. 292, pp. 25-149; Abraham, Ref. 2, pp. 39-106; Jensen; Rickborn, Ref. 2, pp. 100-192. Also see Schlosser, Ref. 292.

[400]For monographs on organolithium compounds, see Wakefield, Ref. 273; Wakefield *The Chemistry of Organolithium Compounds*; Pergamon: Elmsford, NY, 1974.

[401]For a review of the use of activated zinc, see Erdik *Tetrahedron* **1987,** *43,* 2203-2212.

[402]For a review, see Noltes *Bull. Soc. Chim. Fr.* **1972,** 2151-2160.

[403]For a method of preparing organoboranes from RMgX and BF_3, where the RMgX is present only in situ, see Brown; Racherla *Tetrahedron Lett.* **1985,** *26,* 4311.

As, Sb, and Bi, can also be prepared in this manner.[404] Except for alkali-metal alkyls and Grignard reagents, the reaction between RM and M'X is the most common method for the preparation of organometallic compounds.[405]

Lithium dialkylcopper reagents can be prepared by mixing 2 moles of RLi with 1 mole of a cuprous halide in ether at low temperatures:[406]

$$\mathbf{2RLi + CuX \longrightarrow R_2CuLi + LiX}$$

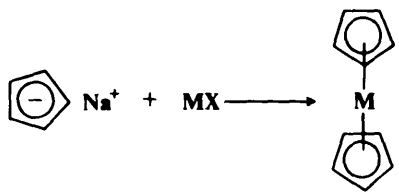
Another way is to dissolve an alkylcopper compound in an alkyllithium solution.

If M' has a valence higher than 1, it is often possible to stop the reaction before all the halogens have been replaced, e.g.,

$$\mathbf{RMgX + SiCl_4 \longrightarrow RSiCl_3}$$

However, it is not always possible: RMgX + BF_3 gives only BR_3, although $BRCl_2$ can be prepared from R_2Zn and BCl_3.

Metallocenes (see p. 47) are usually made by this method:



Among others, metallocenes of Sc, Ti, V, Cr, Mn, Fe, Co, and Ni have been prepared in this manner.[407]

Metal nitrates are sometimes used instead of halides.

OS **I,** 231, 550; **III,** 601; **IV,** 258, 473, 881; **V,** 211, 496, 727, 918, 1001; **VI,** 776, 875, 1033; **VII,** 236, 290, 524; **65,** 61, 108; **67,** 20, 86, 125; **68,** 104, 182. Also see OS **IV,** 476

2-36 Transmetallation with an Organometallic Compound
Metallo-de-metallation

$$\mathbf{RM + R'M' \rightleftharpoons RM' + R'M}$$

This type of metallic exchange is used much less often than **2-34** and **2-35.** It is an equilibrium reaction and is useful only if the equilibrium lies in the desired direction. Usually the goal is to prepare a lithium compound that is not prepared easily in other ways,[408] e.g., a vinylic or an allylic lithium, most commonly from an organotin substrate. Examples are the preparation of vinyllithium from phenyllithium and tetravinyltin and the formation of α-dialkylamino organolithium compounds from the corresponding organotin compounds[409]

$$\mathbf{RR'NCH_2SnBu_3 + BuLi \xrightarrow{0°C} RR'NCH_2Li + Bu_4Sn}$$

[404]For reviews as applied to Si, B, and P, see Wakefield, Ref. 273, pp. 149-158; Kharasch; Reinmuth *Grignard Reactions of Nonmetallic Substances*; Prentice-Hall: Englewood Cliffs, NJ, 1954, pp. 1306-1345.

[405]For a review with respect to Al, see Mole *Organomet. React.* **1970,** *1*, 1-54, pp. 31-43; to Hg, see Larock, Ref. 279, pp. 9-26; Makarova, Ref. 295, pp. 129-178, 227-240; to Cu, Ag, or Au, see van Koten, in Zuckerman, Ref. 246, pp. 219-232; to Zn, Cd, or Hg, see Wardell, in Zuckerman, Ref. 246, pp. 248-270.

[406]House; Chu; Wilkins; Umen *J. Org. Chem.* **1975,** *40*, 1460. But see also Lipshutz; Whitney; Kozlowski; Breneman *Tetrahedron Lett.* **1986,** *27*, 4273; Bertz; Dabbagh *Tetrahedron* **1989,** *45*, 425.

[407]For reviews of the preparation of metallocenes, see Bublitz; Rinehart *Org. React.* **1969,** *17*, 1-154; Birmingham *Adv. Organomet. Chem.* **1965,** *2*, 365-413, pp. 375-382.

[408]For reviews, see Wardell, in Hartley; Patai, Ref. 1, vol. 4, pp. 1-157, pp. 81-89; Kauffmann *Top. Curr. Chem.* **1980,** *92*, 109-147, pp. 130-136.

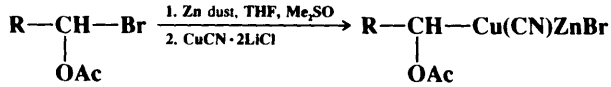
[409]Peterson *J. Am. Chem. Soc.* **1971,** *93*, 4027; Peterson; Ward *J. Organomet. Chem.* **1974,** *66*, 209; Pearson; Lindbeck *J. Org. Chem.* **1989,** *54*, 5651.

The reaction has also been used to prepare 1,3-dilithiopropanes[410] and 1,1-dilithiomethylenecyclohexane[411] from the corresponding mercury compounds. In general, the equilibrium lies in the direction in which the more electropositive metal is bonded to that alkyl or aryl group that is the more stable carbanion (p. 176). The reaction proceeds with retention of configuration;[412] an SEi mechanism is likely.[413]

"Higher order" cuprates (see Ref. 1277 in Chapter 10) have been produced by this reaction starting with a vinylic tin compound:[414]

$$\mathbf{RSnR'_3 + Me_2Cu(CN)Li_2 \longrightarrow RCuMe(CN)Li_2 + MeSnR'_3} \quad \mathbf{R} = \text{a vinylic group}$$

These compounds are not isolated, but used directly in situ for conjugate addition reactions (**5-18**). Another method for the preparation of such reagents (but with Zn instead of Li) allows them to be made from α-acetoxy halides:[415]



OS **V,** 452; **VI,** 815; **68,** 116.

Halogen as Leaving Group

A. Hydrogen as the Electrophile

2-37 Reduction of Alkyl Halides

Although this reaction can proceed by an electrophilic substitution mechanism, it is considered in Chapter 10 (**0-76**).

B. Metal Electrophiles

2-38 Metallo-de-halogenation

$$\mathbf{RX + M \longrightarrow RM}$$

Alkyl halides react directly with certain metals to give organometallic compounds.[416] The most common metal is magnesium, and of course this is by far the most common method for the preparation of Grignard reagents.[417] The order of halide activity is I > Br > Cl. The reaction can be applied to many alkyl halides—primary, secondary, and tertiary—and to aryl halides, though aryl *chlorides* require the use of THF or another higher-boiling solvent instead of the usual ether, or special entrainment methods.[418] Aryl iodides and bromides can be treated in the usual manner. Allylic Grignard reagents can also be prepared

[410]Seetz; Schat; Akkerman; Bickelhaupt *J. Am. Chem. Soc.* **1982,** *104*, 6848.
[411]Maercker; Dujardin *Angew. Chem. Int. Ed. Engl.* **1984,** *23*, 224 [*Angew. Chem. 96*, 222].
[412]Seyferth; Vaughan *J. Am. Chem. Soc.* **1964,** *86*, 883; Sawyer; Kucerovy; Macdonald; McGarvey *J. Am. Chem. Soc.* **1988,** *110*, 842.
[413]Dessy; Kaplan; Coe; Salinger *J. Am. Chem. Soc.* **1963,** *85*, 1191.
[414]Behling; Babiak; Ng; Campbell; Moretti; Koerner; Lipshutz *J. Am. Chem. Soc.* **1988,** *110*, 2641.
[415]Chou; Knochel *J. Org. Chem.* **1990,** *55*, 4791.
[416]For reviews, see Massey; Humphries *Aldrichimica Acta* **1989,** *22*, 31-38; Negishi, Ref. 1, pp. 30-37; Rochow *J. Chem. Educ.* **1966,** *43*, 58-62.
[417]For reviews, see Raston; Salem, in Hartley; Patai, Ref. 1, vol. 4, pp. 159-306, pp. 162-175; Kharasch; Reinmuth, Ref. 404, pp. 5-91.
[418]Pearson; Cowan; Beckler *J. Org. Chem.* **1959,** *24*, 504.

in the usual manner (or in THF),[419] though in the presence of excess halide these may give Wurtz-type coupling products (see **0-87**).[420] Like aryl chlorides, vinylic halides require higher-boiling solvents (see OS **IV,** 258). A good procedure for benzylic and allylic halides is to use magnesium anthracene (prepared from Mg and anthracene in THF)[421] instead of ordinary magnesium,[422] though activated magnesium turnings have also been used.[423] Alkynyl Grignard reagents are not generally prepared by this method at all. For these, **2-21** is used.

Dihalides[424] can be converted to Grignard reagents if the halogens are different and are at least three carbons apart. If the halogens are the same, it is possible to obtain dimagnesium compounds, e.g., $BrMg(CH_2)_4MgBr$.[425] 1,2-Dihalides give elimination[426] instead of Grignard reagent formation (**7-29**), and the reaction is seldom successful with 1,1-dihalides, though the preparation of *gem*-disubstituted compounds, such as $CH_2(MgBr)_2$, has been accomplished with these substrates.[427] α-Halo Grignard reagents and α-halolithium reagents can be prepared by the method given in **2-39.**[428] Alkylmagnesium fluorides can be prepared by refluxing alkyl fluorides with Mg in the presence of appropriate catalysts (e.g., I_2 or EtBr) in THF for several days.[429]

The presence of other functional groups in the halide usually affects the preparation of the Grignard reagent. Groups that contain active hydrogen (defined as any hydrogen that will react with a Grignard reagent), such as OH, NH_2, and COOH, can be present in the molecule, but only if they are converted to the salt form (O^-, NH^-, COO^-, respectively). Groups that react with Grignard reagents, such as C=O, C≡N, NO_2, COOR, etc., inhibit Grignard formation entirely. In general, the only functional groups that may be present in the halide molecule without any interference at all are double and triple bonds (except terminal triple bonds) and OR and NR_2 groups. However, β-halo ethers generally give β elimination when treated with magnesium (see **7-31**), and Grignard reagents from α-halo ethers[430] can only be formed in THF or dimethoxymethane at a low temperature, e.g.,[431]

$$EtOCH_2Cl + Mg \xrightarrow[-30°C]{\text{THF or } CH_2(OMe)_2} EtOCH_2MgCl$$

because such reagents immediately undergo α elimination (see **2-39**) at room temperature in ether solution.

[419]For a review of allyl and crotyl Grignard reagents, see Benkeser *Synthesis* **1971,** 347-358.

[420]For a method of reducing coupling in the formation of allylic Grignard reagents, see Oppolzer; Schneider *Tetrahedron Lett.* **1984,** *25,* 3305.

[421]Freeman; Hutchinson *J. Org. Chem.* **1983,** *48,* 879; Bogdanović; Janke; Kinzelmann *Chem. Ber.* **1990,** *123,* 1507, and other papers in this series.

[422]Gallagher; Harvey; Raston; Sue *J. Chem. Soc., Chem. Commun.* **1988,** 289.

[423]Baker; Brown; Hughes; Skarnulis; Sexton *J. Org. Chem.* **1991,** *56,* 698. For a review of the use of activated magnesium, see Lai *Synthesis* **1981,** 585-604.

[424]For reviews of the preparation of Grignard reagents from dihalides, see Raston; Salem, Ref. 417, pp. 187-193; Heaney *Organomet. Chem. Rev.* **1966,** *1,* 27-42. For a review of di-Grignard reagents, see Bickelhaupt *Angew. Chem. Int. Ed. Engl.* **1987,** *26,* 990-1005 [*Angew. Chem. 99,* 1020-1036].

[425]For example, see Denise; Ducom; Fauvarque *Bull. Soc. Chim. Fr.* **1972,** 990; Seetz; Hartog; Böhm; Blomberg; Akkerman; Bickelhaupt *Tetrahedron Lett.* **1982,** *23,* 1497.

[426]For formation of 1,2-dilithio compounds and 1,2-di-Grignard reagents, but not by this method, see van Eikkema Hommes; Bickelhaupt; Klumpp *Recl. Trav. Chim. Pays-Bas* **1988,** *107,* 393, *Angew. Chem. Int. Ed. Engl.* **1988,** *27,* 1083 [*Angew. Chem. 100,* 1100].

[427]For example, see Bertini; Grasselli; Zubiani; Cainelli *Tetrahedron* **1970,** *26,* 1281; Bruin; Schat; Akkerman; Bickelhaupt *J. Organomet. Chem.* **1985,** *288,* 13. For the synthesis of *gem*-dilithio and 1,1,1-trilithio compounds, see Landro; Gurak; Chinn; Newman; Lagow *J. Am. Chem. Soc.* **1982,** 104, 7345; Baran; Lagow *J. Am. Chem. Soc.* **1990,** *112,* 9415.

[428]For a review of compounds containing both carbon–halogen and carbon–metal bonds, see Chivers *Organomet. Chem. Rev., Sect.* **1970,** *6,* 1-64.

[429]Yu; Ashby *J. Org. Chem.* **1971,** *36,* 2123.

[430]For a review of organometallic compounds containing a hetero atom (N, O, P, S, or Si), see Peterson *Organomet. Chem. Rev., Sect. A* **1972,** *7,* 295-358.

[431]For example, see Normant; Castro, *C. R. Acad. Sci.* **1963,** *257,* 2115, **1964,** *259,* 830; Castro *Bull. Soc. Chim. Fr.* **1967,** 1533, 1540, 1547; Taeger; Kahlert; Walter *J. Prakt. Chem.* **1965,** [4] *28,* 13.

Because Grignard reagents react with water (**2-24**) and with oxygen (**2-25**), it is generally best to prepare them in an anhydrous nitrogen atmosphere. Grignard reagents are generally neither isolated nor stored; solutions of Grignard reagents are used directly for the required synthesis. Grignard reagents can also be prepared in benzene or toluene, if a tertiary amine is added to complex with the RMgX.[432] This method eliminates the need for an ether solvent. With certain primary alkyl halides it is even possible to prepare alkylmagnesium compounds in hydrocarbon solvents in the absence of an organic base.[433] It is also possible to obtain Grignard reagents in powdered form, by complexing them with the chelating agent tris(3,6-dioxaheptyl)amine $N(CH_2CH_2OCH_2CH_2OCH_3)_3$.[434]

Next to the formation of Grignard reagents, the most important application of this reaction is the conversion of alkyl and aryl halides to organolithium compounds,[435] but it has also been carried out with many other metals, e.g., Na, Be, Zn, Hg, As, Sb, and Sn. With sodium, the Wurtz reaction (**0-86**) is an important side reaction. In some cases where the reaction between a halide and a metal is too slow, an alloy of the metal with potassium or sodium can be used instead. The most important example is the preparation of tetraethyllead from ethyl bromide and a Pb–Na alloy.

The efficiency of the reaction can often be improved by use of the metal in its powdered[435a] or vapor[436] form. These techniques have permitted the preparation of some organometallic compounds that cannot be prepared by the standard procedures. Among the metals produced in an activated form are Mg,[437] Ca,[438] Zn,[439] Al, Sn, Cd,[440] Ni, Fe, Ti, Cu,[441] Pd, and Pt.[442]

The mechanism of Grignard reagent formation involves free radicals.[443] There is much evidence for this, from CIDNP[444] (p. 187) and from stereochemical, rate, and product studies.[445] Further evidence is that free radicals have been trapped,[446] and that experiments that studied the intrinsic reactivity of MeBr on a magnesium single-crystal surface showed that Grignard reagent formation does not take place by a single-step insertion mechanism.[447] The following SET mechanism has been proposed:[444]

$$\mathrm{R{-}X + \overline{Mg} \longrightarrow R{-}X^{\bullet -} + Mg_s^{\bullet +}}$$

$$\mathrm{R{-}X^{\bullet -} \longrightarrow R^{\bullet} + X^-}$$

$$\mathrm{X^- + Mg_s^{\bullet +} \longrightarrow XMg_s^{\bullet}}$$

$$\mathrm{R^{\bullet} + XMg_s^{\bullet} \longrightarrow RMgX}$$

[432]Ashby; Reed *J. Org. Chem.* **1966,** *31*, 971; Gitlitz; Considine *J. Organomet. Chem.* **1970,** *23*, 291.

[433]Smith *J. Organomet. Chem.* **1974,** *64*, 25.

[434]Boudin; Cerveau; Chuit; Corriu; Reye *Tetrahedron* **1989,** *45*, 171.

[435]For reviews, see Wakefield, Ref. 273, pp. 21-32; Wardell, in Hartley; Patai, vol. 4, pp. 1-157, pp. 5-27; Newcomb, in Zuckerman, Ref. 246, pp. 3-14.

[435a]For a review, see Rieke *Science* **1989,** *246*, 1260-1264.

[436]For reviews, see Klabunde *React. Intermed. (Plenum)* **1980,** *1*, 37-149, *Acc. Chem. Res.* **1975,** *8*, 393-399; Skell, Havel; McGlinchey *Acc. Chem. Res.* **1973,** *6*, 97-105; Timms *Adv. Inorg. Radiochem.* **1972,** *14*, 121.

[437]Burns; Rieke *J. Org. Chem.* **1987,** *52*, 3674; Ebert; Rieke *J. Org. Chem.* **1988,** *53*, 4482. See also Ref. 423.

[438]Wu; Xiong; Rieke *J. Org. Chem.* **1990,** *55*, 5045.

[439]Rieke; Li; Burns; Uhm *J. Org. Chem.* **1981,** *46*, 4323. See also Grondin; Sebban; Vottero; Blancou; Commeyras *J. Organomet. Chem.* **1989,** *362*, 237; Berk; Yeh; Jeong; Knochel *Organometallics* **1990,** *9*, 3053; Zhu; Wehmeyer; Rieke *J. Org. Chem.* **1991,** *56*, 1445.

[440]Burkhardt; Rieke *J. Org. Chem.* **1985,** *50*, 416.

[441]Stack; Dawson; Rieke *J. Am. Chem. Soc.* **1991,** *113*, 4672, and references cited therein.

[442]For reviews, see Lai, Ref. 423; Rieke *Acc. Chem. Res.* **1977,** *10*, 301-306, *Top. Curr. Chem.* **1975,** *59*, 1-31.

[443]For a review, see Blomberg *Bull. Soc. Chim. Fr.* **1972,** 2143.

[444]Bodewitz; Blomberg; Bickelhaupt *Tetrahedron Lett.* **1972,** 281, **1975,** 2003, *Tetrahedron* **1973,** *29*, 719, **1975,** *31*, 1053. See also Lawler; Livant *J. Am. Chem. Soc.* **1976,** *98*, 3710; Schaart; Blomberg; Akkerman; Bickelhaupt *Can. J. Chem.* **1980,** *58*, 932.

[445]See, for example, Walborsky; Aronoff *J. Organomet. Chem.* **1973,** *51*, 31; Czernecki; Georgoulis; Gross; Prevost *Bull. Soc. Chim. Fr.* **1968,** 3720; Rogers; Hill; Fujiwara; Rogers; Mitchell; Whitesides *J. Am. Chem. Soc.* **1980,** *102*, 217; Barber; Whitesides *J. Am. Chem. Soc.* **1980,** *102*, 239.

[446]Root; Hill; Lawrence; Whitesides *J. Am. Chem. Soc.* **1989,** *111*, 5405.

[447]Nuzzo; Dubois *J. Am. Chem. Soc.* **1986,** *108*, 2881.

The species R—X$^{\bullet}_{s}$ and Mg$^{\ddagger}_{s}$ are radical ions.[448] The subscript "s" is meant to indicate that the species so marked are bound to the surface of the magnesium. It has been suggested that some of the R• radicals diffuse from the magnesium surface into the solution and then return to the surface to react with the XMg•. There is evidence both for[449] and against[450] this suggestion. Another proposal is that the fourth step is not the one shown here, but that the R• is reduced by Mg^+ to the carbanion R^-, which combines with MgX^+ to give RMgX.[451]

There are too many preparations of Grignard reagents in *Organic Syntheses* for us to list here. Use of the reaction to prepare other organometallic compounds can be found in OS **I,** 228; **II,** 184, 517, 607; **III,** 413, 757; **VI,** 240; **VII,** 346; **65,** 42. The preparation of unsolvated butylmagnesium bromide is described at OS **V,** 1141. The preparation of highly reactive (powdered) magnesium is given at OS **VI,** 845.

2-39 Replacement of a Halogen by a Metal from an Organometallic Compound
Metallo-de-halogenation

$$\mathbf{RX + R'M \longrightarrow RM + R'X}$$

The exchange reaction between halides and organometallic compounds is almost entirely limited to the cases where M is lithium and X is bromide or iodide,[452] though it has been shown to occur with magnesium.[453] R′ is usually, though not always, alkyl, and often butyl; R is usually aromatic.[454] Alkyl halides are generally not reactive enough, while allylic and benzylic halides usually give Wurtz coupling. Of course, the R that becomes bonded to the halogen is the one for which RH is the weaker acid. Vinylic halides react with retention of configuration.[455] The reaction can be used to prepare α-halo organolithium and α-halo organomagnesium compounds,[456] e.g.,[457]

$$\mathbf{CCl_4 + BuLi \xrightarrow[-105°C]{THF} Cl_3C{-}Li}$$

Such compounds can also be prepared by hydrogen–metal exchange, e.g.,[458]

$$\mathbf{Br_3CH + iso\text{-}PrMgCl \xrightarrow[-95°C]{THF\text{-}HMPA} Br_3C{-}MgCl + C_3H_8}$$

[448]For additional evidence for this mechanism, see Vogler; Stein; Hayes *J. Am. Chem. Soc.* **1978,** *100,* 3163; Sergeev; Zagorsky; Badaev *J. Organomet. Chem.* **1983,** *243,* 123. However, there is evidence that the mechanism may be more complicated: de Souza-Barboza; Luche; Pétrier *Tetrahedron Lett.* **1987,** *28,* 2013.

[449]Garst; Deutch; Whitesides *J. Am. Chem. Soc.* **1986,** *108,* 2490; Ashby; Oswald *J. Org. Chem.* **1988,** *53,* 6068; Garst; Swift *J. Am. Chem. Soc.* **1989,** *111,* 241; Garst *Acc. Chem. Res.* **1991,** *24,* 95; Garst; Ungváry; Batlaw; Lawrence *J. Am. Chem. Soc.* **1991,** *113,* 5392. For a discussion, see Walling *Acc. Chem. Res.* **1991,** *24,* 255.

[450]Walborsky; Rachon *J. Am. Chem. Soc.* **1989,** *111,* 1896; Rachon; Walborsky *Tetrahedron Lett.* **1989,** *30,* 7345; Walborsky *Acc. Chem. Res.* **1990,** *23,* 286-293.

[451]de Boer; Akkerman; Bickelhaupt *Angew. Chem. Int. Ed. Engl.* **1988,** *27,* 687 [*Angew. Chem. 100,* 735].

[452]For reviews, see Wardell, in Zuckerman, Ref. 246, pp. 107-129; Parham; Bradsher *Acc. Chem. Res.* **1982,** *15,* 300-305.

[453]See, for example, Zakharkin; Okhlobystin; Bilevitch *J. Organomet. Chem.* **1964,** *2,* 309; Tamborski; Moore *J. Organomet. Chem.* **1971,** *26,* 153.

[454]For the preparation of primary alkyllithiums by this reaction, see Bailey; Punzalan *J. Org. Chem.* **1990,** *55,* 5404; Negishi; Swanson; Rousset *J. Org. Chem.* **1990,** *55,* 5406.

[455]For examples of exchange where R = vinylic, see Neumann; Seebach *Chem. Ber.* **1978,** *111,* 2785; Miller; McGarvey *Synth. Commun* **1979,** *9,* 831; Sugita; Sakabe; Sasahara; Tsukuda; Ichikawa *Bull. Chem. Soc. Jpn.* **1984,** *57,* 2319.

[456]For reviews of such compounds, see Siegel *Top. Curr. Chem.* **1982,** *106,* 55-78; Negishi, Ref. 1, pp. 136-151; Kaabrich *Angew. Chem. Int. Ed. Engl.* **1972,** *11,* 473-485, **1967,** *6,* 41-52 [*Angew. Chem. 84,* 557-570, *79,* 15-27]. *Bull. Soc. Chim. Fr.* **1969,** 2712-2720; Villieras *Organomet. Chem. Rev., Sect. A* **1971,** *7,* 81-94. For related reviews, see Krief *Tetrahedron* **1980,** *36,* 2531-2640; Normant *J. Organomet. Chem.* **1975,** *100,* 189-203; Zhil'tsov; Druzhkov *Russ. Chem. Rev.* **1971,** *40,* 126-141.

[457]Hoeg; Lusk; Crumbliss *J. Am. Chem. Soc.* **1965,** *87,* 4147. See also Villieras; Tarhouni; Kirschleger; Rambaud *Bull. Soc. Chim. Fr.* **1985,** 825.

[458]Villieras *Bull. Soc. Chim. Fr.* **1967,** 1520.

This is an example of **2-21.** However, these α-halo organometallic compounds are stable (and configurationally stable as well[458a]) only at low temperatures (~ −100°C) and only in THF or mixtures of THF and other solvents (e.g., HMPA). At ordinary temperatures they lose MX (α elimination) to give carbenes (which then react further) or carbenoid reactions. The α-chloro-α-magnesio sulfones $ArSO_2CH(Cl)MgBr$ are exceptions, being stable in solution at room temperature and even under reflux.[459] Compounds in which a halogen and a transition metal are on the same carbon can be more stable than the ones with lithium.[460]

There is evidence that the mechanism[461] of the reaction of alkyllithium compounds with alkyl and aryl iodides involves free radicals.[462]

$$\mathbf{RX + R'M \rightleftharpoons [R\bullet, X, M, R'\bullet] \rightleftharpoons RM + R'X}$$

Solvent cage

Among the evidence is the obtention of coupling and disproportionation products from R• and R'• and the observation of CIDNP.[463] However, in the degenerate exchange between PhI and PhLi the ate complex $Ph_2I^-\ Li^+$ has been shown to be an intermediate,[464] and there is other evidence that radicals are not involved in all instances of this reaction.[465]

In a completely different kind of process, alkyl halides can be converted to certain organometallic compounds by treatment with organometallate ions, e.g.,

$$\mathbf{RX + R_3'SnLi \longrightarrow RSnR_3' + LiX}$$

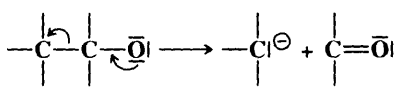
Most of the evidence is in accord with a free radical mechanism involving electron transfer, though an SN2 mechanism can compete under some conditions.[466]

OS **VI,** 82; **VII,** 271, 326, 495; **66,** 67, 210. See also OS **VII,** 512; **66,** 95.

Carbon Leaving Groups

In these reactions (**2-40** to **2-48**) a carbon–carbon bond cleaves. We regard as the substrate that side which retains the electron pair; hence the reactions are considered electrophilic substitutions. The incoming group is hydrogen in all but one (**2-42**) of the cases. The reactions in groups A and B are sometimes called *anionic cleavages*,[467] though they do not always occur by mechanisms involving free carbanions (SE1). When they do, the reactions are facilitated by increasing stability of the carbanion.

A. Carbonyl-Forming Cleavages. These reactions follow the pattern



[458a]Hoffmann; Ruhland; Bewersdorf *J. Chem. Soc., Chem. Commun.* **1991,** 195; Schmidt; Köbrich; Hoffmann *Chem. Ber.* **1991,** *124,* 1253; Hoffmann; Bewersdorf *Chem. Ber.* **1991,** *124,* 1259.

[459]Stetter; Steinbeck *Liebigs Ann. Chem.* **1972,** *766,* 89.

[460]Kauffmann; Fobker; Wensing *Angew. Chem. Int. Ed. Engl.* **1988,** *27,* 943 [*Angew. Chem. 100,* 1005].

[461]For reviews of the mechanism, see Bailey; Patricia *J. Organomet. Chem.* **1988,** *352,* 1-46; Beletskaya; Artamkina; Reutov *Russ. Chem. Rev.* **1976,** *45,* 330-347.

[462]Ward; Lawler; Cooper *J. Am. Chem. Soc.* **1969,** *91,* 746; Lepley; Landau *J. Am. Chem. Soc.* **1969,** *91,* 748; Ashby; Pham *J. Org. Chem.* **1987,** *52,* 1291. See also Bailey; Patricia; Nurmi; Wang *Tetrahedron Lett.* **1986,** *27,* 1861.

[463]Ward; Lawler; Loken *J. Am. Chem. Soc.* **1968,** *90,* 7359; Ref. 462.

[464]See Farnham; Calabrese *J. Am. Chem. Soc.* **1986,** *108,* 2449; Reich; Green; Phillips *J. Am. Chem. Soc.* **1989,** *111,* 3444.

[465]Rogers; Houk *J. Am. Chem. Soc.* **1982,** *104,* 522; Beak; Allen; Lee *J. Am. Chem. Soc.* **1990,** *112,* 1629.

[466]See San Filippo; Silbermann *J. Am. Chem. Soc.* **1982,** *104,* 2831; Ashby; Su; Pham *Organometallics* **1985,** *4,* 1493; Alnajjar; Kuivila *J. Am. Chem. Soc.* **1985,** *107,* 416.

[467]For a review, see Artamkina; Beletskaya *Russ. Chem. Rev.* **1987,** *56,* 983-1001.

The leaving group is stabilized because the electron deficiency at its carbon is satisfied by a pair of electrons from the oxygen. With respect to the leaving group the reaction is elimination to form a C=O bond. Retrograde aldol reactions (**6-39**) and cleavage of cyanohydrins (**6-49**) belong to this classification but are treated in Chapter 16 under their more important reverse reactions. Other eliminations to form C=O bonds are discussed in Chapter 17 (**7-43** and **7-44**).

2-40 Decarboxylation of Aliphatic Acids
Hydro-de-carboxylation

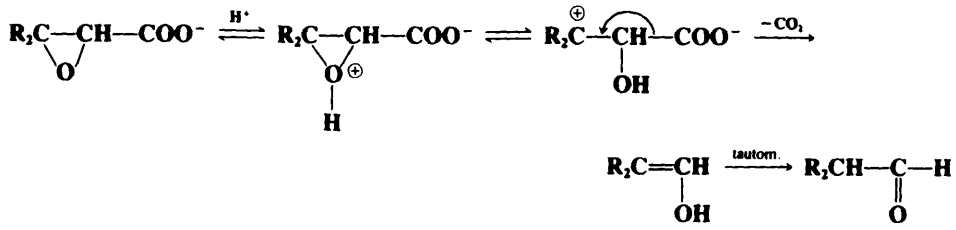
$$\mathbf{RCOOH \longrightarrow RH + CO_2}$$

Many carboxylic acids can be successfully decarboxylated, either as the free acid or in the salt form, but not simple fatty acids.[468] An exception is acetic acid, which as the acetate, heated with base, gives good yields of methane. Aliphatic acids that do undergo successful decarboxylation have certain functional groups or double or triple bonds in the α or β position. Some of these are shown in Table 12.2. For decarboxylation of aromatic acids, see **1-39.** Decarboxylation of an α-cyano acid can give a nitrile or a carboxylic acid, since the cyano group may or may not be hydrolyzed in the course of the reaction. In addition to the compounds listed in Table 12.2, decarboxylation can also be carried out on α,β-unsaturated and α,β-acetylenic acids. α,β-Unsaturated acids can also be decarboxylated with copper and quinoline in a manner similar to that discussed in **1-39.** Glycidic acids give aldehydes on decarboxylation. The following mechanism has been suggested:[469]

TABLE 12.2 Some acids which undergo decarboxylation fairly readily
Others are described in the text

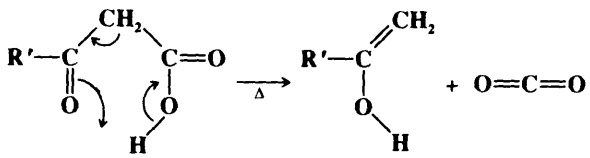
Acid type		Decarboxylation product	
Malonic	HOOC—C(H)—COOH	HOOC—C(H)—H	
α-Cyano	NC—C(H)—COOH	NC—C(H)—H	or HOOC—C(H)—H
α-Nitro	O_2N—C(H)—COOH	O_2N—C(H)—H	
α-Aryl	Ar—C(H)—COOH	Ar—C(H)—H	
α,α,α-Trihalo	X_3C—COOH	X_3CH	
β-Keto	—C(=O)—C(H)—COOH	—C(=O)—C(H)—H	
β,γ-Unsaturated	—C=C—C(H)—COOH	—C=C—C(H)—H	

[468]March *J. Chem. Educ.* **1963,** *40,* 212.
[469]Singh; Kagan *J. Org. Chem.* **1970,** *35,* 2203.

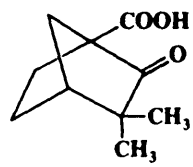


The direct product is an enol that tautomerizes to the aldehyde.[470] This is the usual last step in the Darzens reaction (**6-45**).

Decarboxylations can be regarded as reversals of the addition of carbanions to carbon dioxide (**6-32**), but free carbanions are not always involved.[471] When the carboxylate *ion* is decarboxylated, the mechanism can be either SE1 or SE2. In the case of the SE1 mechanism, the reaction is of course aided by the presence of electron-withdrawing groups, which stabilize the carbanion.[472] Decarboxylations of carboxylate ions can be accelerated by the addition of a suitable crown ether, which in effect removes the metallic ion.[473] The reaction without the metallic ion has also been performed in the gas phase.[474] But some acids can also be decarboxylated directly and, in most of these cases, there is a cyclic, six-center mechanism:



Here too there is an enol that tautomerizes to the product. The mechanism is illustrated for the case of β-keto acids,[475] but it is likely that malonic acids, α-cyano acids, α-nitro acids, and β,γ-unsaturated acids[476] behave similarly, since similar six-membered transition states can be written for them. Some α,β-unsaturated acids are also decarboxylated by this mechanism by isomerizing to the β,γ-isomers before they actually decarboxylate.[477] Evidence is that **36** and similar bicyclic β-keto acids resist decarboxylation.[478] In such compounds the



36

[470]Shiner; Martin *J. Am. Chem. Soc.* **1962,** *84*, 4824.

[471]For reviews of the mechanism, see Richardson; O'Neal, in Bamford; Tipper, Ref. 53, vol. 5, 1972, pp. 447-482; Clark, in Patai *The Chemistry of Carboxylic Acids and Esters*; Wiley: New York, 1969, pp. 589-622. For a review of carbon isotope effect studies, see Dunn *Isot. Org. Chem.* **1977,** *3*, 1-38.

[472]See, for example, Oae; Tagaki; Uneyama; Minamida *Tetrahedron* **1968,** *24*, 5283; Buncel; Venkatachalam; Menon *J. Org. Chem.* **1984,** *49*, 413.

[473]Hunter; Patel; Perry *Can. J. Chem.* **1980,** *58*, 2271, and references cited therein.

[474]Graul; Squires *J. Am. Chem. Soc.* **1988,** *110*, 607.

[475]For a review of the mechanism of the decarboxylation of β-keto acids, see Jencks *Catalysis in Chemistry and Enzmology*; McGraw-Hill: New York, 1969, pp. 116-120

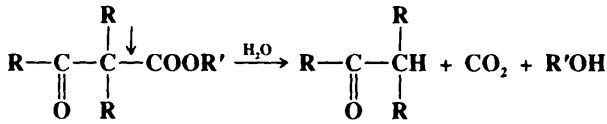
[476]Bigley; Clarke *J. Chem. Soc., Perkin Trans. 2* **1982,** 1, and references cited therein. For a review, see Smith; Kelly, *Prog. Phys. Org. Chem.* **1971,** *8*, 75-234, pp. 150-153.

[477]Bigley *J. Chem. Soc.* **1964,** 3897.

[478]Wasserman, in Newman *Steric Effects in Organic Chemistry*; Wiley: New York, 1956, p. 352. See also Buchanan; Kean; Taylor *Tetrahedron* **1975,** *31*, 1583.

six-membered cyclic transition state cannot form for steric reasons, and if it could, formation of the intermediate enol would violate Bredt's rule (p. 160).[479] Some carboxylic acids that cannot form a six-membered transition state can still be decarboxylated, and these presumably react through an SE1 or SE2 mechanism.[480] Further evidence for the cyclic mechanism is that the reaction rate varies very little with a change from a nonpolar to a polar solvent (even from benzene to water[481]), and is not subject to acid catalysis.[482] The rate of decarboxylation of a β,γ-unsaturated acid was increased about 10^5-10^6 times by introduction of a β-methoxy group, indicating that the cyclic transition state has dipolar character.[483]

β-Keto acids[484] are easily decarboxylated, but such acids are usually prepared from β-keto esters, and the esters are easily decarboxylated themselves on hydrolysis without isolation of the acids.[485] This decarboxylation of β-keto esters involving cleavage on the carboxyl side of the substituted methylene group (arrow) is carried out under acidic, neutral, or



slightly basic conditions to yield a ketone. When strongly basic conditions are used, cleavage occurs on the other side of the CR_2 group (**2-43**). β-Keto esters can be decarbalkoxylated without passing through the free-acid stage by treatment with boric anhydride B_2O_3 at 150°C.[486] The alkyl portion of the ester (R') is converted to an alkene or, if it lacks a β hydrogen, to an ether R'OR'. Another method for the decarbalkoxylation of β-keto esters, malonic esters, and α-cyano esters consists of heating the substrate in wet dimethyl sulfoxide containing NaCl, Na_3PO_4, or some other simple salt.[487] In this method too, the free acid is probably not an intermediate, but here the alkyl portion of the substrate is converted to the corresponding alcohol. Ordinary carboxylic acids, containing no activating groups, can be decarboxylated by conversion to esters of N-hydroxypyridine-2-thione and treatment of these with Bu_3SnH.[488] A free-radical mechanism is likely. α-Amino acids have been decarboxylated by treatment with a catalytic amount of 2-cyclohexenone.[489] Certain decarboxylations can also be accomplished photochemically.[490] See also the decarbonylation of acyl halides, mentioned in **4-41.** In some cases decarboxylations can give organometallic compounds: RCOOM → RM + CO_2.[491]

[479]Sterically hindered β-keto acids decarboxylate more slowly: Meier; Wengenroth; Lauer; Krause *Tetrahedron Lett.* **1989,** *30,* 5253.

[480]For example, see Ferris; Miller *J. Am. Chem. Soc.* **1966,** *88,* 3522.

[481]Westheimer; Jones *J. Am. Chem. Soc.* **1941,** *63,* 3283; Swain; Bader; Esteve; Griffin *J. Am. Chem. Soc.* **1961,** *83,* 1951.

[482]Pedersen *Acta Chem. Scand.* **1961,** *15,* 1718; Noyce; Metesich *J. Org. Chem.* **1967,** *32,* 3243.

[483]Bigley; Al-Borno *J. Chem. Soc., Perkin Trans. 2* **1982,** 15.

[484]For a review of β-keto acids, see Oshry; Rosenfeld *Org. Prep. Proced. Int.* **1982,** *14,* 249-264.

[485]For a list of examples, with references, see Ref. 52, pp. 774-775.

[486]Lalancette; Lachance *Tetrahedron Lett.* **1970,** 3903.

[487]For a review of the synthetic applications of this method, see Krapcho *Synthesis* **1982,** 805-822, 893-914. For other methods, see Aneja; Hollis; Davies; Eaton *Tetrahedron Lett.* **1983,** *24,* 4641; Brown; Jones *J. Chem. Res. (S)* **1984,** 332; Dehmlow; Kunesch *Synthesis* **1985,** 320; Taber; Amedio; Gulino *J. Org. Chem.* **1989,** *54,* 3474.

[488]Barton; Crich; Motherwell *Tetrahedron* **1985,** *41,* 3901; Della; Tsanaktsidis *Aust. J. Chem.* **1987,** *39,* 2061. For another method of more limited scope, see Maier; Roth; Thies; Schleyer *Chem. Ber.* **1982,** *115,* 808.

[489]Hashimoto; Eda; Osanai; Iwai; Aoki *Chem. Lett.* **1986,** 893.

[490]See Davidson; Steiner *J. Chem. Soc., Perkin Trans. 2* **1972,** 1357; Kraeutler; Bard *J. Am. Chem. Soc.* **1978,** *100,* 5985; Hasebe; Tsuchiya *Tetrahedron Lett.* **1987,** *28,* 6207; Okada; Okubo; Oda *Tetrahedron Lett.* **1989,** *30,* 6733.

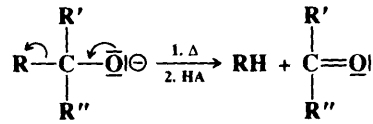
[491]For reviews, see Deacon *Organomet. Chem. Rev. A* **1970,** 355-372; Deacon; Faulks; Pain *Adv. Organomet. Chem.* **1986,** *25,* 237-276.

Some of the decarboxylations listed in *Organic Syntheses* are performed with concomitant ester or nitrile hydrolysis and others are simple decarboxylations.

With ester or nitrile hydrolysis: OS **I,** 290, 451, 523; **II,** 200, 391; **III,** 281, 286, 313, 326, 510, 513, 591; **IV,** 55, 93, 176, 441, 664, 708, 790, 804; **V,** 76, 288, 572, 687, 989; **VI,** 615, 781, 873, 932; **VII,** 50, 210, 319; **67,** 170.

Simple decarboxylations: OS **I,** 351, 401, 440, 473, 475; **II,** 21, 61, 93, 229, 302, 333, 368, 416, 474, 512, 523; **III,** 213, 425, 495, 705, 733, 783; **IV,** 234, 254, 278, 337, 555, 560, 597, 630, 731, 857; **V,** 251, 585; **VI,** 271, 965; **VII,** 249, 359; **65,** 98; **66,** 29; **68,** 210. Also see OS **IV,** 633.

2-41 Cleavage of Alkoxides
Hydro-de-(α-oxidoalkyl)-substitution

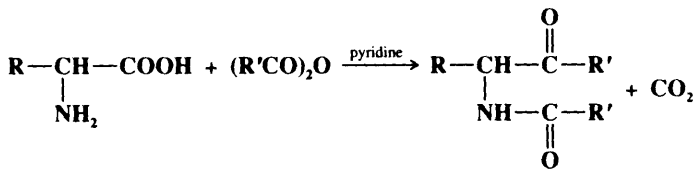


Alkoxides of tertiary alcohols can be cleaved in a reaction that is essentially the reverse of addition of carbanions to ketones (**6-29**).[492] The reaction is unsuccessful when the R groups are simple unbranched alkyl groups, e.g., the alkoxide of triethylcarbinol. Cleavage is accomplished with branched alkoxides such as the alkoxides of diisopropylneopentylcarbinol or tri-*t*-butylcarbinol.[493] Allylic,[494] benzylic,[495] and aryl groups also cleave; for example, the alkoxide of triphenylcarbinol gives benzene and benzophenone. Studies in the gas phase show that the cleavage is a simple one, giving the carbanion and ketone directly in one step.[496] However, with some substrates in solution, substantial amounts of dimer RR have been found, indicating a radical pathway.[497] Hindered alcohols (not the alkoxides) also lose one R group by cleavage, also by a radical pathway.[498]

The reaction has been used for extensive mechanistic studies (see p. 574).

OS **VI,** 268.

2-42 Replacement of a Carboxyl Group by an Acyl Group
Acyl-de-carboxylation



[492]Zook; March; Smith *J. Am. Chem. Soc.* **1959,** *81,* 1617; Barbot; Miginiac *J. Organomet. Chem.* **1977,** *132,* 445; Benkeser; Siklosi; Mozdzen *J. Am. Chem. Soc.* **1978,** *100,* 2134.

[493]Arnett; Small; McIver; Miller *J. Org. Chem.* **1978,** *43,* 815. See also Lomas; Dubois *J. Org. Chem.* **1984,** *49,* 2067.

[494]See Snowden; Linder; Muller; Schulte-Elte *Helv. Chim. Acta* **1987,** *70,* 1858, 1879.

[495]Partington; Watt *J. Chem. Soc., Perkin Trans. 2* **1988,** 983.

[496]Tumas; Foster; Brauman *J. Am. Chem. Soc.* **1988,** *110,* 2714; Ibrahim; Watt; Wilson; Moore *J. Chem. Soc., Chem. Commun.* **1989,** 161.

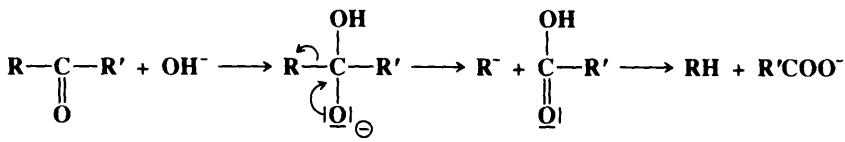
[497]Paquette; Gilday; Maynard *J. Org. Chem.* **1989,** *54,* 5044; Paquette; Maynard *J. Org. Chem.* **1989,** *54,* 5054.

[498]See Lomas; Fain; Briand *J. Org. Chem.* **1990,** *55,* 1052, and references cited therein.

When an α-amino acid is treated with an anhydride in the presence of pyridine, the carboxyl group is replaced by an acyl group and the NH_2 becomes acylated. This is called the *Dakin–West reaction*.[499] The mechanism involves formation of an oxazolone.[500] The reaction sometimes takes place on carboxylic acids even when an α amino group is not present. A number of N-substituted amino acids RCH(NHR')COOH give the corresponding N-alkylated products.

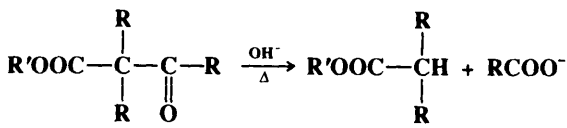
OS **IV,** 5; **V,** 27.

B. Acyl Cleavages. In these reactions (**2-43** to **2-46**) a carbonyl group is attacked by a hydroxide ion (or amide ion), giving an intermediate that undergoes cleavage to a carboxylic acid (or an amide). With respect to the leaving group, this is nucleophilic substitution at a carbonyl group and the mechanism is the tetrahedral one discussed in Chapter 10.

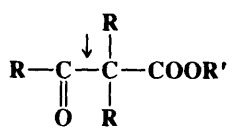


With respect to R this is of course electrophilic substitution. The mechanism is usually SE1.

2-43 Basic Cleavage of β-Keto Esters and β-Diketones
Hydro-de-acylation



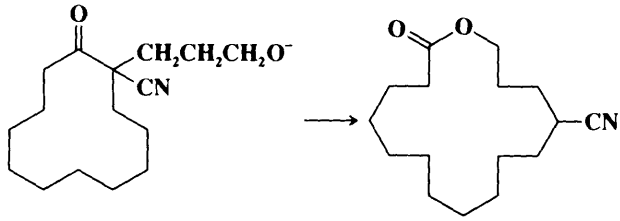
When β-keto esters are treated with concentrated base, cleavage occurs, but is on the keto side of the CR_2 group (arrow) in contrast to the acid cleavage mentioned on page 629. The



products are a carboxylic ester and the salt of an acid. However, the utility of the reaction is somewhat limited by the fact that decarboxylation is a side reaction, even under basic conditions. β-Diketones behave similarly to give a ketone and the salt of a carboxylic acid. With both β-keto esters and β-diketones, OEt^- can be used instead of OH^-, in which case the ethyl esters of the corresponding acids are obtained instead of the salts. In the case of β-keto esters, this is the reverse of Claisen condensation (**0-108**). The similar cleavage of

[499]For a review, see Buchanan *Chem. Soc. Rev.* **1988,** *17,* 91-109.
[500]Allinger; Wang; Dewhurst *J. Org. Chem.* **1974,** *39,* 1730.

cyclic α-cyano ketones, in an intramolecular fashion, has been used to effect a synthesis of macrocyclic lactones, e.g.,[501]



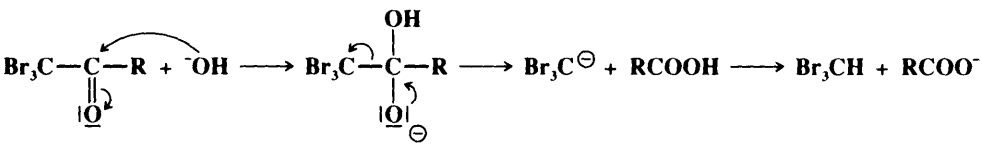
Activated F^- (from KF and a crown ether) has been used as the base to cleave an α-cyano ketone.[502]

OS **II**, 266, 531; **III**, 379; **IV**, 415, 957; **V**, 179, 187, 277, 533, 747, 767.

2-44 Haloform Reaction

$$CH_3{-}\underset{\underset{O}{\|}}{C}{-}R \xrightarrow[OH^-]{Br_2} HCBr_3 + RCOO^-$$

In the *haloform reaction*, methyl ketones (and the only methyl aldehyde, acetaldehyde) are cleaved with halogen and a base.[503] The halogen can be bromine, chlorine, or iodine. What takes place is actually a combination of two reactions. The first is an example of **2-4**, in which, under the basic conditions employed, the methyl group is trihalogenated. Then the resulting trihalo ketone is attacked by hydroxide ion:[504]



Primary or secondary methylcarbinols also give the reaction, because they are oxidized to the carbonyl compounds under the conditions employed. As with **2-4**, the rate-determining step is the preliminary enolization of the methyl ketone.[505] A side reaction is α halogenation of the nonmethyl R group. Sometimes these groups are also cleaved.[506] The reaction cannot be applied to F_2, but ketones of the form $RCOCF_3$ (R = alkyl or aryl) give fluoroform and $RCOO^-$ when treated with base.[507] Rate constants for cleavage of X_3CCOPh (X = F, Cl, Br) were found to be in the ratio $1:5.3 \times 10^{10}: 2.2 \times 10^{13}$, showing that an F_3C^- group cleaves much more slowly than the others.[508] The haloform reaction is often used as a test

[501]Milenkov; Hesse *Helv. Chim. Acta* **1987**, *70*, 308. For a similar preparation of lactams, see Wälchli; Bienz; Hesse *Helv. Chim. Acta* **1985**, *68*, 484.

[502]Beletskaya; Gulyukina; Borodkin; Solov'yanov; Reutov *Doklad. Chem.* **1984**, *276*, 202. See also Mignani; Morel; Grass *Tetrahedron Lett.* **1987**, *28*, 5505.

[503]For a review of this and related reactions, see Chakrabartty, in Trahanovsky *Oxidation in Organic Chemistry*, pt. C; Academic Press: New York, 1978, pp. 343-370.

[504]For a complete kinetic analysis of the chlorination of acetone, see Guthrie; Cossar *Can. J. Chem.* **1986**, *64*, 1250. For a discussion of the mechanism of the cleavage step, see Zucco; Lima; Rezende; Vianna; Nome *J. Org. Chem.* **1987**, *52*, 5356.

[505]Pocker *Chem. Ind. (London)* **1959**, 1383.

[506]Levine; Stephens *J. Am. Chem. Soc.* **1950**, *72*, 1642.

[507]See Hudlicky *Chemistry of Organic Fluorine Compounds*, 2nd ed.; Ellis Horwood: Chichester, 1976, pp. 276-278.

[508]Guthrie; Cossar *Can. J. Chem.* **1990**, *68*, 1640.

for methylcarbinols and methyl ketones. Iodine is most often used as the test reagent, since iodoform is an easily identifiable yellow solid. The reaction is also frequently used for synthetic purposes. Methyl ketones $RCOCH_3$ can be converted directly to methyl esters $RCOOCH_3$ by an electrochemical reaction.[509]

OS **I,** 526; **II,** 428; **III,** 302; **IV,** 345; **V,** 8. Also see OS **VI,** 618.

2-45 Cleavage of Nonenolizable Ketones
Hydro-de-acylation

$$R{-}\underset{\underset{O}{\|}}{C}{-}R' \xrightarrow[Et_2O]{t\text{-BuOK}-H_2O} RH + R'COO^-$$

Ordinary ketones are generally much more difficult to cleave than trihalo ketones or β-diketones, because the carbanion intermediates in these cases are more stable than simple carbanions. However, nonenolizable ketones can be cleaved by treatment with a 10:3 mixture of *t*-BuOK–H_2O in an aprotic solvent such as ether, dimethyl sulfoxide, 1,2-dimethoxyethane (glyme), etc.,[510] or with solid *t*-BuOK in the absence of a solvent.[511] When the reaction is applied to monosubstituted diaryl ketones, that aryl group preferentially cleaves that comes off as the more stable carbanion, except that aryl groups substituted in the ortho position are more readily cleaved than otherwise because of the steric effect (relief of stain).[512] In certain cases, cyclic ketones can be cleaved by base treatment, even if they are enolizable.[513]

OS **VI,** 625. See also OS **VII,** 297.

2-46 The Haller-Bauer Reaction
Hydro-de-acylation

$$R{-}\underset{\underset{O}{\|}}{C}{-}R' \xrightarrow{NH_2^-} RH + R'{-}\underset{\underset{O}{\|}}{C}{-}NH^-$$

Cleavage of ketones with sodium amide is called the *Haller–Bauer reaction.*[514] As with **2-45,** which is exactly analogous, the reaction is usually applied only to nonenolizable ketones, most often to ketones of the form $ArCOCR_3$, where the products R_3CCONH_2 are not easily attainable by other methods. However, many other ketones have been used, though benzophenone is virtually unaffected. It has been shown that the configuration of optically active R is retained.[515] The NH_2 loses its proton before the R is cleaved:[516]

$$R{-}\underset{\underset{\ddot{O}|}{\|}}{C}{-}R' + NH_2^- \longrightarrow R{-}\underset{\underset{|\ddot{O}|_{\ominus}}{|}}{\overset{\overset{NH_2}{|}}{C}}{-}R' \longrightarrow R{-}\underset{\underset{|\ddot{O}|_{\ominus}}{|}}{\overset{\overset{NH^{\ominus}}{|}}{C}}{-}R' \xrightarrow{HA} RH + \underset{\underset{\ddot{O}|}{\|}}{\overset{\overset{NH^{\ominus}}{|}}{C}}{-}R'$$

OS **V,** 384, 1074.

[509]Nikishin; Elinson; Makhova *Tetrahedron* **1991,** *47,* 895.
[510]Swan *J. Chem. Soc.* **1948,** 1408; Gassman; Lumb; Zalar *J. Am. Chem. Soc.* **1967,** *89,* 946.
[511]March; Plankl *J. Chem. Soc., Perkin Trans. 1* **1977,** 460.
[512]Davies; Derenberg; Hodge *J. Chem. Soc. C* **1971,** 455; Ref. 511.
[513]For example, see Swaminathan; Newman *Tetrahedron* **1958,** *2,* 88; Hoffman; Cram, Ref. 25.
[514]For a review, see Gilday; Paquette *Org. Prep. Proced. Int.* **1990,** *22,* 167-201. For an improved procedure, see Kaiser; Warner *Synthesis* **1975,** 395.
[515]Impastato; Walborsky *J. Am. Chem. Soc.* **1962,** *84,* 4838; Paquette; Gilday *J. Org. Chem.* **1988,** *53,* 4972; Paquette; Ra *J. Org. Chem.* **1988,** *53,* 4978.
[516]Bunnett; Hrutfiord *J. Org. Chem.* **1962,** *27,* 4152.

C. Other Cleavages

2-47 The Cleavage of Alkanes
Hydro-de-*t*-butylation, etc.

$$(CH_3)_4C \xrightarrow{FSO_3H\text{-}SbF_5} CH_4 + (CH_3)_3C^+$$

The C—C bonds of alkanes can be cleaved by treatment with super acids[44] (p. 249). For example, neopentane in FSO_3H–SbF_5 can cleave to give methane and the *t*-butyl cation. C—H cleavage (see **2-1**) is a competing reaction and, for example, neopentane can give H_2 and the *t*-pentyl cation (formed by rearrangement of the initially formed neopentyl cation) by this pathway. In general, the order of reactivity is tertiary C—H > C—C > secondary C—H ≫ primary C—H, though steric factors cause a shift in favor of C—C cleavage in such a hindered compound as tri-*t*-butylmethane. The mechanism is similar to that shown in **2-1** and **2-18** and involves attack by H^+ on the C—C bond to give a pentavalent cation.

Catalytic hydrogenation seldom breaks unactivated C—C bonds (i.e., R—R′ + H_2 → RH + R′H), but methyl and ethyl groups have been cleaved from substituted adamantanes by hydrogenation with a Ni–Al_2O_3 catalyst at about 250°C.[517] Certain C—C bonds have been cleaved by alkali metals.[518]

2-48 Decyanation or Hydro-de-cyanation

$$RCN \xrightarrow[\text{or}\ \text{Na-Fe(acac)}_3]{\text{Na-NH}_3} RH$$

The cyano group of alkyl nitriles can be removed[519] by treatment with metallic sodium, either in liquid ammonia,[520] or together with tris(acetylacetonato)iron(III) $Fe(acac)_3$[521] or, with lower yields, titanocene. The two procedures are complementary. Although both can be used to decyanate many kinds of nitriles, the Na–NH_3 method gives high yields with R groups such as trityl, benzyl, phenyl, and tertiary alkyl, but lower yields (~35 to 50%) when R = primary or secondary alkyl. On the other hand, primary and secondary alkyl nitriles are decyanated in high yields by the Na–$Fe(acac)_3$ procedure. Sodium in liquid ammonia is known to be a source of solvated electrons, and the reaction may proceed through the free radical R• which would then be reduced to the carbanion R^-, which by abstraction of a proton from the solvent, would give RH. The mechanism with $Fe(acac)_3$ is presumably different. Another procedure,[522] which is successful for R = primary, secondary, or tertiary, involves the use of potassium metal and the crown ether dicyclohexano-18-crown-6 in toluene.[523]

α-Amino and α-amido nitriles $RCH(CN)NR_2'$ and RCH(CN)NHCOR′ can be decyanated in high yield by treatment with $NaBH_4$.[524]

[517]Grubmüller; Schleyer; McKervey *Tetrahedron Lett.* **1979,** 181.

[518]For examples and references, see Grovenstein; Bhatti; Quest; Sengupta; VanDerveer *J. Am. Chem. Soc.* **1983,** *105*, 6290.

[519]For a list of procedures, with references, see Ref. 52, pp. 42-43.

[520]Büchner; Dufaux *Helv. Chim. Acta* **1966,** *49*, 1145; Arapakos; Scott; Huber *J. Am. Chem. Soc.* **1969,** *91*, 2059; Birch; Hutchinson *J. Chem. Soc., Perkin Trans. 1* **1972,** 1546; Yamada; Tomioka; Koga *Tetrahedron Lett.* **1976,** 61.

[521]Van Tamelen; Rudler; Bjorklund *J. Am. Chem. Soc.* **1971,** *93*, 7113.

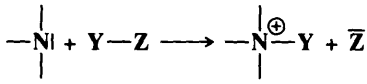
[522]For other procedures, see Cuvigny; Larcheveque; Normant *Bull. Soc. Chim. Fr.* **1973,** 1174; Berkoff; Rivard; Kirkpatrick; Ives *Synth. Commun.* **1980,** *10*, 939; Savoia; Tagliavini; Trombini; Umani-Ronchi *J. Org. Chem.* **1980,** *45*, 3227; Ozawa; Iri; Yamamoto *Chem. Lett.* **1982,** 1707.

[523]Ohsawa; Kobayashi; Mizuguchi; Saitoh; Oishi *Tetrahedron Lett.* **1985,** *26*, 6103.

[524]Yamada; Akimoto *Tetrahedron Lett.* **1969,** 3105; Fabre; Hadj Ali Salem; Welvart *Bull. Soc. Chim. Fr.* **1975,** 178. See also Ogura; Shimamura; Fujita *J. Org. Chem.* **1991,** *56*, 2920.

Electrophilic Substitution at Nitrogen

In most of the reactions in this section, an electrophile bonds with the unshared pair of a nitrogen atom. The electrophile may be a free positive ion or a positive species attached to a carrier that breaks off in the course of the attack or shortly after:

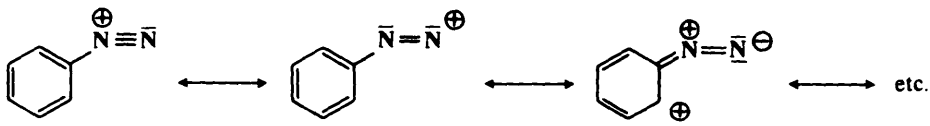


37

Further reaction of **37** depends on the nature of Y and of the other groups attached to the nitrogen.

2-49 Diazotization

When primary aromatic amines are treated with nitrous acid, diazonium salts are formed.[525] The reaction also occurs with aliphatic primary amines, but aliphatic diazonium ions are extremely unstable, even in solution (see p. 355). Aromatic diazonium ions are more stable, because of the resonance interaction between the nitrogens and the ring:



38 **39**

Incidentally, **38** contributes more to the hybrid than **39**, as shown by bond-distance measurements.[526] In benzenediazonium chloride, the C—N distance is ~1.42 Å, and the N—N distance ~1.08 Å,[527] which values fit more closely to a single and a triple bond than to two double bonds (see Table 1.5). Even aromatic diazonium salts are stable only at low temperatures, usually only below 5°C, though more stable ones, such as the diazonium salt obtained from sulfanilic acid, are stable up to 10 or 15°C. Diazonium salts are usually prepared in aqueous solution and used without isolation,[528] though it is possible to prepare solid diazonium salts if desired (see **3-24**). The stability of aryl diazonium salts can be increased by crown ether complexion.[529]

For aromatic amines, the reaction is very general. Halogen, nitro, alkyl, aldehyde, sulfonic acid, etc., groups do not interfere. Since aliphatic amines do not react with nitrous acid

[525]For reviews, see, in Patai, *The Chemistry of Diazonium and Diazo Groups*; Wiley: New York, 1978, the articles by Hegarty, pt. 2, pp. 511-591, and Schank, pt. 2, pp. 645-657; Godovikova; Rakitin; Khmel'nitskii *Russ. Chem. Rev.* **1983,** *52*, 440-445; Challis; Butler, in Patai *The Chemistry of the Amino Group*; Wiley: New York, 1968, pp. 305-320. For a review with respect to heterocyclic amines, see Butler *Chem. Rev.* **1975,** *75*, 241-257.

[526]For a review of diazonium salt structures, see Sorriso, in Patai *The Chemistry of Diazonium and Diazo Groups*, pt. 1, Ref. 525, pp. 95-105.

[527]Rømming *Acta Chem. Scand.* **1959,** *13*, 1260, **1963,** *17*, 1444; Sorriso, Ref. 526, p. 98; Cygler; Przybylska; Elofson *Can. J. Chem.* **1982,** *60*, 2852; Ball; Elofson *Can. J. Chem.* **1985,** *63*, 332.

[528]For a review of reactions of diazonium salts, see Wulfman, in Patai, Ref. 526, pt. 1, pp. 247-339.

[529]Korzeniowski; Leopold; Beadle; Ahern; Sheppard; Khanna; Gokel *J. Org. Chem.* **1981,** *46*, 2153, and references cited therein. For reviews, see Bartsch, in Patai; Rappoport *The Chemistry of Functional Groups, Supplement C*, pt.1; Wiley: New York, 1983, pp. 889-915; Bartsch *Prog. Macrocyclic Chem.* **1981,** *2*, 1-39.

below a pH of about 3, it is even possible, by working at a pH of about 1, to diazotize an aromatic amine without disturbing an aliphatic amino group in the same molecule.[530]

If an aliphatic amino group is α to a COOR, CN, CHO, COR, etc. and has an α hydrogen, treatment with nitrous acid gives not a diazonium salt, but a *diazo compound*.[531] Such diazo

$$\mathbf{EtOOC{-}CH_2{-}NH_2 + HONO \longrightarrow EtOOC{-}CH{=}\overset{\oplus}{N}{=}\overset{\ominus}{N}}$$

compounds can also be prepared, often more conveniently, by treatment of the substrate with isoamyl nitrite and a small amount of acid.[532] Certain heterocyclic amines also give diazo compounds rather than diazonium salts.[533]

Despite the fact that diazotization takes place in acid solution, the actual species attacked is not the salt of the amine, but the small amount of free amine present.[534] It is because aliphatic amines are stronger bases than aromatic ones that at pH values below 3 there is not enough free amine present for the former to be diazotized, while the latter still undergo the reaction. In dilute acid the actual attacking species is N_2O_3, which acts as a carrier of NO^+. Evidence is that the reaction is second order in nitrous acid and, at sufficiently low acidities, the amine does not appear in the rate expression.[535] Under these conditions the mechanism is

Step 1 $\quad 2HONO \xrightarrow{\text{slow}} N_2O_3 + H_2O$

Step 2 $\quad ArNH_2 + N_2O_3 \longrightarrow Ar{-}\overset{H}{\underset{H}{\overset{|}{\underset{|}{N}}}}{-}\overset{\oplus}{N}{=}O + NO_2^-$

Step 3 $\quad Ar{-}\overset{H}{\underset{H}{\overset{|}{\underset{|}{N}}}}{-}\overset{\oplus}{N}{=}O \xrightarrow{-H^+} Ar{-}\underset{H}{\overset{|}{N}}{-}N{=}O$

40

Step 4 $\quad Ar{-}\underset{H}{\overset{|}{N}}{-}N{=}O \overset{\text{tautom.}}{\rightleftharpoons} Ar{-}N{=}N{-}O{-}H$

Step 5 $\quad Ar{-}N{=}N{-}O{-}H \xrightarrow{H^+} Ar{-}\overset{\oplus}{N}{\equiv}N + H_2O$

There exists other evidence for this mechanism.[536] Other attacking species can be NOCl, $H_2NO_2^+$, and at high acidities even NO^+. Nucleophiles (e.g., Cl^-, SCN^-, thiourea) catalyze the reaction by converting the HONO to a better electrophile, e.g., $HNO_2 + Cl^- + H^+ \rightarrow NOCl + H_2O$.[537]

[530]Kornblum; Iffland *J. Am. Chem. Soc.* **1949,** *71*, 2137.

[531]For a monograph on diazo compounds, see Regitz; Maas, Ref. 164. For reviews, see, in Patai, Ref. 526, the articles by Regitz, pt. 2, pp. 659-708, 751-820, and Wulfman; Linstrumelle; Cooper, pt. 2, pp. 821-976.

[532]Takamura; Mizoguchi; Koga; Yamada *Tetrahedron* **1975,** *31*, 227.

[533]Butler, Ref. 525.

[534]Challis; Ridd *J. Chem. Soc.* **1962,** 5197, 5208; Challis; Larkworthy; Ridd *J. Chem. Soc.* **1962,** 5203.

[535]Hughes; Ingold; Ridd *J. Chem. Soc.* **1958,** 58, 65, 77, 88; Hughes; Ridd *J. Chem. Soc.* **1958,** 70, 82.

[536]For discussions, see Ref. 157, pp. 95-109; Ridd, Ref. 540, pp. 422-424.

[537]Ref. 157, pp. 84-93.

There are many preparations of diazonium salts listed in *Organic Syntheses*, but they are always prepared for use in other reactions. We do not list them here, but under reactions in which they are used. The preparation of aliphatic diazo compounds can be found in OS **III,** 392; **IV,** 424. See also OS **VI,** 840.

2-50 The Conversion of Hydrazines to Azides
Hydrazine-azide transformation

$$RNHNH_2 + HONO \longrightarrow R{-}\bar{N}{=}\overset{\oplus}{N}{=}\bar{N}^{\ominus}$$

Monosubstituted hydrazines treated with nitrous acid give azides in a reaction exactly analogous to the formation of aliphatic diazo compounds mentioned in **2-49.** Among other reagents used for this conversion have been N_2O_4[538] and nitrosyl tetrafluoroborate $NOBF_4$.[539]

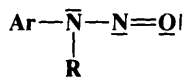
OS **III,** 710; **IV,** 819; **V,** 157.

2-51 *N*-Nitrosation or *N*-Nitroso-de-hydrogenation

$$R_2NH + HONO \longrightarrow R_2N{-}NO$$

When secondary amines are treated with nitrous acid, N-nitroso compounds (also called nitrosamines) are formed.[540] The reaction can be accomplished with dialkyl-, diaryl-, or alkylarylamines, and even with mono-N-substituted amides: RCONHR′ + HONO → RCON(NO)R′.[541] Tertiary amines have also been N-nitrosated, but in these cases one group cleaves, so that the product is the nitroso derivative of a secondary amine.[542] The group that cleaves appears as an aldehyde or ketone. Other reagents have also been used, for example NOCl, which is useful for amines or amides that are not soluble in an acidic aqueous solution or where the N-nitroso compounds are highly reactive. N-Nitroso compounds can be prepared in basic solution by treatment of secondary amines with gaseous N_2O_3, N_2O_4,[543] or alkyl nitrites,[544] and, in aqueous or organic solvents, by treatment with $BrCH_2NO_2$.[545]

The mechanism of nitrosation is essentially the same as in **2-49** up to the point where **41** (analogous to **40**) is formed. Since this species cannot lose a proton, it is stable and the



41

[538]Kim; Kim; Shim *Tetrahedron Lett.* **1986,** *27,* 4749.

[539]Pozsgay; Jennings *Tetrahedron Lett.* **1987,** *28,* 5091.

[540]For reviews, see Williams, Ref. 157, pp. 95-109; Kostyukovskii; Melamed *Russ. Chem. Rev.* **1988,** *57,* 350-366; Saavedra *Org. Prep. Proced. Int.* **1987,** *19,* 83-159; Ref. 158; Challis; Challis, in Patai; Rappoport, Ref. 172, pt. 2, pp. 1151-1223; Ridd, *Q. Rev., Chem. Soc.* **1961,** *15,* 418-441. For a review of the chemistry of aliphatic N-nitroso compounds, including methods of synthesis, see Fridman; Mukhametshin; Novikov *Russ. Chem. Rev.* **1971,** *40,* 34-50.

[541]For a discussion of the mechanism with amides, see Castro; Iglesias; Leis; Peña; Tato *J. Chem. Soc., Perkin Trans. 2* **1986,** 1725.

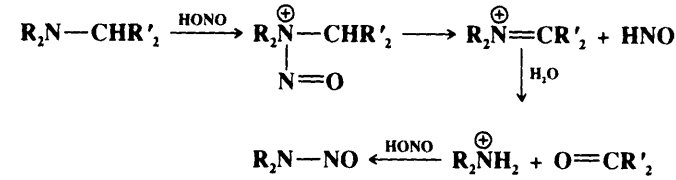
[542]Hein *J. Chem. Educ.* **1963,** *40,* 181. See also Verardo; Giumanini; Strazzolini *Tetrahedron* **1990,** *46,* 4303.

[543]Challis; Kyrtopoulos *J. Chem. Soc., Perkin Trans. 1* **1979,** 299.

[544]Casado; Castro; Lorenzo; Meijide *Monatsh. Chem.* **1986,** *117,* 335.

[545]Challis; Yousaf *J. Chem. Soc., Chem. Commun.* **1990,** 1598.

reaction ends there. The attacking entity can be any of those mentioned in **2-49.** The following has been suggested as the mechanism for the reaction with tertiary amines:[546]



The evidence for this mechanism includes the facts that nitrous oxide is a product (formed by $2HNO \rightarrow H_2O + N_2O$) and that quinuclidine, where the nitrogen is at a bridgehead and therefore cannot give elimination, does not react. Tertiary amines have also been converted to nitrosamines with nitric acid in Ac_2O[547] and with N_2O_4.[548]

Amines and amides can be N-*nitrated*[549] with nitric acid,[550] N_2O_5,[551] or NO_2^+,[552] and aromatic amines can be converted to triazenes with diazonium salts. Aliphatic primary amines can also be converted to triazenes if the diazonium salts contain electron-withdrawing groups.[553] C-Nitrosation is discussed at **1-3** and **2-8.**

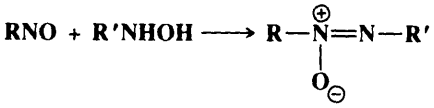
OS **I,** 177, 399, 417; **II,** 163, 211, 290, 460, 461, 462, 464 (also see **V,** 842); **III,** 106, 244; **IV,** 718, 780, 943; **V,** 336, 650, 797, 839, 962; **VI,** 542, 981. Also see OS **III,** 711.

2-52 Conversion of Amines to Azo Compounds
N-Arylimino-de-dihydro-bisubstitution

$$ArNH_2 + Ar'NO \xrightarrow{HOAc} Ar{-}N{=}N{-}Ar'$$

Aromatic nitroso compounds combine with primary arylamines in glacial acetic acid to give symmetrical or unsymmetrical azo compounds (the *Mills reaction*).[554] A wide variety of substituents may be present in both aryl groups. Unsymmetrical azo compounds have also been prepared by the reaction between aromatic nitro compounds $ArNO_2$ and N-acyl aromatic amines Ar'NHAc.[555] The use of phase transfer catalysis increased the yields.

2-53 Conversion of Nitroso Compounds to Azoxy Compounds



[546]Smith; Loeppky *J. Am. Chem. Soc.* **1967,** *89,* 1147; Smith; Pars *J. Org. Chem.* **1959,** *24,* 1324; Gowenlock; Hutchison; Little; Pfab *J. Chem. Soc., Perkin Trans. 2* **1979,** 1110. See also Loeppky; Outram; Tomasik; Faulconer *Tetrahedron Lett.* **1983,** *24,* 4271.

[547]Boyer; Pillai; Ramakrishnan *Synthesis* **1985,** 677.

[548]Boyer; Kumar; Pillai *J. Chem. Soc., Perkin Trans. 1* **1986,** 1751.

[549]For other reagents, see Mayants; Pyreseva; Gordeichuk *J. Org. Chem. USSR* **1986,** *22,* 1900; Bottaro; Schmitt; Bedford *J. Org. Chem.* **1987,** *52,* 2292; Suri; Chapman *Synthesis* **1988,** 743; Carvalho; Iley; Norberto; Rosa *J. Chem. Res. (S)* **1989,** 260.

[550]Cherednichenko; Dmitrieva; Kuznetsov; Gidaspov *J. Org. Chem. USSR* **1976,** *12,* 2101, 2105.

[551]Emmons; Pagano; Stevens *J. Org. Chem.* **1958,** *23,* 311; Runge; Treibs *J. Prakt. Chem.* **1962,** [4] *15,* 223; Halevi; Ron; Speiser *J. Chem. Soc.* **1965,** 2560.

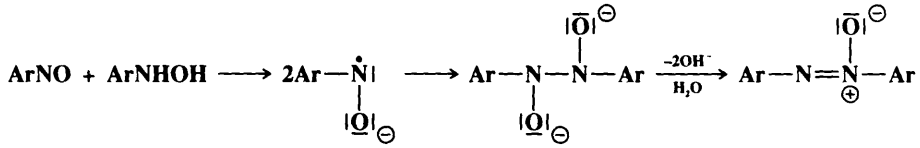
[552]Ilyushin; Golod; Gidaspov *J. Org. Chem. USSR* **1977,** *13,* 8; Andreev; Lededev; Tselinskii *J. Org. Chem. USSR* **1980,** *16,* 1166, 1170, 1175, 1179.

[553]For a reveiw of alkyl traizenes, see Vaughan; Stevens *Chem. Soc. Rev.* **1978,** 7, 377-397.

[554]For a review, see Boyer, in Feuer *The Chemistry of the Nitro and Nitroso Groups,* pt. 1; Wiley: New York, 1969, pp. 278-283.

[555]Ayyangar; Naik; Srinivasan *Tetrahedron Lett.* **1989,** *30,* 7253.

In a reaction similar to **2-52,** azoxy compounds can be prepared by the condensation of a nitroso compound with a hydroxylamine.[556] The position of the oxygen in the final product is determined by the nature of the R groups, not by which R groups came from which starting compound. Both R and R′ can be alkyl or aryl, but when two different aryl groups are involved, mixtures of azoxy compounds (ArNONAr, ArNONAr′, and Ar′NONAr′) are obtained[557] and the unsymmetrical product (ArNONAr′) is likely to be formed in the smallest amount. This behavior is probably caused by an equilibration between the starting compounds prior to the actual reaction (ArNO + Ar′NHOH → Ar′NO + ArNHOH).[558] The mechanism[559] has been investigated in the presence of base. Under these conditions both reactants are converted to radical anions, which couple:



These radical anions have been detected by esr.[560] This mechanism is consistent with the following result: when nitrosobenzene and phenylhydroxylamine are coupled, ^{18}O and ^{15}N labeling show that the two nitrogens and the two oxygens become equivalent.[561] Unsymmetrical azoxy compounds can be prepared[562] by combination of a nitroso compound with an N,N-dibromoamine. Symmetrical and unsymmetrical azo and azoxy compounds are produced when aromatic nitro compounds react with aryliminodimagnesium reagents $ArN(MgBr)_2$.[563]

2-54 *N*-Halogenation or *N*-Halo-de-hydrogenation

$$\mathbf{RNH_2 + NaOCl \longrightarrow RNHCl}$$

Treatment with sodium hypochlorite or hypobromite converts primary amines into N-halo- or N,N-dihaloamines. Secondary amines can be converted to N-halo secondary amines. Similar reactions can be carried out on unsubstituted and N-substituted amides and on sulfonamides. With unsubstituted amides the N-halogen product is seldom isolated but usually rearranges (see **8-14**); however, N-halo-N-alkyl amides and N-halo imides are quite stable. The important reagent N-bromosuccinimide is made in this manner. N-Halogenation has also been accomplished with other reagents, e.g., *t*-BuOCl,[564] sodium bromite $NaBrO_2$,[565] benzyltrimethylammonium tribromide $PhCH_2NMe_3^+ Br_3^-$,[566] and N-chlorosuccinimide.[567] The mechanisms of these reactions[568] involve attack by a positive halogen and are probably

[556]Boyer, Ref. 554.
[557]See, for example, Ogata; Tsuchida; Takagi *J. Am. Chem. Soc.* **1957,** *79,* 3397.
[558]Knight; Saville *J. Chem. Soc., Perkin Trans. 2* **1973,** 1550.
[559]For discussions of the mechanism in the absence of base, see Darchen; Moinet *Bull. Soc. Chim. Fr.* **1976,** 812; Becker; Sternson *J. Org. Chem.* **1980,** *45,* 1708. See also Pizzolatti; Yunes *J. Chem. Soc., Perkin Trans. 1* **1990,** 759.
[560]Russell; Geels; Smentowski; Chang; Reynolds; Kaupp *J. Am. Chem. Soc.* **1967,** *89,* 3821.
[561]Shemyakin; Maimind; Vaichunaite *Izv. Akad. Nauk SSSR, Ser. Khim.* **1957,** 1260; Oae; Fukumoto; Yamagami *Bull. Chem. Soc. Jpn.* **1963,** *36,* 728.
[562]Zawalski; Kovacic *J. Org. Chem.* **1979,** *44,* 2130. For another method, see Moriarty; Hopkins; Prakash; Vaid; Vaid *Synth. Commun.* **1990,** *20,* 2353.
[563]Okubo; Matsuo; Yamauchi *Bull. Chem. Soc. Jpn.* **1989,** *62,* 915, and other papers in this series.
[564]Altenkirk; Isrealstam *J. Org. Chem.* **1962,** *27,* 4532.
[565]Kajigaeshi; Nakagawa; Fujisaki *Chem. Lett.* **1984,** 2045.
[566]Kajigaeshi; Murakawa; Asano; Fujisaki; Kakinami *J. Chem. Soc., Perkin Trans. 1* **1989,** 1702.
[567]See Deno; Fishbein; Wyckoff *J. Am. Chem. Soc.* **1971,** *93,* 2065; Guillemin; Denis *Synthesis* **1985,** 1131.
[568]For a study of the mechanism, see Matte; Solastiouk; Merlin; Deglise *Can. J. Chem.* **1989,** *67,* 786.

similar to those of **2-49** and **2-51.**[569] N-Fluorination can be accomplished by direct treatment of amines[570] or amides[571] with F_2. Fluorination of N-alkyl-N-fluoro amides results in cleavage to N,N-difluoroamines.[572]

$$\mathbf{RNFCOR' \xrightarrow{F_2} RNF_2}$$

OS **III,** 159; **IV,** 104, 157; **V,** 208, 663, 909; **VI,** 968; **VII,** 223; **65,** 159; **67,** 222.

2-55 The Reaction of Amines with Carbon Monoxide *N*-Formylation or *N*-Formyl-de-hydrogenation, etc.

$$\mathbf{RNH_2 + CO \xrightarrow{catalyst} RNH{-}\overset{\overset{O}{\|}}{C}{-}H \text{ or } RNH{-}\overset{\overset{O}{\|}}{C}{-}NHR \text{ or } RNCO}$$

Three types of product can be obtained from the reaction of amines with carbon monoxide, depending on the catalyst. (1) Both primary and secondary amines react with CO in the presence of various catalysts [e.g., $Cu(CN)_2$, Me_3N–H_2Se, rhodium or ruthenium complexes] to give N-substituted and N,N-disubstituted formamides, respectively.[573] (2) Symmetrically substituted ureas can be prepared by treatment of a primary amine (or ammonia) with CO in the presence of selenium[574] or sulfur.[575] R can be alkyl or aryl. The same thing can be done with secondary amines, by using $Pd(OAc)_2$–I_2–K_2CO_3.[576] (3) When $PdCl_2$ is the catalyst, primary amines yield isocyanates.[577] Isocyanates can also be obtained by treatment of CO with azides: $RN_3 + CO \rightarrow RNCO$,[578] or with an aromatic nitroso or nitro compound and a rhodium complex catalyst.[579] A fourth type of product, a carbamate RNHCOOR', can be obtained from primary or secondary amines, if these are treated with CO, O_2, and an alcohol R'OH in the presence of a catalyst.[580] Carbamates can also be obtained from nitroso compounds, by treatment with CO, R'OH, $Pd(OAc)_2$, and $Cu(OAc)_2$,[581] and from nitro compounds.[582] When allylic amines $R_2C{=}CHCHRNR'_2$ are treated with CO and a palladium–phosphine catalyst, the CO inserts to produce the β,γ-unsaturated amides $R_2C{=}CHRCHRCONR'_2$ in good yields.[583] See also **6-19.**

[569]For studies of reactivitiy in this reaction, see Thomm; Wayman *Can. J. Chem.* **1969,** *47*, 3289; Higuchi; Hussain; Pitman *J. Chem. Soc. B* **1969,** 626.

[570]Sharts *J. Org. Chem.* **1968,** *33*, 1008.

[571]Grakauskas; Baum *J. Org. Chem.* **1969,** *34*, 2840, **1970,** *35*, 1545.

[572]Ref. 571. See also Wiesboeck; Ruff *Tetrahedron* **1970,** *26*, 837; Barton; Hesse; Klose; Pechet *J. Chem. Soc., Chem. Commun.* **1975,** 97.

[573]See Tsuji; Iwamoto *Chem. Commun.* **1966,** 380; Durand; Lassau *Tetrahedron Lett.* **1969,** 2329; Saegusa; Kobayashi; Hirota; Ito *Bull. Chem. Soc. Jpn.* **1969,** *42*, 2610; Nefedov; Sergeeva; Éidus *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1973,** *22*, 784; Kondo; Sonoda; Sakurai *J. Chem. Soc., Chem. Commun.* **1973,** 853; Yoshida; Asano; Inoue *Chem. Lett.* **1984,** 1073; Bitsi; Jenner *J. Organomet. Chem.* **1987,** *330*, 429.

[574]Sonoda; Yasuhara; Kondo; Ikeda; Tsutsumi *J. Am. Chem. Soc.* **1971,** *93*, 6344.

[575]Franz; Applegath; Morriss; Baiocchi; Bolze *J. Org. Chem.* **1961,** *26*, 3309.

[576]Pri-Bar; Alper *Can. J. Chem.* **1990,** *68*, 1544.

[577]Stern; Spector *J. Org. Chem.* **1966,** *31*, 596.

[578]Bennett; Hardy *J. Am. Chem. Soc.* **1968,** *90*, 3295.

[579]Unverferth; Rüger; Schwetlick *J. Prakt. Chem.* **1977,** *319*, 841; Unverferth; Tietz; Schwetlick *J. Prakt. Chem.* **1985,** *327*, 932. See also Braunstein; Bender; Kervennal *Organometallics* **1982,** *1*, 1236; Kunin; Noirot; Gladfelter *J. Am. Chem. Soc.* **1989,** *111*, 2739.

[580]Fukuoka; Chono; Kohno *J. Org. Chem.* **1984,** *49*, 1458, *J. Chem. Soc., Chem. Commun.* **1984,** 399. See also Alper; Vasapollo; Hartstock; Mlekuz; Smith; Morris *Organometallics* **1987,** *6*, 2391.

[581]Alper; Vasapollo *Tetrahedron Lett.* **1987,** *28*, 6411.

[582]Cenini; Crotti; Pizzotti; Porta *J. Org. Chem.* **1988,** *53*, 1243.

[583]Murahashi; Imada; Nishimura *J. Chem. Soc., Chem. Commun.* **1988,** 1578.