

in HF-BF_3 ³⁶⁶ or H_2O_2 catalyzed by AlCl_3 ³⁶⁷ or liquid HF, in some cases under CO_2 pressure.³⁶⁸ With the last procedure even benzene could be converted to phenol in 37% yield (though 37% hydroquinone and 16% catechol were also obtained). Aromatic amines, N-acyl amines, and phenols were hydroxylated with H_2O_2 in $\text{SbF}_5\text{-HF}$.³⁶⁹ Pyridine and quinoline were converted to their 2-acetoxy derivatives in high yields with acetyl hypofluorite AcOF at -75°C .³⁷⁰

Another hydroxylation reaction is the *Elbs reaction*.³⁷¹ In this method phenols can be oxidized to *p*-diphenols with $\text{K}_2\text{S}_2\text{O}_8$ in alkaline solution.³⁷² Primary, secondary, or tertiary aromatic amines give predominant or exclusive ortho substitution unless both ortho positions are blocked, in which case para substitution is found. The reaction with amines is called the *Boyland-Sims oxidation*. Yields are low with either phenols or amines, generally under 50%. The mechanisms are not clear,³⁷³ but for the Boyland-Sims oxidation there is evidence that the $\text{S}_2\text{O}_8^{2-}$ ion attacks at the ipso position, and then a migration follows.³⁷⁴

G. Metal Electrophiles Reactions in which a metal replaces the hydrogen of an aromatic ring are considered along with their aliphatic counterparts in Chapter 12 (2-21 and 2-22).

Hydrogen as the Leaving Group in Rearrangement Reactions

In these reactions a group is detached from a *side chain* and then attacks the ring, but in other aspects they resemble the reactions already treated in this chapter.³⁷⁵ Since a group moves from one position to another in a molecule, these are rearrangements. In all these reactions the question arises as to whether the group that cleaves from a given molecule attacks the same molecule or another one, i.e., is the reaction intramolecular or intermolecular? For intermolecular reactions the mechanism is the same as ordinary aromatic substitution, but for intramolecular cases the migrating group could never be completely free, or else it would be able to attack another molecule. Since the migrating species in intramolecular rearrangements is thus likely to remain near the atom from which it cleaved, it has been suggested that intramolecular reactions are more likely to lead to ortho products than are the intermolecular type. This characteristic has been used, among others, to help decide whether a given rearrangement is inter- or intramolecular, though there is evidence that at least in some cases, an intermolecular mechanism can still result in a high degree of ortho migration.³⁷⁶

³⁶⁶Olah; Fung; Keumi *J. Org. Chem.* **1981**, *46*, 4305. See also Gesson; Jacquesy; Joannetaud *Nouv. J. Chem.* **1982**, *6*, 477.

³⁶⁷Kurz; Johnson *J. Org. Chem.* **1971**, *36*, 3184.

³⁶⁸Vesely; Schmerling *J. Org. Chem.* **1970**, *35*, 4028. For other hydroxylations, see Chambers; Goggin; Musgrave *J. Chem. Soc.* **1959**, 1804; Hamilton; Friedman *J. Am. Chem. Soc.* **1963**, *85*, 1008; Kovacic; Kurz *J. Am. Chem. Soc.* **1965**, *87*, 4811; *J. Org. Chem.* **1966**, *31*, 2011, 2549; Walling; Camaioni *J. Am. Chem. Soc.* **1975**, *97*, 1603; So; Miller *Synthesis* **1976**, 468; Ogata; Sawaki; Tomizawa; Ohno *Tetrahedron* **1981**, *37*, 1485; Galliani; Rindone *Tetrahedron* **1981**, *37*, 2313.

³⁶⁹Jacquesy; Joannetaud; Morellet; Vidal *Tetrahedron Lett.* **1984**, *25*, 1479; Berrier; Carreyre; Jacquesy; Joannetaud *New J. Chem.* **1990**, *14*, 283, and references cited in these papers.

³⁷⁰Rozen; Hebel; Zamir *J. Am. Chem. Soc.* **1987**, *109*, 3789.

³⁷¹For a review of the Elbs and Boyland-Sims reactions, see Behrman *Org. React.* **1988**, *35*, 421-511.

³⁷²For a method for the ortho hydroxylation of phenols, see Capdevielle; Maumy *Tetrahedron Lett.* **1982**, *23*, 1573, 1577.

³⁷³Behrman *J. Am. Chem. Soc.* **1967**, *89*, 2424; Ogata; Akada *Tetrahedron* **1970**, *26*, 5945; Walling; Camaioni; Kim *J. Am. Chem. Soc.* **1978**, *100*, 4814.

³⁷⁴Srinivasan; Perumal; Arumugam *J. Chem. Soc., Perkin Trans. 2* **1985**, 1855.

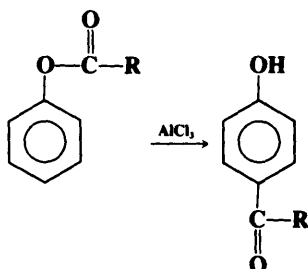
³⁷⁵For a monograph, see Shine *Aromatic Rearrangements*; Elsevier: New York, 1967. For reviews, see Williams; Buncl *Isot. Org. Chem.* **1980**, *5*, 147-230; Williams, in Bamford; Tipper, Ref. 1, pp. 433-486.

³⁷⁶See Dawson; Hart; Littler *J. Chem. Soc., Perkin Trans. 2* **1985**, 1601.

The Claisen (8-35) and benzidine (8-38) rearrangements, which superficially resemble those in this section, have different mechanisms and are treated in Chapter 18.

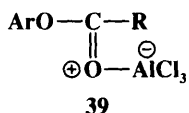
A. Groups Cleaving From Oxygen

1-30 The Fries Rearrangement 1/*C*-Hydro,5/*O*-acyl-interchange³⁷⁷



Phenolic esters can be rearranged by heating with Friedel–Crafts catalysts in a synthetically useful reaction known as the *Fries rearrangement*.³⁷⁸ Both *o*- and *p*-acylphenols can be produced, and it is often possible to select conditions so that either one predominates. the ortho/para ratio is dependent on the temperature, solvent, and amount of catalyst used. Though exceptions are known, low temperatures generally favor the para product and high temperatures the ortho product. R may be aliphatic or aromatic. Any meta-directing substituent on the ring interferes with the reactions, as might be expected for a Friedel–Crafts process. In the case of aryl benzoates treated with $\text{F}_3\text{CSO}_2\text{OH}$, the Fries rearrangement was shown to be reversible and an equilibrium was established.³⁷⁹

The exact mechanism has still not been completely worked out. Opinions have been expressed that it is completely intermolecular,³⁸⁰ completely intramolecular,³⁸¹ and partially inter- and intramolecular.³⁸² One way to decide between inter- and intramolecular processes is to run the reaction of the phenolic ester in the presence of another aromatic compound, say, toluene. If some of the toluene is acylated, the reaction must be, at least in part, intermolecular. If the toluene is not acylated, the presumption is that the reaction is intramolecular, though this is not certain, for it may be that the toluene is not attacked because it is less active than the other. A number of such experiments (called *crossover experiments*) have been carried out; sometimes crossover products have been found and sometimes not. As in 1-14, an initial complex (39) is formed between the substrate and the catalyst, so that a catalyst/substrate molar ratio of at least 1:1 is required.



³⁷⁷This is the name for the para migration. For the ortho migration, the name is 1/*C*-hydro,3/*O*-acyl-interchange.

³⁷⁸For reviews, see Shine, Ref. 375, pp. 72-82, 365-368; Gerecs, in Olah, Ref. 261, vol. 3, 1964, pp. 499-533. For a list of references, see Larock, Ref. 171, pp. 642.

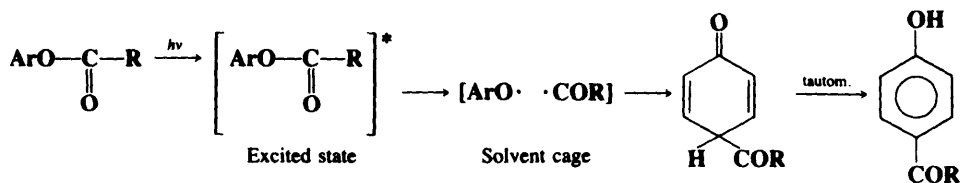
³⁷⁹Effenberger; Gutmann *Chem. Ber.* **1982**, 115, 1089.

³⁸⁰Krausz; Martin *Bull. Soc. Chim. Fr.* **1965**, 2192; Martin *Bull. Soc. Chim. Fr.* **1974**, 983, **1979**, 11-373; Martin; Gavard; Delfly; Demerseman; Tromelin *Bull. Soc. Chim. Fr.* **1986**, 659.

³⁸¹Ogata; Tabuchi *Tetrahedron* **1964**, 20, 1661.

³⁸²Munavilli *Chem. Ind. (London)* **1972**, 293; Warshawsky; Kalir; Patchornik *J. Am. Chem. Soc.* **1978**, 100, 4544; Ref. 376.

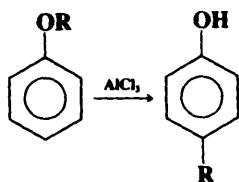
The Fries rearrangement can also be carried out with uv light, in the absence of a catalyst.³⁸³ This reaction, called the *photo-Fries rearrangement*,³⁸⁴ is predominantly an intramolecular free-radical process. Both ortho and para migration are observed.³⁸⁵ Unlike the Lewis-acid-catalyzed Fries rearrangement, the photo-Fries reaction can be accomplished, though often in low yields, when meta-directing groups are on the ring. The available evidence strongly suggests the following mechanism³⁸⁶ for the photo-Fries rearrangement³⁸⁷ (illustrated for para attack):



The phenol ArOH is always a side product, resulting from some ArO• that leaks from the solvent cage and abstracts a hydrogen atom from a neighboring molecule. When the reaction was performed on phenyl acetate in the gas phase, where there are no solvent molecules to form a cage (but in the presence of isobutane as a source of abstractable hydrogens), phenol was the chief product and virtually no *o*- or *p*-hydroxyacetophenone was found.³⁸⁸ Other evidence³⁸⁹ for the mechanism is that CIDNP has been observed during the course of the reaction³⁹⁰ and that the ArO• radical has been detected by flash photolysis³⁹¹ and by nanosecond time-resolved Raman spectroscopy.³⁹²

OS II, 543; III, 280, 282.

1-31 Rearrangement of Phenolic Ethers 1/*C*-Hydro,5/*O*-alkyl-interchange



This reaction bears the same relationship to **1-30** that **1-12** bears to **1-14**.³⁹³ However, yields are generally low and this reaction is much less useful synthetically. Isomerization of the R

³⁸³Kobsa *J. Org. Chem.* **1962**, 27, 2293; Anderson; Reese *J. Chem. Soc.* **1963**, 1781; Finnegan; Matice *Tetrahedron* **1965**, 21, 1015.

³⁸⁴For reviews, see Belluš *Adv. Photochem.* **1971**, 8, 109-159; Belluš; Hrdlovič *Chem. Rev.* **1967**, 67, 599-609; Stenberg *Org. Photochem.* **1967**, 1, 127-153.

³⁸⁵The migration can be made almost entirely ortho by cyclodextrin encapsulation (see p. 91); Syamala; Rao; Ramamurthy *Tetrahedron* **1988**, 44, 7234. See also Veglia; Sanchez; de Rossi *J. Org. Chem.* **1990**, 55, 4083.

³⁸⁶Proposed by Kobsa, Ref. 383.

³⁸⁷It has been suggested that a second mechanism, involving a four-center transition state, is also possible; Belluš; Schaffner; Hoigné *Helv. Chim. Acta* **1968**, 51, 1980; Sander; Hedaya; Trecker *J. Am. Chem. Soc.* **1968**, 90, 7249; Belluš Ref. 384.

³⁸⁸Meyer; Hammond *J. Am. Chem. Soc.* **1970**, 92, 2187, **1972**, 94, 2219.

³⁸⁹For evidence from isotope effect studies, see Shinc; Subotkowski *J. Org. Chem.* **1987**, 52, 3815.

³⁹⁰Adam; Arce de Sanabia; Fischer *J. Org. Chem.* **1973**, 38, 2571; Adam *J. Chem. Soc., Chem. Commun.* **1974**, 289.

³⁹¹Kalmus; Hercules *J. Am. Chem. Soc.* **1974**, 96, 449.

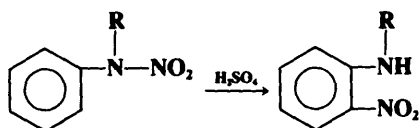
³⁹²Beck; Brus *J. Am. Chem. Soc.* **1982**, 104, 1805.

³⁹³For reviews, see Dalrymple; Kruger; White, in Patai *The Chemistry of the Ether Linkage*, Ref. 34, pp. 628-635; Shinc, Ref. 375, pp. 82-89, 368-370.

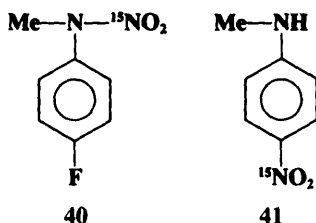
group is usually found when that is possible. Evidence has been found for both inter- and intramolecular processes.³⁹⁴ The fact that dialkylphenols can often be isolated shows that at least some intermolecular processes occur. Evidence for intramolecular reaction is that conversion of optically active *p*-tolyl *sec*-butyl ether to 2-*sec*-butyl-4-methylphenol proceeded with some retention of configuration.³⁹⁵ The mechanism is probably similar to that of **1-14**.

B. Groups Cleaving from Nitrogen³⁹⁶ It has been shown that PhNH_2^+ rearranges to *o*- and *p*-deuterioaniline.³⁹⁷ The migration of OH, formally similar to reactions **1-32** to **1-36**, is a nucleophilic substitution and is treated in Chapter 13 (**3-27**).

1-32 Migration of the Nitro Group 1/C-Hydro,3/N-nitro-interchange



N-Nitro aromatic amines rearrange on treatment with acids to *o*- and *p*-nitroamines with the ortho compounds predominating.³⁹⁸ Aside from this indication of an intramolecular process, there is also the fact that virtually no meta isomer is produced in this reaction,³⁹⁹ though direct nitration of an aromatic amine generally gives a fair amount of meta product. Thus a mechanism in which NO_2^+ is dissociated from the ring and then attacks another molecule must be ruled out. Further results indicating an intramolecular process are that rearrangement of several substrates in the presence of K^{15}NO_3 gave products containing no ^{15}N ⁴⁰⁰ and that rearrangement of a mixture of $\text{PhNH}^{15}\text{NO}_2$ and unlabeled *p*- $\text{MeC}_6\text{H}_4\text{NHNO}_2$ gave 2-nitro-4-methylaniline containing no ^{15}N .⁴⁰¹ On the other hand, rearrangement of **40**



in the presence of unlabeled PhNMeNO_2 gave labeled **41**, which did not arise by displacement of F.⁴⁰² R may be hydrogen or alkyl. Two principal mechanisms have been suggested, one

³⁹⁴For mechanistic discussions, see Tarbell; Petropoulos *J. Am. Chem. Soc.* **1952**, 74, 244; Hart; Waddington *J. Chem. Soc., Perkin Trans. 2* **1985**, 1607.

³⁹⁵Sprung; Wallis *J. Am. Chem. Soc.* **1934**, 56, 1715. See also Hart; Elia *J. Am. Chem. Soc.* **1954**, 76, 3031.

³⁹⁶For a review, see Stevens; Watts *Selected Molecular Rearrangements*; Van Nostrand-Reinhold: Princeton, 1973, pp. 192-199.

³⁹⁷Okazaki; Okumura *Bull. Chem. Soc. Jpn.* **1961**, 34, 989.

³⁹⁸For reviews, see Williams, in Patai *The Chemistry of Functional Groups, Supplement F*, pt. 1; Wiley: New York, 1982, pp. 127-153; White, *Mech. Mol. Migr.* **1971**, 3, 109-143; Shine, *Ref. 375*, pp. 235-249.

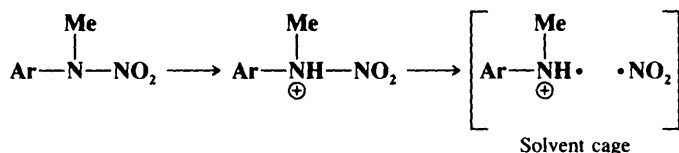
³⁹⁹Hughes; Jones *J. Chem. Soc.* **1950**, 2678.

⁴⁰⁰Brownstein; Bunton; Hughes *J. Chem. Soc.* **1958**, 4354; Banthorpe; Thomas; Williams *J. Chem. Soc.* **1965**, 6135.

⁴⁰¹Geller; Dubrova *J. Gen. Chem. USSR* **1960**, 30, 2627.

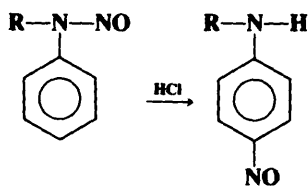
⁴⁰²White; Golden *J. Org. Chem.* **1970**, 35, 2759.

involving cyclic attack by the oxygen of the nitro group at the ortho position before the group cleaves,⁴⁰³ and the other involving a cleavage into a radical and a radical ion held together in a solvent cage.⁴⁰⁴ Among the evidence for the latter view⁴⁰⁵ are the effects of



substituents on the rate of the reaction,⁴⁰⁶ ¹⁵N and ¹⁴C kinetic isotope effects that show nonconcertedness,⁴⁰⁷ and the fact that both N-methylaniline and nitrous acid are produced in sizable and comparable amounts in addition to the normal products *o*- and *p*-nitro-N-methylaniline.⁴⁰⁸ These side products are formed when the radicals escape from the solvent cage.

1-33 Migration of the Nitroso Group. The Fischer–Hepp Rearrangement 1/*C*-Hydro-5/*N*-nitroso-interchange



The migration of a nitroso group, formally similar to **1-32**, is important because *p*-nitroso secondary aromatic amines cannot generally be prepared by direct C-nitrosation of secondary aromatic amines (see **2-51**). The reaction, known as the *Fischer–Hepp rearrangement*,⁴⁰⁹ is brought about by treatment of N-nitroso secondary aromatic amines with HCl. Other acids give poor or no results. In benzene systems the para product is usually formed exclusively.⁴¹⁰ The mechanism of the rearrangement is not completely understood. The fact that the reaction takes place in a large excess of urea⁴¹¹ shows that it is intramolecular⁴¹² since, if NO⁺, NOCl,

⁴⁰³Banthorpe; Hughes; Williams *J. Chem. Soc.* **1964**, 5349; Banthorpe; Thomas *J. Chem. Soc.* **1965**, 7149, 7158. Also see Ref. 400.

⁴⁰⁴White; Lazdins; White *J. Am. Chem. Soc.* **1964**, 86, 1517; White; White; Fentiman *J. Org. Chem.* **1976**, 41, 3166.

⁴⁰⁵For additional evidence, see White; Hathaway; Huston *J. Org. Chem.* **1970**, 35, 737; White; Golden; Lazdins *J. Org. Chem.* **1970**, 35, 2048; White; Klink *J. Org. Chem.* **1977**, 42, 166; Ridd; Sandall *J. Chem. Soc., Chem. Commun.* **1982**, 261.

⁴⁰⁶White; Klink *J. Org. Chem.* **1970**, 35, 965.

⁴⁰⁷Shine; Zygmunt; Brownawell; San Filippo *J. Am. Chem. Soc.* **1984**, 106, 3610.

⁴⁰⁸White; White *J. Org. Chem.* **1970**, 35, 1803.

⁴⁰⁹For reviews, see Williams, Ref. 123, pp. 113-128; Williams, Ref. 398; Shine, Ref. 375, pp. 231-235.

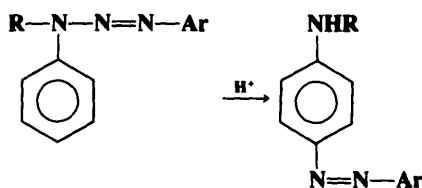
⁴¹⁰For a report of formation of about 15% ortho product in the case of N,N-diaryl-N-nitroso amides, see Titova; Arinich; Gorelik *J. Org. Chem. USSR* **1986**, 22, 1407.

⁴¹¹Aslapovskaya; Belyaev; Kumarev; Porai-Koshits *Org. React. USSR* **1968**, 5, 189; Morgan; Williams *J. Chem. Soc., Perkins Trans. 2* **1972**, 74.

⁴¹²See also Belyaev; Nikulicheva *Org. React. USSR* **1971**, 7, 165; Williams; Wilson *J. Chem. Soc., Perkin Trans. 2* **1974**, 13; Williams *Tetrahedron* **1975**, 31, 1343, *J. Chem. Soc., Perkin Trans. 2* **1975**, 655, **1982**, 801.

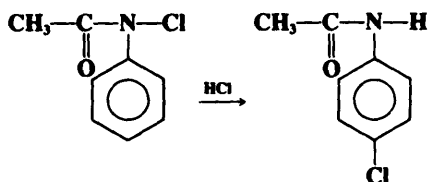
or some similar species were free in the solution, it would be captured by the urea, preventing the rearrangement.

1-34 Migration of an Arylazo Group
1/C-Hydro-5/N-arylazo-interchange



Rearrangement of aryl triazenes can be used to prepare azo derivatives of primary and secondary aromatic amines.⁴¹³ These are first diazotized at the amino group (see **1-4**) to give triazenes, which are then rearranged by treatment with acid. The rearrangement always gives the para isomer, unless that position is occupied.

1-35 Migration of Halogen. The Orton Rearrangement
1/C-Hydro-5/N-halo-interchange



Migration of a halogen from a nitrogen side chain to the ring by treatment with HCl is called the *Orton rearrangement*.⁴¹⁴ The main product is the para isomer, though some ortho product may also be formed. The reaction has been carried out with N-chloro- and N-bromoamines and less often with N-iodo compounds. The amine must be acylated, except that PhNCl_2 gives 2,4-dichloroaniline. The reaction is usually performed in water or acetic acid. There is much evidence (cross-halogenation, labeling, etc.) that this is an intermolecular process.⁴¹⁵ First the HCl reacts with the starting material to give ArNHCOCH_3 and Cl_2 ; then the chlorine halogenates the ring as in **1-11**. Among the evidence is that chlorine has been isolated from the reaction mixture. The Orton rearrangement can also be brought about photochemically⁴¹⁶ and by heating in the presence of benzoyl peroxide.⁴¹⁷ These are free-radical processes.

⁴¹³For a review, see Shine, Ref. 375, pp. 212-221.

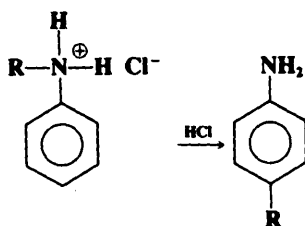
⁴¹⁴For reviews, see Shine, Ref. 375, pp. 221-230, 362-364; Bieron; Dinan, in Zabicky *The Chemistry of Amides*; Wiley: New York, 1970, pp. 263-269.

⁴¹⁵The reaction has been found to be intramolecular in aprotic solvents: Golding; Reddy; Scott; White; Winter *Can. J. Chem.* **1981**, 59, 839.

⁴¹⁶For example, see Hodges *J. Chem. Soc.* **1933**, 240.

⁴¹⁷For example, Ayad; Beard; Garwood; Hickinbottom *J. Chem. Soc.* **1957**, 2981; Coulson; Williams; Johnston *J. Chem. Soc. B* **1967**, 174.

1-36 Migration of an Alkyl Group⁴¹⁸
1/C-Hydro-5/N-alkyl-interchange



When HCl salts of arylalkylamines are heated at about 200 to 300°C, migration occurs. This is called the *Hofmann-Martius reaction*. It is an intermolecular reaction, since crossing is found. For example, methylanilinium bromide gave not only the normal products *o*- and *p*-toluidine but also aniline and di- and trimethylanilines.⁴¹⁹ As would be expected for an intermolecular process, there is isomerization when R is primary.

With primary R, the reaction probably goes through the alkyl halide formed initially in an S_N2 reaction:



Evidence for this view is that alkyl halides have been isolated from the reaction mixture and that Br⁻, Cl⁻, and I⁻ gave different ortho/para ratios, which indicates that the halogen is involved in the reaction.⁴¹⁹ Further evidence is that the alkyl halides isolated are unrearranged (as would be expected if they are formed by an S_N2 mechanism), even though the alkyl groups in the ring are rearranged. Once the alkyl halide is formed, it reacts with the substrate by a normal Friedel-Crafts alkylation process (1-12), accounting for the rearrangement. When R is secondary or tertiary, carbocations may be directly formed so that the reaction does not go through the alkyl halides.⁴²⁰

It is also possible to carry out the reaction by heating the amine (not the salt) at a temperature between 200 and 350°C with a metal halide such as CoCl₂, CdCl₂, or ZnCl₂. When this is done, the reaction is called the *Reilly-Hickinbottom rearrangement*. Primary R groups larger than ethyl give both rearranged and unrearranged products.⁴²¹ The reaction is not generally useful for secondary and tertiary R groups, which are usually cleaved to olefins under these conditions.

When acylated arylamines are photolyzed, migration of an acyl group takes place⁴²² in a process that resembles the photo-Fries reaction (1-30).

⁴¹⁸For reviews, see Grillot *Mech. Mol. Migr.* **1971**, 3 237-270; Shine, Ref. 375, pp. 249-257.

⁴¹⁹Ogata; Tabuchi; Yoshida *Tetrahedron* **1964**, 20, 2717.

⁴²⁰Hart; Kosak *J. Org. Chem.* **1962**, 27, 116.

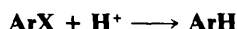
⁴²¹For example, see Birchall; Clark; Goldwhite; Thorpe *J. Chem. Soc., Perkin Trans. 1* **1972**, 2579.

⁴²²For examples, see Elad; Rao; Stenberg *J. Org. Chem.* **1965**, 30, 3252; Shizuka; Tanaka *Bull. Chem. Soc. Jpn.* **1968**, 41, 2343, **1969**, 42, 909; Fischer *Tetrahedron Lett.* **1968**, 4295; Hageman *Recl. Trav. Chim. Pays-Bas* **1972**, 91, 1447; Chênevert; Plante *Can. J. Chem.* **1983**, 61, 1092; Abdel-Malik; de Mayo *Can. J. Chem.* **1984**, 62, 1275; Nassetta; de Rossi; Cosa *Can. J. Chem.* **1988**, 66, 2794.

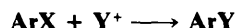
Other Leaving Groups

Three types of reactions are considered in this section.

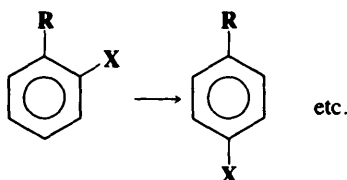
1. Reactions in which hydrogen replaces another leaving group:



2. Reactions in which an electrophile other than hydrogen replaces another leaving group:



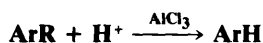
3. Reactions in which a group (other than hydrogen) migrates from one position in a ring to another. Such migrations can be either inter- or intramolecular:



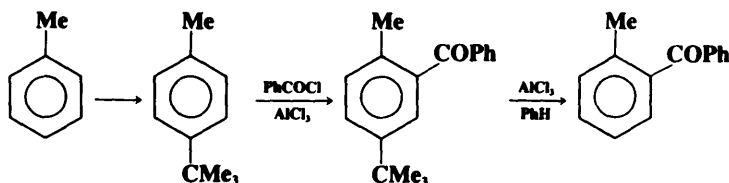
The three types are not treated separately, but reactions are classified by leaving group.

A. Carbon Leaving Groups

1-37 Reversal of Friedel–Crafts Alkylation Hydro-de-alkylation or Dealkylation



Alkyl groups can be cleaved from aromatic rings by treatment with proton and/or Lewis acids. Tertiary R groups are the most easily cleaved; because this is true, the *t*-butyl group is occasionally introduced into a ring, used to direct another group, and then removed.⁴²³ For example,⁴²⁴



Secondary R groups are harder to cleave, and primary R harder still. Because of this reaction, care must be taken when using Friedel–Crafts catalysts (Lewis or proton acids) on aromatic compounds containing alkyl groups. True cleavage, in which the R becomes an olefin, occurs only at high temperatures—above 400°C.⁴²⁵ At ordinary temperatures, the R group attacks

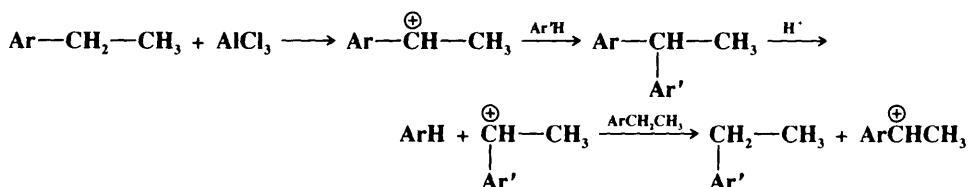
⁴²³For reviews of such reactions, where the blocking group is *t*-butyl, benzyl, or a halogen, see Tashiro, *Synthesis* **1979**, 921-936; Tashiro; Fukata *Org. Prep. Proced. Int.* **1976**, 8, 51-74.

⁴²⁴Hofman; Reiding; Nauta *Recl. Trav. Chim. Pays-Bas* **1960**, 79, 790.

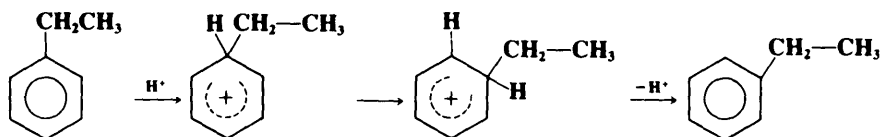
⁴²⁵Olah, in Olah, *Ref.* 261, vol. 1, 1963, pp. 36-38.

another ring, so that the bulk of the product may be dealkylated, but there is a residue of heavily alkylated material. The isomerization reaction, in which a group migrates from one position in a ring to another or to a different ring, is therefore more important than true cleavage. In these reactions, the meta isomer is generally the most favored product among the dialkylbenzenes; and the 1,3,5 product the most favored among the trialkylbenzenes, because they have the highest thermodynamic stabilities. Alkyl migrations can be inter- or intramolecular, depending on the conditions and on the R group. The following experiments can be cited: Ethylbenzene treated with HF and BF_3 gave, almost completely, benzene and diethylbenzenes⁴²⁶ (entirely intermolecular); propylbenzene labeled in the β position gave benzene, propylbenzene, and di- and tripropylbenzenes, but the propylbenzene recovered was partly labeled in the α position and not at all in the γ position⁴²⁷ (both intra- and intermolecular); *o*-xylene treated with HBr and AlBr_3 gave a mixture of *o*- and *m*- but no *p*-xylene, while *p*-xylene gave *p*- and *m*- but no *o*-xylene, and no trimethyl compounds could be isolated in these experiments⁴²⁸ (exclusively intramolecular rearrangement). Apparently, methyl groups migrate only intramolecularly, while other groups may follow either path.⁴²⁹

The mechanism⁴³⁰ of intermolecular rearrangement can involve free alkyl cations, but there is much evidence to show that this is not necessarily the case. For example, many of them occur without rearrangement within the alkyl group. The following mechanism has been proposed for intermolecular rearrangement without the involvement of carbocations that are separated from the ring.⁴³¹



Evidence for this mechanism is that optically active PhCHDCH_3 labeled in the ring with ^{14}C and treated with GaBr_3 in the presence of benzene gave ethylbenzene containing no deuterium and two deuteriums and that the rate of loss of radioactivity was about equal to the rate of loss of optical activity.⁴³¹ The mechanism of intramolecular rearrangement is not very clear. 1,2 shifts of this kind have been proposed:⁴³²



There is evidence from ^{14}C labeling that intramolecular migration occurs only through 1,2 shifts.⁴³³ Any 1,3 or 1,4 migration takes place by a series of two or more 1,2 shifts.

⁴²⁶ McCaulay; Lien *J. Am. Chem. Soc.* **1953**, 75, 2407. For similar results, see Roberts; Roengsumran *J. Org. Chem.* **1981**, 46, 3689; Bakoss; Roberts; Sadri *J. Org. Chem.* **1982**, 47, 4053.

⁴²⁷ Roberts; Brandenberger *J. Am. Chem. Soc.* **1957**, 79, 5484; Roberts; Douglass *J. Org. Chem.* **1963**, 28, 1225.

⁴²⁸ Brown; Jung *J. Am. Chem. Soc.* **1955**, 77, 5579; Allen; Yats *J. Am. Chem. Soc.* **1959**, 81, 5289.

⁴²⁹ Allen; Alfrey; Yats *J. Am. Chem. Soc.* **1959**, 81, 42; Allen *J. Am. Chem. Soc.* **1960**, 82, 4856.

⁴³⁰ For a review of the mechanism of this and closely related reactions, see Shine, Ref. 375, pp. 1-55.

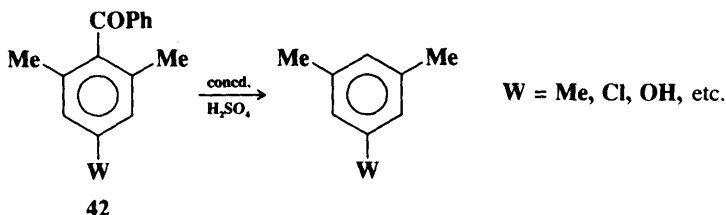
⁴³¹ Streitwieser; Reif *J. Am. Chem. Soc.* **1964**, 86, 1988.

⁴³² Olah; Meyer; Overchuk *J. Org. Chem.* **1964**, 29, 2313.

⁴³³ See, for example, Steinberg; Sixma, *Recl. Trav. Chim. Pays-Bas* **1962**, 81, 185; Koptyug; Isaev; Vorozhtsov *Doklady Akad. Nauk SSSR* **1963**, 149, 100.

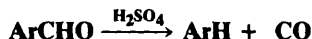
Phenyl groups have also been found to migrate. Thus *o*-terphenyl, heated with $\text{AlCl}_3\text{-H}_2\text{O}$, gave a mixture containing 7% *o*-, 70% *m*-, and 23% *p*-terphenyl.⁴³⁴ Alkyl groups have also been replaced by groups other than hydrogen, e.g., nitro groups.

Unlike alkylation, Friedel–Crafts *acylation* has been generally considered to be irreversible, but a number of instances of electrofugal acyl groups have been reported,⁴³⁵ especially where there are two ortho substituents, for example, the hydro-de-benzoylation of **42**.⁴³⁶



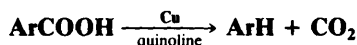
OS V, 332. Also see OS III, 282, 653; V, 598.

1-38 Decarbonylation of Aromatic Aldehydes Hydro-de-formylation or Deformylation



The decarbonylation of aromatic aldehydes with sulfuric acid⁴³⁷ is the reverse of the Gatterman–Koch reaction (**1-16**). It has been carried out with trialkyl- and trialkoxybenzaldehydes. The reaction takes place by the ordinary arenium ion mechanism: the attacking species is H^+ and the leaving group is HCO^+ , which can lose a proton to give CO or combine with OH^- from the water solvent to give formic acid.⁴³⁸ Aromatic aldehydes have also been decarbonylated with basic catalysts.⁴³⁹ When basic catalysts are used, the mechanism is probably similar to the SEI process of **1-39**. See also **4-41**.

1-39 Decarboxylation of Aromatic Acids Hydro-de-carboxylation or Decarboxylation



The decarboxylation of aromatic acids is most often carried out by heating with copper and quinoline. However, two other methods can be used with certain substrates. In one method the salt of the acid (ArCOO^-) is heated, and in the other the carboxylic acid is heated with a strong acid, often sulfuric. The latter method is accelerated by the presence of electron-donating groups in ortho and para positions and by the steric effect of groups in the ortho positions; in benzene systems it is generally limited to substrates that contain such groups.

⁴³⁴Olah; Meyer *J. Org. Chem.* **1962**, 27, 3682.

⁴³⁵For some other examples, see Agranat; Bentor; Shih *J. Am. Chem. Soc.* **1977**, 99, 7068; Bokova; Buchina *J. Org. Chem. USSR* **1984**, 20, 1199; Benedikt; Traynor *Tetrahedron Lett.* **1987**, 28, 763; Gore; Moonga; Short *J. Chem. Soc., Perkin Trans. 2* **1988**, 485; Keumi; Morita; Ozawa; Kitajima *Bull. Chem. Soc. Jpn.* **1989**, 62, 599; Giordano; Villa; Annunziata *Synth. Commun.* **1990**, 20, 383.

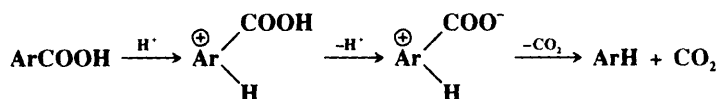
⁴³⁶Al-Ka'bi; Farooqi; Gore; Moonga; Waters *J. Chem. Res. (S)* **1989**, 80.

⁴³⁷For reviews of the mechanism, see Taylor, in Bamford; Tipper, Ref. 1, pp. 316-323; Schubert; Kintner, in Patai *The Chemistry of the Carbonyl Group*, vol. 1; Wiley: New York, 1966, pp. 695-760.

⁴³⁸Burkett; Schubert; Schultz; Murphy; Talbott *J. Am. Chem. Soc.* **1959**, 81, 3923.

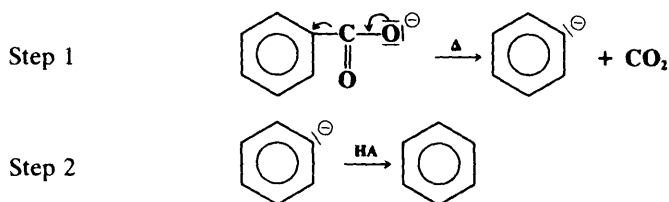
⁴³⁹Bunnett; Miles; Nahabedian *J. Am. Chem. Soc.* **1961**, 83, 2512; Forbes; Gregory *J. Chem. Soc. B* **1968**, 205.

In this method decarboxylation takes place by the arenium ion mechanism,⁴⁴⁰ with H^+ as the electrophile and CO_2 as the leaving group.⁴⁴¹ Evidently, the order of electrofugal ability



is $\text{CO}_2 > \text{H}^+ > \text{COOH}^+$, so that it is necessary, at least in most cases, for the COOH to lose a proton before it can cleave.

When carboxylate *ions* are decarboxylated, the mechanism is entirely different, being of the $\text{S}_{\text{E}}1$ type. Evidence for this mechanism is that the reaction is first order and that electron-withdrawing groups, which would stabilize a carbanion, facilitate the reaction.⁴⁴²



Despite its synthetic importance, the mechanism of the copper–quinoline method has been studied very little, but it has been shown that the actual catalyst is cuprous ion.⁴⁴³ In fact, the reaction proceeds much faster if the acid is heated in quinoline with cuprous oxide instead of copper, provided that atmospheric oxygen is rigorously excluded. A mechanism has been suggested in which it is the cuprous salt of the acid that actually undergoes the decarboxylation.⁴⁴³ It has been shown that cuprous salts of aromatic acids are easily decarboxylated by heating in quinoline⁴⁴⁴ and that arylcopper compounds are intermediates that can be isolated in some cases.⁴⁴⁵ Metallic silver has been used in place of copper, with higher yields.⁴⁴⁶

In certain cases the carboxyl group can be replaced by electrophiles other than hydrogen, e.g., NO ,⁴⁴⁶ I ,⁴⁴⁷ Br ,⁴⁴⁸ or Hg .⁴⁴⁹

Rearrangements are also known to take place. For example, when the phthalate ion is heated with a catalytic amount of cadmium, the terphthalate ion (**43**) is produced:⁴⁵⁰

⁴⁴⁰For a review, see Taylor, in Bamford; Tipper, Ref. 1, pp. 303-316. For a review of isotope effect studies of this reaction, see Willi *Isot. Org. Chem.* **1977**, 3, 257-267.

⁴⁴¹See, for example, Los; Rekker; Tonsbeeck *Recl. Trav. Chim. Pays-Bas* **1967**, 86, 622; Huang; Long *J. Am. Chem. Soc.* **1969**, 91, 2872; Willi; Cho; Won *Helv. Chim. Acta* **1970**, 53, 663.

⁴⁴²See, for example, Segura; Bunnett; Villanova *J. Org. Chem.* **1985**, 50, 1041.

⁴⁴³Cohen; Schambach *J. Am. Chem. Soc.* **1970**, 92, 3189. See also Aalten; van Koten; Tromp; Stam; Goubitz; Mak *Recl. Trav. Chim. Pays-Bas* **1989**, 108, 295.

⁴⁴⁴Cairncross; Roland; Henderson; Sheppard *J. Am. Chem. Soc.* **1970**, 92, 3187; Cohen; Berninger; Wood *J. Org. Chem.* **1978**, 43, 37.

⁴⁴⁵For example, see Ibne-Rasa *J. Am. Chem. Soc.* **1962**, 84, 4962; Tedder; Theaker *J. Chem. Soc.* **1959**, 257.

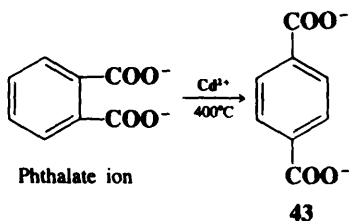
⁴⁴⁶Chodowska-Palicka; Nilsson *Acta Chem. Scand.* **1970**, 24, 3353.

⁴⁴⁷Singh; Just *Synth. Commun.* **1988**, 18, 1327.

⁴⁴⁸For example, see Grovenstein; Ropp *J. Am. Chem. Soc.* **1956**, 78, 2560.

⁴⁴⁹For a review, see Larock *Organomercury Compounds in Organic Synthesis*; Springer: New York, 1985, pp. 101-105.

⁴⁵⁰Raecke *Angew. Chem.* **1958**, 70, 1; Riedel; Kienitz *Angew. Chem.* **1960**, 72, 738; McNelis *J. Org. Chem.* **1965**, 30, 1209; Ogata; Nakajima *Tetrahedron* **1965**, 21, 2393; Ratuský; Šorm *Chem. Ind. (London)* **1966**, 1798.

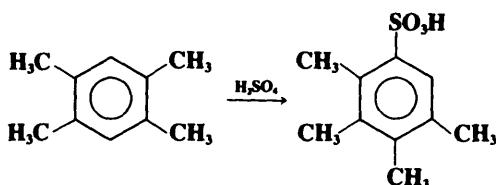


In a similar process, potassium benzoate heated with cadmium salts disproportionates to benzene and **43**. The term *Henkel reaction* (named for the company that patented the process) is used for these rearrangements.⁴⁵¹ An SEI mechanism has been suggested.⁴⁵² The terphthalate is the main product because it crystallizes from the reaction mixture, driving the equilibrium in that direction.⁴⁵³

For aliphatic decarboxylation, see **2-40**.

OS **I**, 274, 455, 541; **II**, 100, 214, 217, 341; **III**, 267, 272, 471, 637; **IV**, 590, 628; **V**, 635, 813, 982, 985. Also see OS **I**, 56.

1-40 The Jacobsen Reaction



When polalkyl- or polyhalobenzenes are treated with sulfuric acid, the ring is sulfonated, but rearrangement also takes place. The reaction, known as the *Jacobsen reaction*, is limited to benzene rings that have at least four substituents, which can be any combination of alkyl and halogen groups, where the alkyl groups can be ethyl or methyl and the halogen iodo, chloro, or bromo. When isopropyl or *t*-butyl groups are on the ring, these groups are cleaved to give olefins. Since a sulfo group can later be removed (**1-41**), the Jacobsen reaction can be used as a means of rearranging polyalkylbenzenes. The rearrangement always brings the alkyl or halo groups closer together than they were originally. Side products in the case illustrated above are pentamethylbenzenesulfonic acid, 2,4,5-trimethylbenzenesulfonic acid, etc., indicating an intermolecular process, at least partially.

The mechanism of the Jacobsen reaction is not established,⁴⁵⁴ but there is evidence, at least for polymethylbenzenes, that the rearrangement is intermolecular, and that the species to which the methyl group migrates is a polymethylbenzene, not a sulfonic acid. Sulfonation takes place after the migration.⁴⁵⁵ It has been shown by labeling that ethyl groups migrate without internal rearrangement.⁴⁵⁶

⁴⁵¹For a review, see Ratuský, in Patai *The Chemistry of Acid Derivatives*, pt. 1; Wiley: New York, 1979, pp. 915-944.

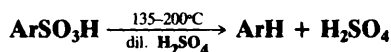
⁴⁵²See, for example, Ratuský *Collect. Czech. Chem. Commun.* **1967**, 32, 2504, **1972**, 37, 2436, **1973**, 38, 74, 87.

⁴⁵³Ratuský *Chem. Ind. (London)* **1967**, 1093, *Collect. Czech. Chem. Commun.* **1968**, 33, 2346.

⁴⁵⁴For discussions, see Suzuki *Bull. Chem. Soc. Jpn.* **1963**, 36, 1642; Koeberg-Telder; Cerfontain *J. Chem. Soc., Perkin Trans. 2* **1977**, 717; Cerfontain, *Mechanistic Aspects in Aromatic Sulfonation and Desulfonation*, Ref. 155, pp. 214-226; Taylor, in Bamford; Tipper, Ref. 1, pp. 22-32, 48-55.

⁴⁵⁵Koeberg-Telder; Cerfontain *Recl. Trav. Chim. Pays-Bas* **1987**, 106, 85; Cerfontain; Koeberg-Telder *Can. J. Chem.* **1988**, 66, 162.

⁴⁵⁶Marvell; Webb *J. Org. Chem.* **1962**, 27, 4408.

B. Sulfur Leaving Groups**1-41 Desulfonation or Hydro-de-sulfonation**

The cleavage of sulfo groups from aromatic rings is the reverse of 1-7.⁴⁵⁷ By the principle of microscopic reversibility, the mechanism is also the reverse.⁴⁵⁸ Dilute H₂SO₄ is generally used, as the reversibility of sulfonation decreases with increasing H₂SO₄ concentration. The reaction permits the sulfo group to be used as a blocking group to direct meta and then to be removed. The sulfo group has also been replaced by nitro and halogen groups. Sulfo groups have also been removed from the ring by heating with an alkaline solution of Raney nickel.⁴⁵⁹ In another catalytic process, aromatic sulfonyl bromides or chlorides are converted to aryl bromides or chlorides, respectively, on heating with chlorotris(triphenylphosphine)rhodium(I).⁴⁶⁰ This reaction is similar to the decarbonylation of aromatic acyl halides mentioned in 4-41.



OS I, 388; II, 97; III, 262; IV, 364. Also see OS I, 519; II, 128; V, 1070.

C. Halogen Leaving Groups**1-42 Dehalogenation or Hydro-de-halogenation**

Aryl halides can be dehalogenated by Friedel-Crafts catalysts. Iodine is the most easily cleaved. Dechlorination is seldom performed and defluorination apparently never. The reaction is most successful when a reducing agent, say, Br⁻ or I⁻ is present to combine with the I⁺ or Br⁺ coming off.⁴⁶¹ Except for deiodination, the reaction is seldom used for preparative purposes. Migration of halogen is also found,⁴⁶² both intramolecular⁴⁶³ and intermolecular.⁴⁶⁴ The mechanism is probably the reverse of that of 1-11.⁴⁶⁵

Rearrangement of polyhalobenzenes can also be catalyzed by very strong bases; e.g., 1,2,4-tribromobenzene is converted to 1,3,5-tribromobenzene by treatment with PhNHK.⁴⁶⁶

⁴⁵⁷For reviews, see Cerfontain, Ref. 454, pp. 185-214; Taylor, in Bamford; Tipper, Ref. 1, pp. 349-355; Gilbert, Ref. 152, pp. 427-442. See also Krylov *J. Org. Chem. USSR* **1988**, 24, 709.

⁴⁵⁸For a discussion, see Kozlov; Bagrovskaya *J. Org. Chem. USSR* **1989**, 25, 1152.

⁴⁵⁹Feigl *Angew. Chem.* **1961**, 73, 113.

⁴⁶⁰Blum; Scharf *J. Org. Chem.* **1970**, 35, 1895.

⁴⁶¹Pettit; Piatak *J. Org. Chem.* **1960**, 25, 721.

⁴⁶²Olah; Tolgyesi; Dear *J. Org. Chem.* **1962**, 27, 3441, 3449, 3455; De Valois; Van Albada; Veenland *Tetrahedron* **1968**, 24, 1835; Olah; Meidar; Olah *Nouv. J. Chim.* **1979**, 3, 275.

⁴⁶³Koptyug; Isaev; Gershtein; Berezovskii *J. Gen. Chem. USSR* **1964**, 34, 3830; Erykalov; Becker; Belokurova *J. Org. Chem. USSR* **1968**, 4, 2054; Jacquesy; Jouannetaud *Tetrahedron Lett.* **1982**, 23, 1673.

⁴⁶⁴Kooyman; Louw *Recl. Trav. Chim. Pays-Bas* **1962**, 81, 365; Augustijn; Kooyman; Louw *Recl. Trav. Chim. Pays-Bas* **1963**, 82, 965.

⁴⁶⁵Choguill; Ridd *J. Chem. Soc.* **1961**, 822; Ref. 430; Ref. 462.

⁴⁶⁶Moyer; Bunnett *J. Am. Chem. Soc.* **1963**, 85, 1891.

This reaction, which involves aryl carbanion intermediates (SE1 mechanism), has been called the *halogen dance*.⁴⁶⁷

Removal of halogen from aromatic rings can also be accomplished by various reducing agents, among them Ph_3SnH ,⁴⁶⁸ HI , Sn and HBr , Ph_3P ,⁴⁶⁹ Zn and an acid or base,⁴⁷⁰ catalytic hydrogenolysis,⁴⁷¹ catalytic transfer hydrogenolysis,⁴⁷² Zn-Ag couple,⁴⁷³ Na-Hg in liquid NH_3 ,⁴⁷⁴ LiAlH_4 ,⁴⁷⁵ LiAlH_4 irradiated with light⁴⁷⁶ or with ultrasound,⁴⁷⁷ NaAlH_4 ,⁴⁷⁸ NaBH_4 and a catalyst,⁴⁷⁹ NaH ,⁴⁸⁰ and Raney nickel in alkaline solution,⁴⁸¹ the last method being effective for fluorine as well as for the other halogens. Carbon monoxide, with potassium tetracarbonylhydridoferrate KHFe(CO)_4 as a catalyst, specifically reduces aryl iodides.⁴⁸² Not all these reagents operate by electrophilic substitution mechanisms. Some are nucleophilic substitutions and some are free-radical processes. Photochemical⁴⁸³ and electrochemical⁴⁸⁴ reduction are also known. Halogen can also be removed from aromatic rings indirectly by conversion to Grignard reagents (2-38) followed by hydrolysis (1-44).

OS III, 132, 475, 519; V, 149, 346, 998; VI, 82, 821.

1-43 Formation of Organometallic Compounds

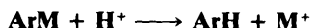


These reactions are considered along with their aliphatic counterparts at reactions 2-38 and 2-39.

D. Metal Leaving Groups

1-44 Hydrolysis of Organometallic Compounds

Hydro-de-metallation or Demetallation



Organometallic compounds can be hydrolyzed by acid treatment. For active metals such as Mg , Li , etc., water is sufficiently acidic. The most important example of this reaction is

⁴⁶⁷Bunnett; McLennan *J. Am. Chem. Soc.* **1968**, 90, 2190; Bunnett *Acc. Chem. Res.* **1972**, 5, 139-147; Mach; Bunnett *J. Org. Chem.* **1980**, 45, 4660; Sauter; Fröhlich; Kalt *Synthesis*, **1989**, 771.

⁴⁶⁸Lorenz; Shapiro; Stern; Becker *J. Org. Chem.* **1963**, 28, 2332; Neumann; Hillgärtner *Synthesis* **1971**, 537.

⁴⁶⁹Hoffmann; Michael *Chem. Ber.* **1962**, 95, 528.

⁴⁷⁰Tashiro; Fukuta *J. Org. Chem.* **1977**, 42, 835. See also Colon *J. Org. Chem.* **1982**, 47, 2622.

⁴⁷¹For example, see Subba Rao; Mukkanti; Choudary *J. Organomet. Chem.* **1989**, 367, C29.

⁴⁷²Anwer; Spatola *Tetrahedron Lett.* **1985**, 26, 1381.

⁴⁷³Chung; Ho; Lun; Wong; Wong; Tam *Synth. Commun.* **1988**, 18, 507.

⁴⁷⁴Austin; Alonso; Rossi *J. Chem. Res. (S)* **1990**, 190.

⁴⁷⁵Karabatsos; Shone *J. Org. Chem.* **1968**, 33, 619; Brown; Krishnamurthy *J. Org. Chem.* **1969**, 34, 3918; Virtanen; Jaakkola *Tetrahedron Lett.* **1969**, 1223; Ricci; Danieli; Pirazzini *Gazz. Chim. Ital.* **1975**, 105, 37; Chung; Chung *Tetrahedron Lett.* **1979**, 2473. Evidence for a free-radical mechanism has been found in this reaction; see Chung; Filmore *J. Chem. Soc., Chem Commun.* **1983**, 358; Beckwith; Goh *J. Chem. Soc., Chem Commun.* **1983**, 905.

⁴⁷⁶Beckwith; Goh *J. Chem. Soc., Chem. Commun.* **1983**, 907.

⁴⁷⁷Han; Baudjouk *Tetrahedron Lett.* **1982**, 23, 1643.

⁴⁷⁸Zakharkin; Gavrilenko; Rukasov *Dokl. Chem.* **1972**, 205, 551.

⁴⁷⁹Egli *Helv. Chim. Acta* **1968**, 51, 2090; Bosin; Raymond; Buckpitt *Tetrahedron Lett.* **1974**, 4699; Lin; Roth *J. Org. Chem.* **1979**, 44, 309; Narisada; Horibe; Watanabe; Takeda *J. Org. Chem.* **1989**, 54, 5308. See also Epling; Florio *J. Chem. Soc., Perkin Trans. 1* **1988**, 703.

⁴⁸⁰Nelson; Gribble *J. Org. Chem.* **1974**, 39, 1425.

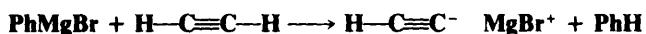
⁴⁸¹Buu-Hoi; Xuong; van Bac *Bull. Soc. Chim. Fr.* **1963**, 2442; de Koning *Org. Prep. Proced. Int.* **1975**, 7, 31.

⁴⁸²Brunet; Taillefer *J. Organomet. Chem.* **1988**, 348, C5.

⁴⁸³See, for example, Pinhey; Rigby *Tetrahedron Lett.* **1969**, 1267, 1271; Barltrop; Bradbury *J. Am. Chem. Soc.* **1973**, 95, 5085.

⁴⁸⁴See Fry *Synthetic Organic Electrochemistry*, 2nd ed.; Wiley: New York, 1989, pp. 142-143.

hydrolysis of Grignard reagents, but M may be many other metals or metalloids. Examples are SiR_3 , HgR , Na , and $\text{B}(\text{OH})_2$. Since aryl Grignard and aryllithium compounds are fairly easy to prepare, they are often used to prepare salts of weak acids, e.g.,



Where the bond between the metal and the ring is covalent, the usual arenium ion mechanism operates.⁴⁸⁵ Where the bonding is essentially ionic, this is a simple acid-base reaction. For the aliphatic counterpart of this reaction, see reaction 2-24.

Other reactions of aryl organometallic compounds are treated with their aliphatic analogs: reactions 2-25 through 2-36.

⁴⁸⁵For a discussion of the mechanism, see Taylor, in Bamford; Tipper, Ref. 1, pp. 278-303, 324-349.

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 ($\text{RC}\equiv\text{CH}$). 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 SE_1 , SE_2 (front), SE_2 (back), and SE_i . The SE_1 is unimolecular; the other three are bimolecular.

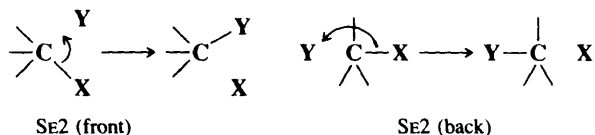
Bimolecular Mechanisms. SE_2 and SE_i

The bimolecular mechanisms for electrophilic aliphatic substitution are analogous to the $\text{S}_\text{N}2$ mechanism in that the new bond forms as the old one breaks. However, in the $\text{S}_\text{N}2$

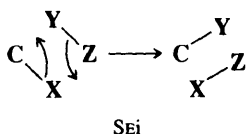
¹For books on the preparation and reactions of organometallic compounds, see Hartley; Patai *The Chemistry of the Metal-Carbon Bond*, 5 vols.; Wiley: New York, 1984-1990; Haiduc; Zuckerman *Basic Organometallic Chemistry*; Walter de Gruyter: New York, 1985; Negishi *Organometallics in Organic Synthesis*; 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.

²For 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):



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:



This mechanism, which we call the SEi mechanism³ (IUPAC designation: cyclo- $D_EA_E D_nA_n$), 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

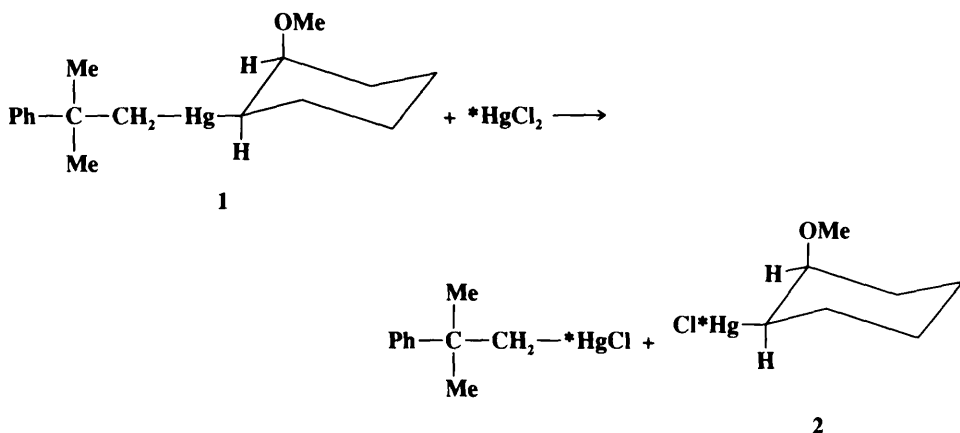
³The names for these mechanisms vary throughout the literature. For example, the SEi mechanism has also been called the SF2, the SE2 (closed), and the SE2 (cyclic) mechanism. The original designations, SE1, SE2, etc., were devised by the Hughes-Ingold school.

⁴It 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.

⁵For 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.

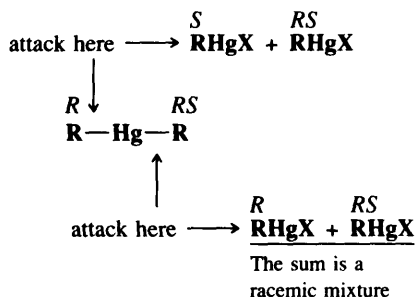
⁶Winstein; Traylor; Garner *J. Am. Chem. Soc.* **1955**, *77*, 3741.

⁷Winstein; 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.

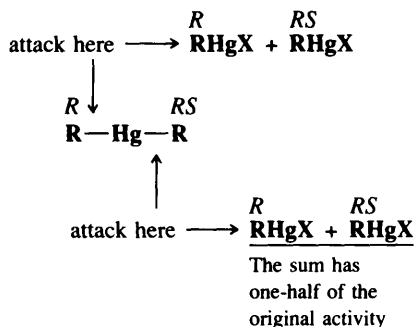


neopentyl as a substrate. S_N2 reactions at neopentyl are extremely slow (p. 339), because attack from the rear is blocked. The fact that neopentyl systems undergo electrophilic substitution only slightly more slowly than ethyl⁸ is further evidence for frontside attack. One final elegant experiment may 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,

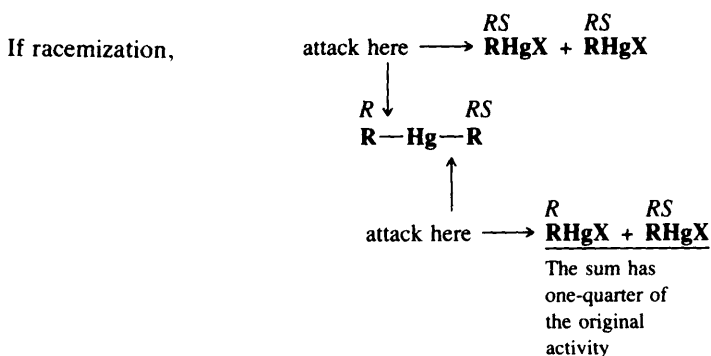


If retention,



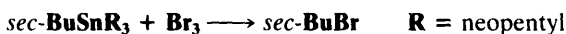
⁸Hughes; Volger *J. Chem. Soc.* **1961**, 2359.

⁹Jensen *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 $\text{S}_{\text{E}}2$ (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



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 exist¹³ 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 prepared¹⁵ (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

¹⁰Jensen; Davis *J. Am. Chem. Soc.* **1971**, *93*, 4048. For a review of the stereochemistry of $\text{S}_{\text{E}}2$ reactions with organotin substrates, see Fukuto; Jensen *Acc. Chem. Res.* **1983**, *16*, 177-184.

¹¹For 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.

¹²See, 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.

¹³Cases 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.

¹⁴Organomercury 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.

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

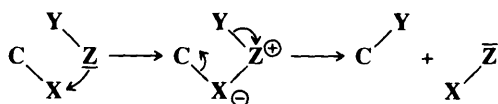
been shown to proceed with retention of configuration.¹⁶ It is likely that inversion takes place only when steric hindrance prevents frontside attack and when the electrophile does not carry a Z group (p. 570).

The S_E2 (back) mechanism can therefore be identified in certain cases (if inversion of configuration is found), but it is plain that stereochemical investigations cannot distinguish between the S_E2 (front) and the S_Ei mechanisms and that, in the many cases where configurationally stable substrates cannot be prepared, such investigations are of no help at all in distinguishing among all three of the second-order mechanisms. Unfortunately, there are not many other methods that lead to unequivocal conclusions. One method that has been used in an attempt to distinguish between the S_Ei mechanism on the one hand and the S_E2 pathways on the other involves the study of salt effects on the rate. It may be recalled (p. 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 S_Ei mechanism would be less influenced by salt effects than would either of the S_E2 mechanisms. On this basis Abraham and co-workers¹⁷ concluded that the reactions $R_4Sn + HgX_2 \rightarrow RHgX + R_3SnX$ (X = Cl or I) take place by S_E2 and not by S_Ei mechanisms. Similar investigations involve changes in solvent polarity¹⁸ (see also p. 580). In the case of the reaction



(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 suggested²⁰ that a variation of the S_Ei mechanism is possible in which the group Z becomes attached to X before the latter becomes detached:



This process has been called the S_EC²⁰ or S_E2 (co-ord)²¹ mechanism (IUPAC designation A_n + cyclo-D_EA_ED_n).

It has been shown that in certain cases (e.g., Me₄Sn + I₂) the reactants in an S_E2 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 S_E1 Mechanism

The S_E1 mechanism is analogous to the S_N1. It involves two steps—a slow ionization and a fast combination.



¹⁶Jensen; Nakamaye *J. Am. Chem. Soc.* **1966**, 88, 3437.

¹⁷Abraham; Spalding *J. Chem. Soc. A* **1969**, 784; Abraham; Johnston *J. Chem. Soc. A* **1970**, 188.

¹⁸See, for example, Abraham; Dorrell *J. Chem. Soc., Perkin Trans. 2* **1973**, 444.

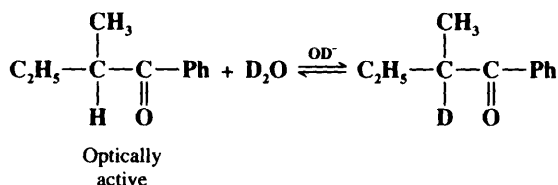
¹⁹Fukuto; Newman; Jensen *Organometallics* **1987**, 6, 415.

²⁰Abraham; Hill *J. Organomet. Chem.* **1967**, 7, 11.

²¹Abraham, Ref. 2, p. 15.

²²Fukuzumi; Kochi *J. Am. Chem. Soc.* **1980**, 102, 2141, 7290.

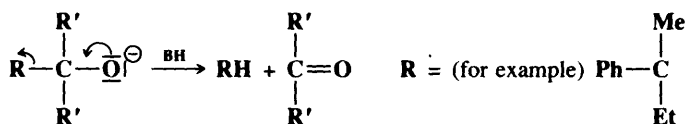
The IUPAC designation is $D_E + A_E$. First-order kinetics are predicted and many such examples have been found. Other evidence for the $SE1$ mechanism was obtained in a study of base-catalyzed tautomerization. In the reaction



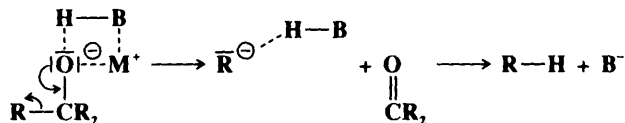
the rate of deuterium exchange was the same as the rate of racemization²³ and there was an isotope effect.²⁴

$SN1$ 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; $SE1$ 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 $SE1$ 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 $SE1$ 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 $SE1$ 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 :

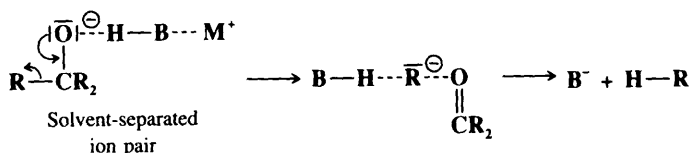


²³Hsu; Ingold; Wilson *J. Chem. Soc.* **1938**, 78.

²⁴Wilson *J. Chem. Soc.* **1936**, 1550.

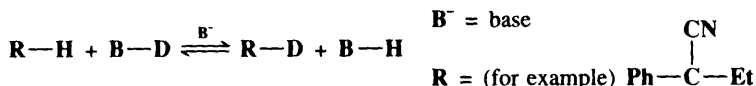
²⁵See Cram; Langemann; Allinger; Kopecky *J. Am. Chem. Soc.* **1959**, *81*, 5740; Hoffman; Cram *J. Am. Chem. Soc.* **1969**, *91*, 1009. For a discussion, see Cram *Fundamentals of Carbanion Chemistry*; Academic Press: New York, 1965, pp. 138-158.

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:

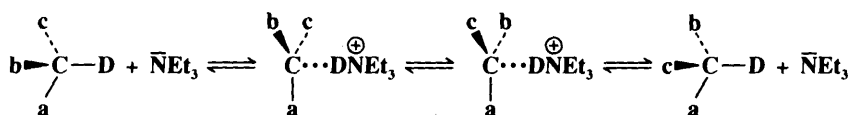


When C—H bond formation occurs, the result is inversion. Racemization results in polar aprotic solvents such as dimethyl sulfoxide. In these solvents the carbanions are relatively long-lived (because the solvent has no proton to donate) and symmetrically solvated.

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_a (rate constant for racemization). A k_e/k_a 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_a 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_a ratio was found to be *less* than 0.5, indicating that racemization took place *faster* than isotopic exchange (this process is known as *isoracemization*). Under these conditions, the conjugate acid of the amine remains associated with the carbanion as an ion pair. Occasionally, the ion pair dissociates long enough for the carbanion to turn over and recapture the proton:

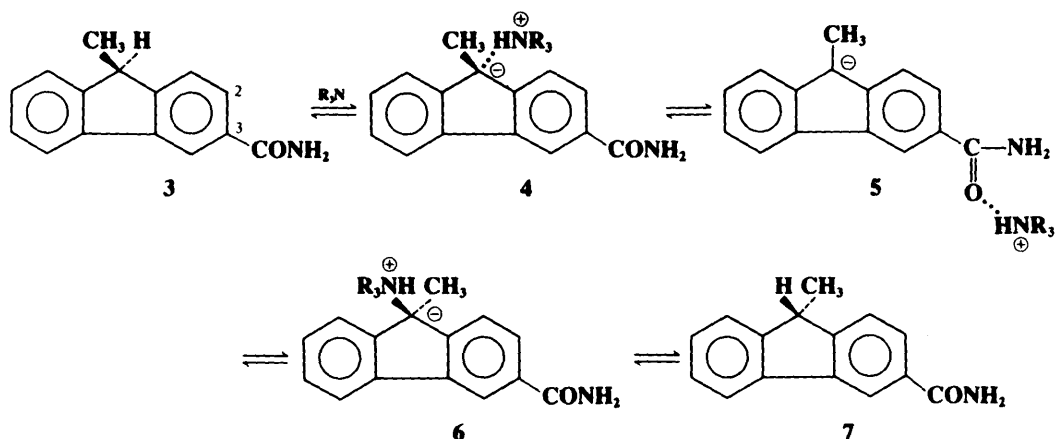


Thus, inversion (and hence racemization, which is produced by repeated acts of inversion) occurs without exchange. A single act of inversion without exchange is called *isoinversion*.

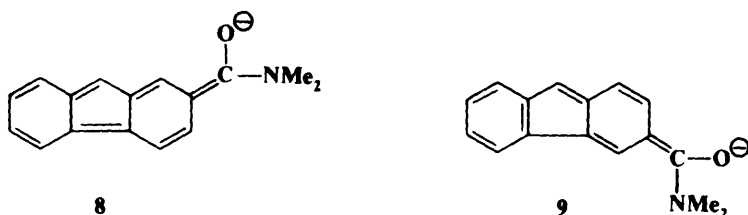
The isoinversion process can take place by a pathway in which a positive species migrates in a stepwise fashion around a molecule from one nucleophilic position to another. For example, in the exchange reaction of 3-carboxamido-9-methylfluorene (**3**) with Pr_3N in *t*-

²⁶See 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

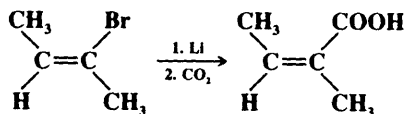


the opposite face of the anion. Collapse of **6** gives the inverted product **7**. Of course **5** could also go back to **3**, but a molecule that undergoes the total process $3 \rightarrow 4 \rightarrow 5 \rightarrow 6 \rightarrow 7$ has experienced an inversion without an exchange. Evidence for this pathway, called the *conducted tour mechanism*,²⁷ is that the 2-carboxamido isomer of **3** does not give isomerization. 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



disruption of the aromatic sextet in both benzene rings (compare **9** where one benzene ring is intact). Whether the isomerization 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



²⁷Cram; 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].

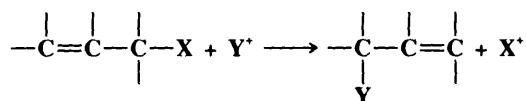
²⁸Chu; Cram *J. Am. Chem. Soc.* **1972**, *94*, 3521; Almy; Hoffman; Chu; Cram *J. Am. Chem. Soc.* **1973**, *95*, 1185.

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

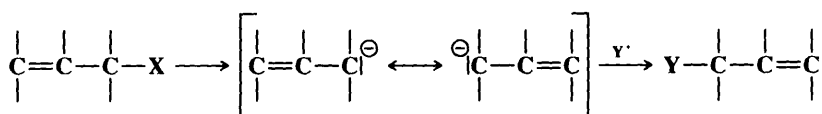
Only about 5% of the *cis* isomer, tiglic acid, was produced. In addition, certain carbanions in which the negative charge is stabilized by *d*-orbital overlap can maintain configuration (p. 181) and S_N1 reactions involving them proceed with retention of configuration.

Electrophilic Substitution Accompanied by Double-Bond Shifts

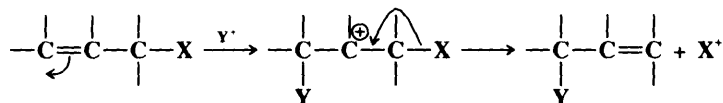
When electrophilic substitution is carried out at an allylic substrate, the product may be rearranged:



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 S_N1 mechanism in that the leaving group is first removed, giving a resonance-stabilized allylic carbanion, and then the electrophile attacks.

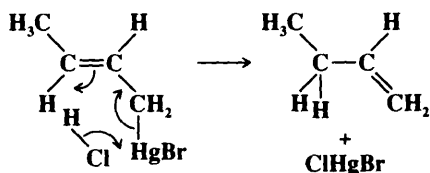


In the other pathway the Y group first attacks, giving a carbocation, which then loses X.



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

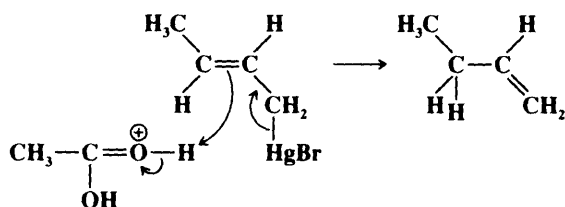
Most electrophilic allylic rearrangements involve hydrogen as the leaving group, but they have also been observed with metallic leaving groups.³⁰ Slezzer, Winstein, and Young found that crotylmercuric bromide reacted with HCl about 10^7 times faster than *n*-butylmercuric bromide and the product was more than 99% 1-butene.³¹ These facts point to an S_N1' mechanism (IUPAC designation cyclo-1/3/ $D_EA_E D_nA_n$):



The reaction of the same compound with acetic acid–perchloric acid seems to proceed by an S_N2' mechanism (IUPAC designation 1/3/ D_EA_E):³¹

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

³¹Slezzer; Winstein; Young *J. Am. Chem. Soc.* **1963**, 85, 1890. See also Cunningham; Overton *J. Chem. Soc., Perkin Trans. I* **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 SE_1 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 SE_2 (back) mechanism, Jensen and Davis¹⁰ showed that the reactivity of alkyl groups is similar to that for the SN_2 mechanism (i.e., $\text{Me} > \text{Et} > \text{Pr} > \text{iso-Pr} > \text{neopentyl}$), 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 SE_2 (back) mechanism in cases where stereochemical investigation is not feasible.³⁶ For SE_2 reactions that proceed with retention, several studies have been made with varying results, depending on the reaction.³⁷ One such study, which examined the

³²Hayashi; 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.

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

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

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

³⁶Another method involves measurement of the susceptibility of the rate to increased pressure: See Isaacs; Javard *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 $\text{RHgBr} + \text{Br}_2 \rightarrow \text{RBr}$ 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 ascribed⁴⁰ to an SE_2 mechanism involving ion pairs, analogous to Snee's ion-pair mechanism for nucleophilic substitution (p. 305).

2. Effect of leaving group. For both SE_1 and second-order mechanisms, the more polar the $\text{C}-\text{X}$ 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 $\text{C}-\text{Hg}$ 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 $\text{Hg-}t\text{-Bu} > \text{Hg-iso-Pr} > \text{HgEt} > \text{HgMe}$, 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, SE_1 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 SE_1 , while for metallic leaving groups the mechanism is almost always SE_2 or SE_i . A number of reports of SE_1 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-workers⁴¹ have expressed the view that in such reactions a nucleophile (which

³⁷For 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.

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

³⁹A 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.

⁴⁰Beletskaya; 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.

⁴¹For 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.

⁴²For 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

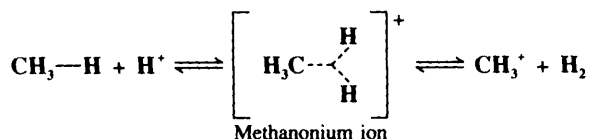
A. Hydrogen as the Electrophile

2-1 Hydrogen Exchange

Deuterio-de-hydrogenation or Deuteriation



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,



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

⁴⁴Hogeveen; 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.

⁴⁵The 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_3^+ 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 trivalent carbocations) by treatment with pure SbF_5 in the absence of any source of H^+ .⁴⁹ Complete or almost complete perdeuteration of cyclic alkenes has been achieved by treatment with dilute $\text{DCl}/\text{D}_2\text{O}$ in sealed Pyrex tubes at 165-280°C.⁵⁰

Exchange with bases involves an SE1 mechanism.



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 perdeuterated 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



The double bonds of many unsaturated compounds are shifted⁵² 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

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

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

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

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

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

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

⁵²For 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.

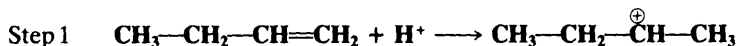
⁵³For reviews of double-bond migrations, see Pines; Stalick *Base-Catalyzed Reactions of Hydrocarbons and Related Compounds*; Academic Press: New York, 1977, pp. 25-123; DeWolfe, in Bamford; Tipper *Comprehensive Chemical Kinetics*, vol. 9; Elsevier, New York, 1973, pp. 437-449; Yanovskaya; Shakhidayatov *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.

⁵⁴For lists of which double bonds are more stable in conversions of $\text{XCH}_2\text{CH}=\text{CHY}$ to $\text{XCH}=\text{CHCH}_2\text{Y}$, see Hine; Skoglund *J. Org. Chem.* **1982**, *47*, 4766. See also Hine; Linden *J. Org. Chem.* **1983**, *48*, 584.

⁵⁵For 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.

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 $\text{NH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NHK}^{63}$), 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 Lewis⁶⁵ acids can be used. The mechanism in the case of proton acids is the reverse of the previous one; first a proton is gained, giving a carbocation, and then another is lost:



As in the case of the base-catalyzed reaction, the thermodynamically most stable 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*:



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

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

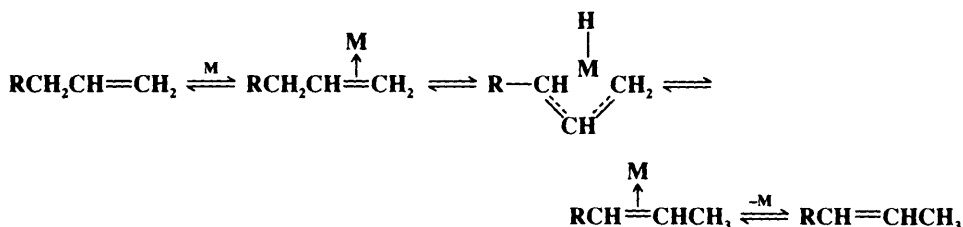
⁶⁵For an example of a Lewis-acid catalyzed rearrangement, see Cameron; Stimson *Aust. J. Chem.* **1977**, 30, 923.

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

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

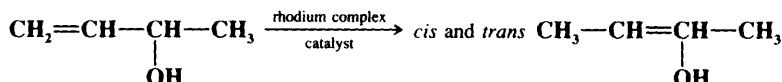
⁶⁸For reviews, see Rodríguez; Brun; Waegell *Bull. Soc. Chim. Fr.* **1989**, 799-823; Jardine, in Harley; Patai, Ref. 1, vol. 4, pp. 733-818, pp. 736-740; Otsuka; Tani, in Morrison *Asymmetric Synthesis*, vol. 5; Academic Press: New York, 1985, pp. 171-191 (enantioselective); Colquhoun; Holton; Thompson; 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:



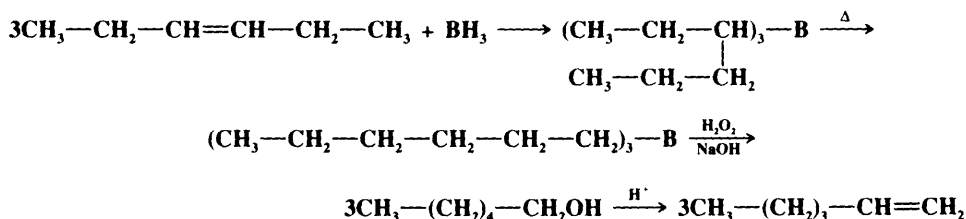
Another difference between the two mechanisms is that the former involves 1,2 and the latter 1,3 shifts. The isomerization of 1-butene by rhodium(I) is an example of a reaction that takes place by the metal hydride mechanism,⁶⁹ while an example of the π -allyl complex mechanism is found in the $\text{Fe}_3(\text{CO})_{12}$ -catalyzed isomerization of 3-ethyl-1-pentene.⁷⁰ A palladium acetate or palladium complex catalyst was used to convert alkynes $\text{RCOC}\equiv\text{CCH}_2\text{CH}_2\text{R}'$ to 2,4-alkadien-1-ones $\text{RCOCH}=\text{CHCH}=\text{CHCHR}'$.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

⁶⁹Cramer *J. Am. Chem. Soc.* **1966**, *88*, 2272.

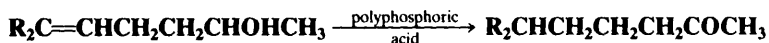
⁷⁰Casey; Cyr *J. Am. Chem. Soc.* **1973**, *95*, 2248.

⁷¹Trost; Schmidt *J. Am. Chem. Soc.* **1988**, *110*, 2301.

^{71a}Bergens; Bosnich *J. Am. Chem. Soc.* **1991**, *113*, 958.

⁷²For 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

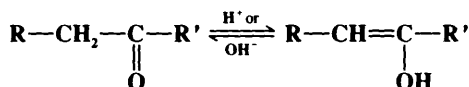


Similarly, α -hydroxy triple-bond compounds have given α,β -unsaturated ketones.⁷⁴

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

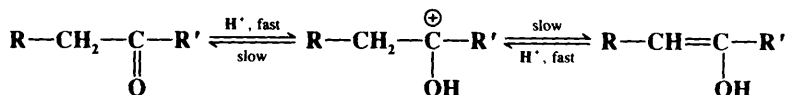
3/O-Hydro-de-hydrogenation



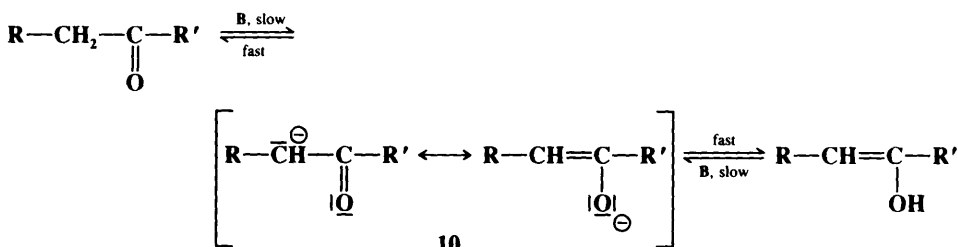
The tautomeric equilibrium between enols and ketones or aldehydes is not normally a preparative reaction, though for some ketones both forms can be prepared (see p. 69 for a discussion of this and other aspects of tautomerism). For most ketones and aldehydes only the keto form is detectable under ordinary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



Base-catalyzed⁷⁷



10

⁷³Colonge; 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.

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

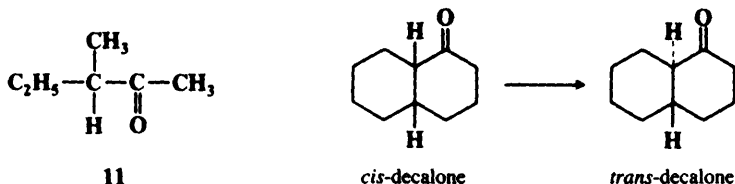
⁷⁵In the case of the "uncatalyzed" ketonization of $\text{CH}_2=\text{C}(\text{Ph})\text{OH}$, it was shown that water functions as the basic catalyst: Chiang; Kresge; Santaballa; Wirz *J. Am. Chem. Soc.* **1988**, 110, 5506.

⁷⁶For 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.

⁷⁷Another 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.

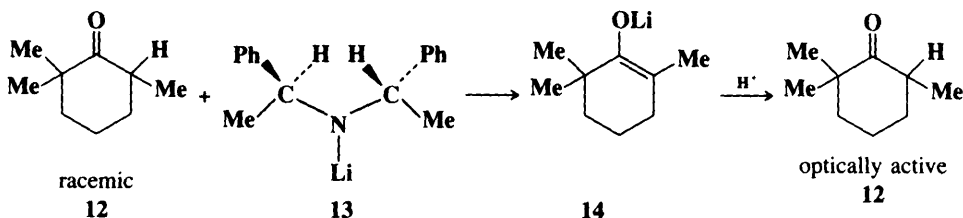
For each catalyst, the mechanism for one direction is the exact reverse of the other, by the principle of microscopic reversibility.⁷⁸ As expected from mechanisms in which the C—H bond is broken in the rate-determining step, substrates of the type RCD_2COR show deuterium isotope effects (of about 5) in both the basic⁷⁹ and the acid⁸⁰-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 isolated⁸¹ (see, for example, **0-95**).⁸² When enol ethers or esters are hydrolyzed, the enols initially formed immediately tautomerize to the aldehydes or ketones. In addition, the overall processes (forward plus reverse reactions) are often used for equilibration purposes. When an optically active compound in which the chirality is due to an asymmetric carbon α to a carbonyl group (as in **11**) is treated with acid or base, racemization results.⁸³ If there is another asymmetric



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



⁷⁸It 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.

⁷⁹Riley, 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.

⁸⁰Swain; 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.

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

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

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

⁸⁴Elevedt; 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.

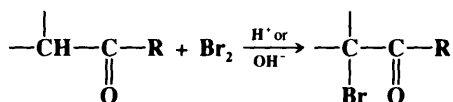
Enolizable hydrogens can be replaced by deuterium (and ^{16}O by ^{18}O) by passage of a sample through a deuterated (or ^{18}O -containing) gas-chromatography column.⁸⁵

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-alkylsulfonamide⁸⁹ (this can result in enantioselective fluorination, if an optically active N-fluorosulfonamide is used⁹⁰), 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 FCIO_3 .⁹⁵ (However, FCIO_3 can be a dangerous reagent. Several explosions have been reported.⁹⁶) If the carbon attacked with FCIO_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 FCIO_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%

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

⁸⁶For 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 Kimpé; Verhé *The Chemistry of α Haloketones, α Haloaldehydes, and α Haloimines*; Wiley: New York, 1988.

⁸⁷For 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.

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

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

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

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

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

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

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

⁹⁵Inman; 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.

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

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

⁹⁸Barton; 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.

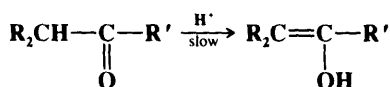
⁹⁹Tsushima; Kawada; Tsuji *Tetrahedron Lett.* **1982**, 23, 1165.

F_2 in N_2 at $-78^\circ C$ 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 chloride¹⁰⁷ 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

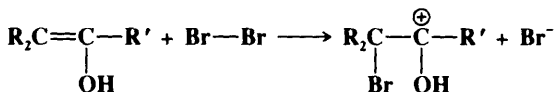
For unsymmetrical ketones the preferred position of halogenation is usually a CH group, then a CH_2 group, and then CH_3 ;¹¹³ however, mixtures are frequent. With aldehydes the aldehydic hydrogen is sometimes replaced (see 4-3). It is also possible to prepare di- and polyhalides. When basic catalysts 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

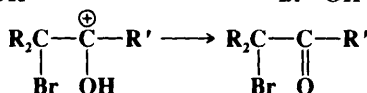
Step 1



Step 2



Step 3



¹⁰⁰Purrrington; Bumgardner; Lazaridis; Singh *J. Org. Chem.* **1987**, 52, 4307.

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

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

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

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

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

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

¹⁰⁷For 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.

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

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

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

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

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

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

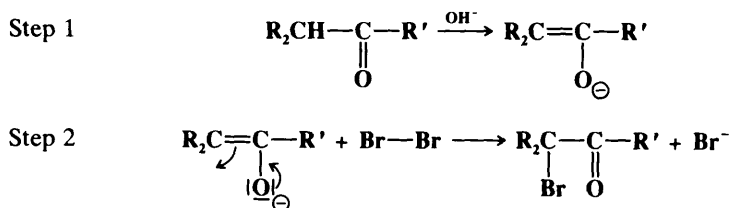
¹¹⁴Rappe *Ark. Kemi.* **1965**, 24, 321. But see also Teo; Warnhoff *J. Am. Chem. Soc.* **1973**, 95, 2728.

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

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

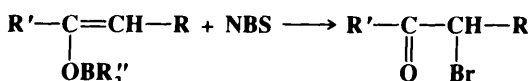
The first step, as we have already seen (2-3), actually consists of two steps. The second step is very similar to the first step in electrophilic addition to double bonds (p. 734). There is a great deal of evidence for this mechanism: (1) the rate is first order in substrate; (2) bromine does not appear 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:



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 $\text{C}=\text{O}$ 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 temperature¹²² (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 $\text{R}_2\text{C}=\text{CHOSiMe}_3$ 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) acetate¹²⁶ or copper(II)

¹¹⁷When 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 concentration, 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.

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

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

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

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

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

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

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

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

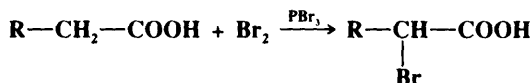
¹²⁶Cambie; Hayward; Jurlina; Rutledge; Woodgate *J. Chem. Soc., Perkin Trans 1* **1978**, 126.

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



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.

¹²⁷Horiuchi; Satoh *Synthesis* **1981**, 312.

¹²⁸Ley; Whittle *Tetrahedron Lett.* **1981**, 22, 3301.

¹²⁹Hegde; Wolinsky *Tetrahedron Lett.* **1981**, 22, 5019.

¹³⁰For a review, see Harwood, *Chem. Rev.* **1962**, 62, 99-154, pp. 102-103.

¹³¹See, however, Kwart; Scalzi *J. Am. Chem. Soc.* **1964**, 86, 5496.

¹³²Ogata; Watanabe *J. Org. Chem.* **1979**, 44, 2768, **1980**, 45, 2831.

¹³³Ogata; Sugimoto *J. Org. Chem.* **1978**, 43, 3684; Ogata; Adachi *J. Org. Chem.* **1982**, 47, 1182.

¹³⁴For a list of reagents, with references, see Ref. 52, pp. 378-380.

¹³⁵Louw *Chem. Commun.* **1966**, 544.

¹³⁶Gleason; Harpp *Tetrahedron Lett.* **1970**, 3431; Harpp; Bao; Black; Gleason; Smith *J. Org. Chem.* **1975**, 40, 3420.

¹³⁷Horiuchi; Satoh *Chem. Lett.* **1984**, 1509.

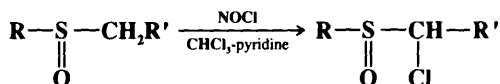
¹³⁸Rathke; Lindert *Tetrahedron Lett.* **1971**, 3995.

¹³⁹Arnold; Kulenovic *J. Org. Chem.* **1978**, 43, 3687.

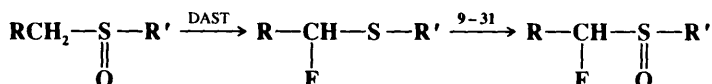
¹⁴⁰Purrinton; Woodard *J. Org. Chem.* **1990**, 55, 3423.

2-6 Halogenation of Sulfoxides and Sulfones

Halogenation or Halo-de-hydrogenation



Sulfoxides can be chlorinated in the α position¹⁴¹ 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 bromine¹⁴⁵ and with N-bromosuccinimide-bromine¹⁴⁸ have also been reported. Sulfones have been chlorinated by treatment of their conjugate bases $\text{RSO}_2\text{CHR}'$ 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-

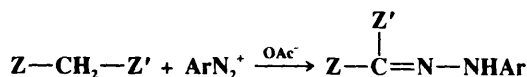


cedure. Treatment with diethylaminosulfur trifluoride Et_2NSF_3 (DAST) produces an α -fluoro thioether, usually in high yield. Oxidation of this compound with *m*-chloroperbenzoic acid gives the sulfoxide.¹⁵²

C. Nitrogen Electrophiles

2-7 Aliphatic Diazonium Coupling

Aryldiazono-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 $\text{Z}-\text{CH}_2-\text{Z}'$, where Z and Z' are as defined on p. 464, e.g., β -keto esters, β -keto amides, malonic ester.

¹⁴¹For a review, see Venier; Barager *Org. Prep. Proced. Int.* **1974**, 6, 77-102, pp. 81-84.

¹⁴²Tsuchihashi; Iriuchijima *Bull. Chem. Soc. Jpn.* **1970**, 43, 2271.

¹⁴³Hojo; Yoshida *J. Am. Chem. Soc.* **1968**, 90, 4496.

¹⁴⁴Ogura; Imaizumi; Iida; Tsuchihashi *Chem. Lett.* **1980**, 1587.

¹⁴⁵Cinquini; Colonna *J. Chem. Soc., Perkin Trans. 1* **1972**, 1883. See also Cinquini; Colonna *Synthesis* **1972**, 259.

¹⁴⁶Iriuchijima; Tsuchihashi *Tetrahedron Lett.* **1969**, 5259.

¹⁴⁷Tin; Durst *Tetrahedron Lett.* **1970**, 4643.

¹⁴⁸Iriuchijima; Tsuchihashi *Synthesis* **1970**, 588.

¹⁴⁹Regis; Doweyko *Tetrahedron Lett.* **1982**, 23, 2539.

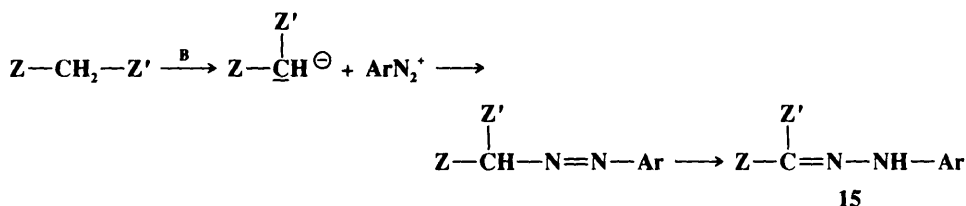
¹⁵⁰Paquette; Houser *J. Am. Chem. Soc.* **1969**, 91, 3870, *J. Org. Chem.* **1971**, 36, 1015.

¹⁵¹Kattenberg; de Waard; Huisman *Tetrahedron* **1973**, 29, 4149, **1974**, 30, 463.

¹⁵²McCarthy; Peet; LeTourneau; Inbasekaran *J. Am. Chem. Soc.* **1985**, 107, 735. See also Umemoto; Tomizawa *Bull. Chem. Soc. Jpn.* **1986**, 59, 3625.

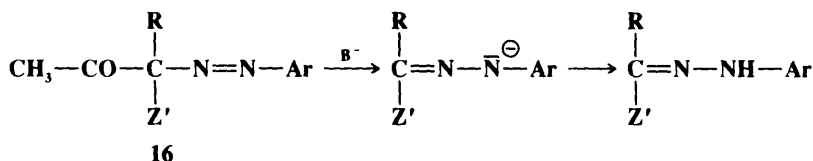
¹⁵³For a review, see Parmerter *Org. React.* **1959**, 10, 1-142.

The mechanism is probably of the simple S_E1 type:

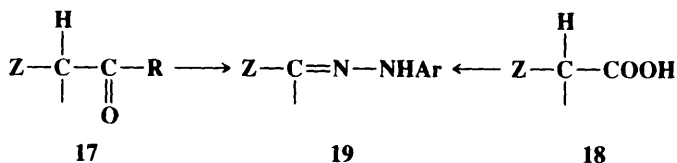


Aliphatic azo compounds in which the carbon containing the azo group is attached to a hydrogen are unstable and tautomerize to the isomeric hydrazones (15), which are therefore the products of the reaction.

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 carboxyl 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

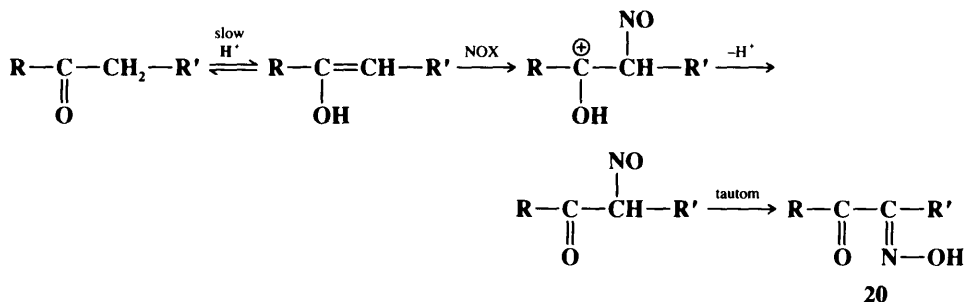


¹⁵⁴See, for example, Yao; Resnick *J. Am. Chem. Soc.* **1962**, *84*, 3514.

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

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

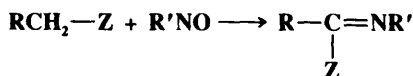
Carbons adjacent to a Z group (as defined on p. 464) can be nitrosated with nitrous acid or alkyl nitrites.¹⁵⁷ The initial product is the C-nitroso compound, but these are stable only when there is no tautomerizable hydrogen. When there is, the product is the more stable oxime. The situation is analogous to that with azo compounds and hydrazones (2-7). The mechanism is similar to that in 2-7:¹⁵⁸ $R-H \rightarrow R^- + {}^+N=O \rightarrow R-N=O$. 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):



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 $HONO + X^- + H^+ \rightarrow HOX + H_2O$. 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:

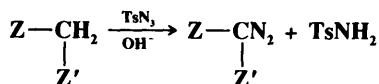


Alkanes can be nitrosated photochemically, by treatment with $NOCl$ and uv light.¹⁶³ For nitration at an activated carbon, see 4-13.

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



¹⁵⁷For a review, see Williams *Nitrosation*; Cambridge University Press: Cambridge, 1988, pp. 1-45.

¹⁵⁸For a review, see Williams *Adv. Phys. Org. Chem.* **1983**, 19, 381-428. See also Ref. 157.

¹⁵⁹Leis; Peña; Williams; Mawson *J. Chem. Soc., Perkin Trans. 2* **1988**, 157.

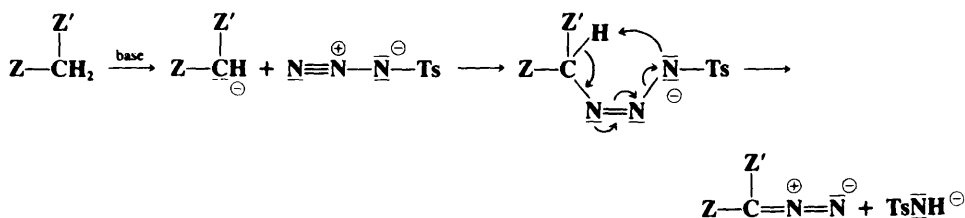
¹⁶⁰Iglesias; Williams *J. Chem. Soc., Perkin Trans. 2* **1989**, 343; Crookes; Roy; Williams *J. Chem. Soc., Perkin Trans. 2* **1989**, 1015. See also Graham; Williams *J. Chem. Soc., Chem. Commun.* **1991**, 407.

¹⁶¹Rasmussen; Hassner *J. Org. Chem.* **1974**, 39, 2558.

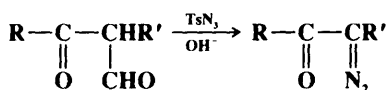
¹⁶²Kim; Park; Kim *Tetrahedron Lett.* **1989**, 30, 2833.

¹⁶³For 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 azide¹⁶⁸ 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:

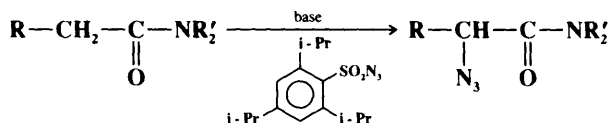


A diazo group can be introduced adjacent to a single carbonyl group indirectly by first converting the ketone to an α -formyl ketone (**0-108**) and then treating it with tosyl azide.



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 $\text{Z}-\text{CH}_2-\text{Z}'$ 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

¹⁶⁴For 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.

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

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

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

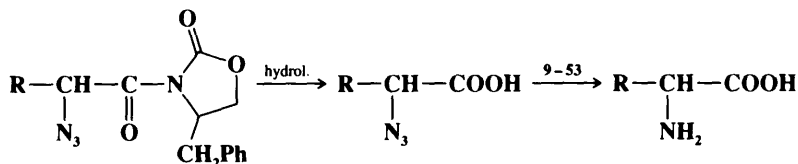
¹⁶⁸Baum; Shook; Davies; Smith *Synth. Commun.* **1987**, 17, 1709.

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

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

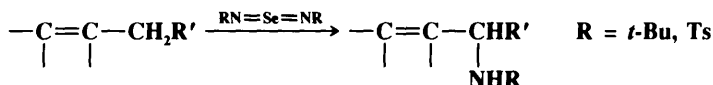
¹⁷¹Evans; Britton *J. Am. Chem. Soc.* **1987**, 109, 6881, and references cited therein.

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

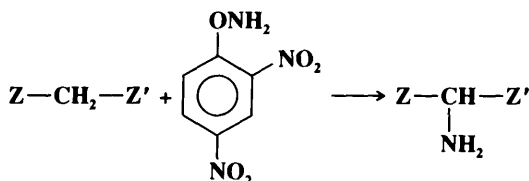


2-11 Direct Amination at an Activated Position

Alkylamino-de-hydrogenation, etc.



Alkenes can be aminated¹⁷² 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 $R = t\text{-Bu}$ 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**.

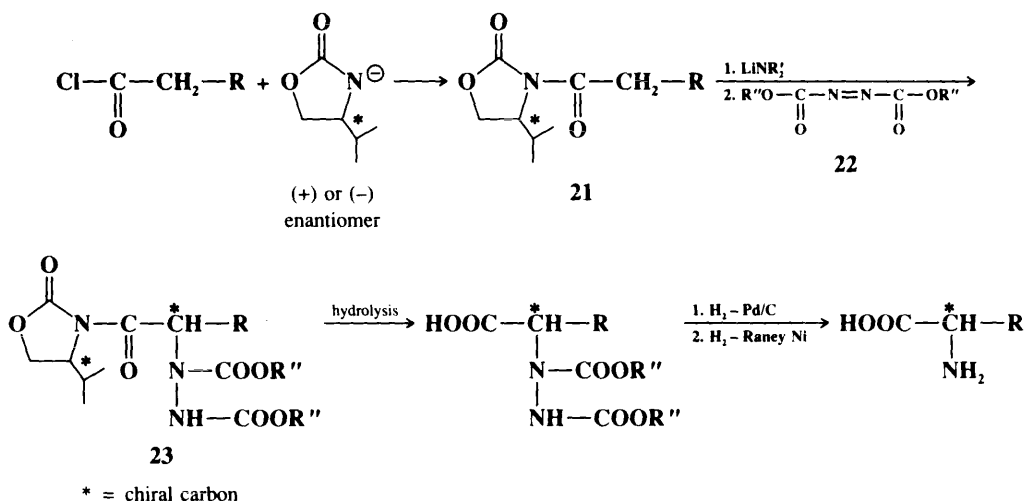
¹⁷²For a review of direct aminations, see Sheradsky, in Patai *The Chemistry of Functional Groups, Supplement F*, pt. 1; Wiley: New York, 1982, pp. 395-416.

¹⁷³Sharpless; 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.

¹⁷⁴Sharpless; 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.

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

¹⁷⁶Trimble; 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.

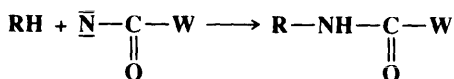


In this process the presence of a chiral carbon in **21** induces chirality at the newly formed C—N bond in **23**.

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 NCN¹⁸¹ and aryl nitrenes NAr¹⁸²) can also insert into C—H bonds, but alkyl nitrenes 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

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

¹⁷⁸For 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.

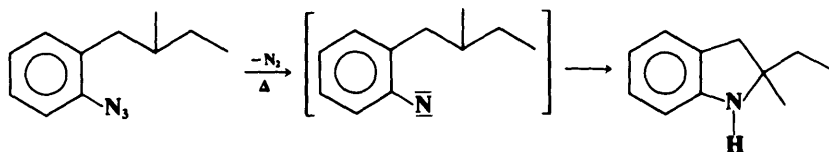
¹⁷⁹For example, see Simson; Lwowski *J. Am. Chem. Soc.* **1969**, *91*, 5107; Inagaki; Shingaki; Nagai *Chem. Lett.* **1981**, 1419.

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

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

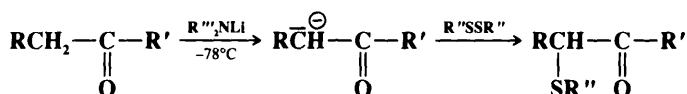
¹⁸²For a review of aryl nitrenes, see Scriven *Azides and Nitrenes*; Academic Press: New York, 1984, pp. 95-204.

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 $\text{RCH}(\text{SePh})\text{COR}'$ and α -phenylseleno esters $\text{RCH}(\text{SePh})\text{COOR}'$ can be prepared¹⁸⁸ by treatment of the corresponding enolates with PhSeBr ,¹⁸⁹ PhSeSePh ,¹⁹⁰ or benzeneseleninic anhydride $\text{PhSe}(\text{O})\text{OSe}(\text{O})\text{Ph}$.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 $\text{R}'\text{COCHRSe}^-$ ion, which is treated with MeI , producing the α -methylseleno ketone $\text{R}'\text{COCHRSeMe}$.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

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

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

¹⁸⁵Trost; Salzmann *J. Am. Chem. Soc.* **1973**, 95, 6840; Seebach; Teschner *Tetrahedron Lett.* **1973**, 5113. For discussions, see Trost *Pure Appl. 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.

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

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

¹⁸⁸For 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.

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

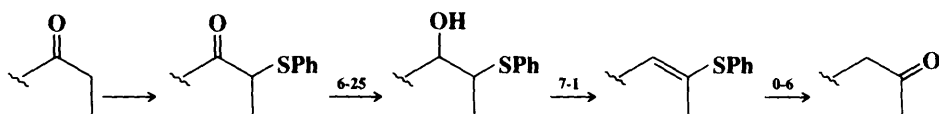
¹⁹⁰Grieco; Miyashita *J. Org. Chem.* **1974**, 39, 120. α Phenylselenation can also be accomplished with PhSeSePh , SeO_2 , and an acid catalyst: Miyoshi; Yamamoto; Kambe; Murai; Sonoda *Tetrahedron Lett.* **1982**, 23, 4813.

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

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

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

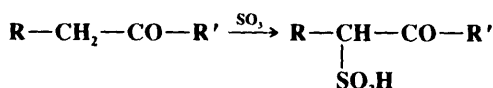
been used¹⁹⁴ as a key step in a sequence for moving the position of a carbonyl group to an adjacent carbon.¹⁹⁵



OS VI, 23, 109; 68, 8.

2-14 Sulfonation of Aldehydes, Ketones, and Carboxylic Acids

Sulfonation or Sulfo-de-hydrogenation



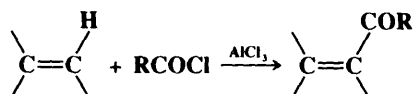
Aldehydes, ketones, and carboxylic acids containing α hydrogens can be sulfonated with sulfur trioxide.¹⁹⁶ The mechanism is presumably similar to that of 2-4. Sulfonation has also been accomplished at vinylic hydrogen.

OS IV, 846, 862.

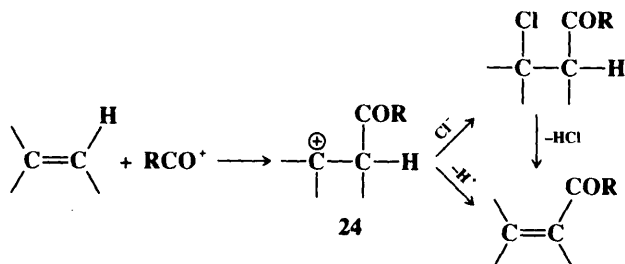
E. Carbon Electrophiles. With respect to the attacking molecule, these are nucleophilic substitutions.

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:



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

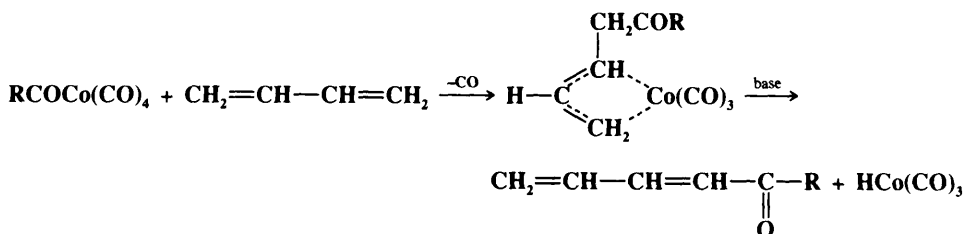
¹⁹⁵There are numerous other ways of achieving this conversion. For reviews, see Morris *Chem. Soc. Rev.* **1982**, 11, 397-434; Kane; Singh; Martin; Doyle *Tetrahedron* **1983**, 39, 345-394.

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

¹⁹⁷For 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.

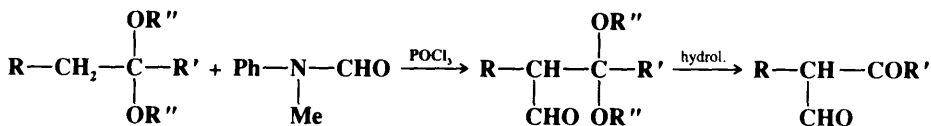
Ion **24** can either lose a proton or combine with chloride ion. If it loses a proton, the product is an unsaturated ketone; the mechanism is similar to the tetrahedral mechanism of Chapter 10, but with the charges reversed. If it combines with chloride, the product is a β -halo ketone, which can be 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: $\text{ROCH}=\text{CH}_2 \rightarrow \text{ROCH}=\text{CHCOAr}$.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,

¹⁹⁸Deno; 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**, 11-133; Grignon-Dubois; Cazaux *Bull. Soc. Chim. Fr.* **1986**, 332.

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

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

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

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

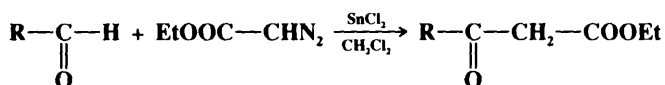
²⁰³Youssefyeh *J. Am. Chem. Soc.* **1963**, 85, 3901.

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

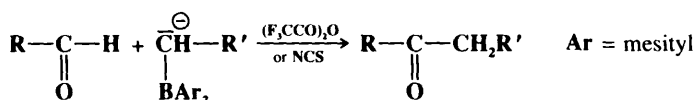
OS IV, 555, 560; VI, 744. Also see OS VI, 28.

2-16 Conversion of Aldehydes to β -Keto Esters or Ketones

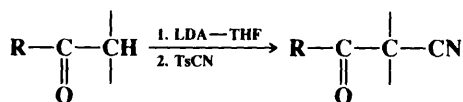
Alkoxy-carbonylalkylation or Alkoxy-carbonylalkyl-de-hydrogenation



β -Keto esters have been prepared in moderate to high yields by treatment of aldehydes with diethyl diazoacetate in the presence of a catalytic amount of a Lewis acid such as SnCl_2 , BF_3 , or GeCl_2 .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 $(\text{F}_3\text{CCO})_2\text{O}$ or N-chlorosuccinimide, to give ketones.²⁰⁶



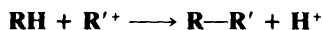
2-17 Cyanation or Cyano-de-hydrogenation



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 $\text{K}_3\text{Fe}(\text{CN})_6$.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



Alkanes can be alkylated by treatment with solutions of stable carbocations²¹¹ (p. 166), though the reaction is not generally useful for synthesis. Mixtures are usually obtained. In

²⁰⁴See, for example, van der Zeeuw; Gersmann *Recl. Trav. Chim. Pays-Bas* **1965**, 84, 1535.

²⁰⁵Holmquist; Roskamp *J. Org. Chem.* **1989**, 54, 3258.

²⁰⁶Pelter; Smith; Elgendy; Rowlands *Tetrahedron Lett.* **1989**, 30, 5643.

²⁰⁷Kahne; Collum *Tetrahedron Lett.* **1981**, 22, 5011.

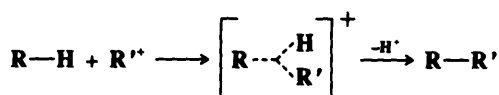
²⁰⁸Matacz; Piotrowska; Urbanski *Pol. J. Chem.* **1979**, 53, 187; Kornblum; Singh; Kelly *J. Org. Chem.* **1983**, 48, 332.

²⁰⁹Barton; Billon; Boivin *Tetrahedron Lett.* **1985**, 26, 1229.

²¹⁰Lemaire; Doussot; Guy *Chem. Lett.* **1988**, 1581. See also Hayashi; Mukaiyama *Chem. Lett.* **1987**, 1811.

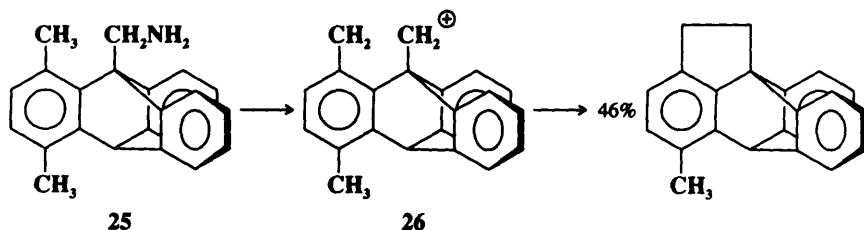
²¹¹Olah; Mo; Olah *J. Am. Chem. Soc.* **1973**, 95, 4939. For reviews, see Olah; Farooq; Prakash, in *Hill Activation and Functionalization of Alkanes*; Wiley: New York, 1989, pp. 27-78; Olah; Prakash; Sommer, Ref. 44, pp. 270-277. For a review of the thermodynamic behavior of alkanes in super-acid media, see Fabre; Devynck; Trémillon *Chem. Rev.* **1982**, 82, 591-614. See also Ref. 46.

a typical experiment, the treatment of propane with isopropyl fluoroantimonate ($\text{Me}_2\text{C}^+ \text{SbF}_6^-$) 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 ($\text{RH} + \text{R}'^+ \rightleftharpoons \text{R}^+ + \text{R}'\text{H}$) 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 $\text{C}_2\text{H}_5\text{F}$ and SbF_5 .²¹² The mechanism of alkylation can be formulated (similar to that shown in hydrogen exchange with super acids, 2-1) as

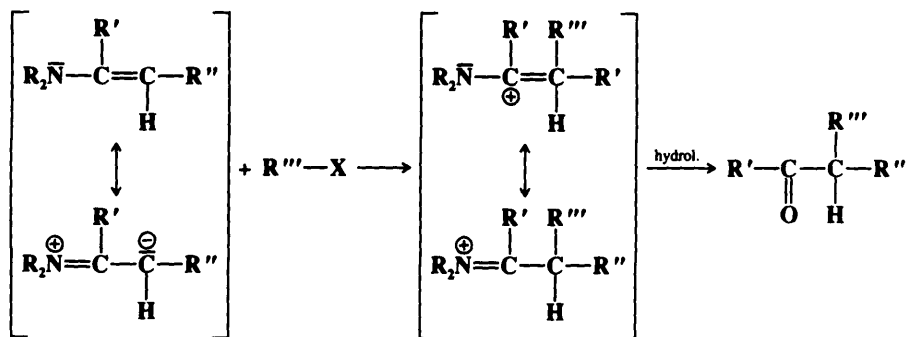


It is by means of successive reactions of this sort that simple alkanes like methane and ethane give *t*-butyl cations in super-acid solutions (p. 168).²¹³

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



2-19 The Stork Enamine Reaction α -Acylalkyl-de-halogenation²¹⁵



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

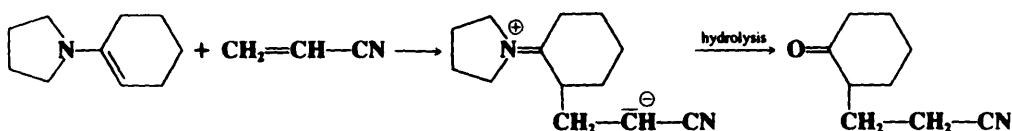
²¹³For example, see Hogeveen; Roobek *Recl. Trav. Chim. Pays-Bas* **1972**, 91, 137.

²¹⁴Yamamoto; Ōki *Chem. Lett.* **1987**, 1163.

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

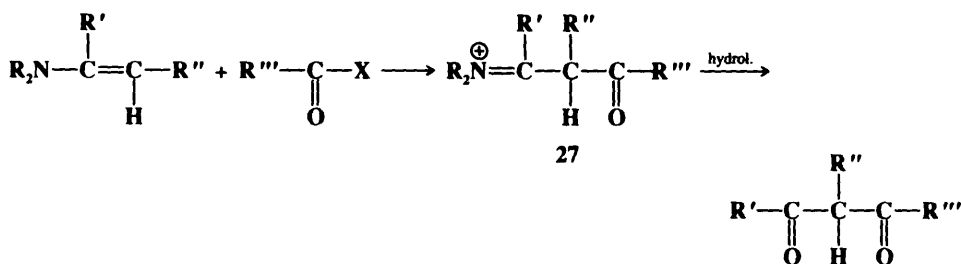
When enamines are treated with alkyl halides, an alkylation occurs that is analogous to the first step of 2-15. Hydrolysis of the imine salt gives a ketone. Since the enamine is normally formed from a ketone (6-14), the net result is alkylation of the ketone at the α position. The method, known as the *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 particularly 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.

Acylation²¹⁸ 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 chloride²²⁰ (not cyanogen bromide or iodide, which leads to halogenation of the enamine), a CHO group with the mixed anhydride of formic and acetic acids²¹⁹ or with DMF and phosgene,²²¹ and a

²¹⁶Stork; Brizzolara; Landesman; Szmuszkovicz; Terrell *J. Am. Chem. Soc.* **1963**, 85, 207. For general reviews of enamines, see Hickmott *Tetrahedron* **1964**, 40, 2989-3051, **1962**, 38, 1975-2050, 3363-3446; Granik *Russ. Chem. Rev.* **1964**, 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.

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

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

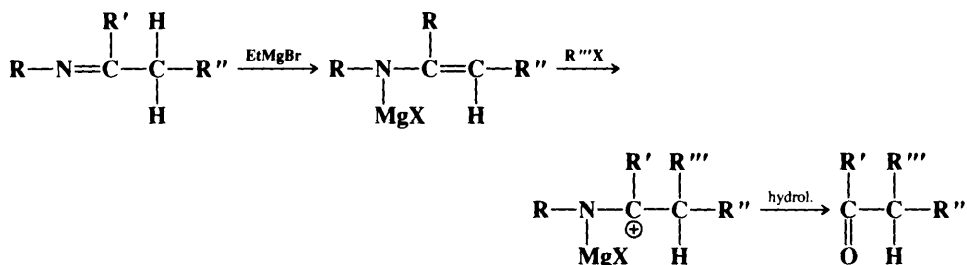
²¹⁹Stork et al., Ref. 216.

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

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

$C(R)=NR'$ group with a nitrilium salt $RC\equiv N^+R'$.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



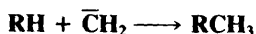
The imines are prepared by **6-14**. The enamine salt method has also been used to give good yields of mono α alkylation of α,β -unsaturated ketones.²²⁵ Enamines prepared from aldehydes and butylisobutylamine can be alkylated by simple primary alkyl halides in good yields.²²⁶ N-alkylation in this case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



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-

²²²Baudoux; Fuks *Bull. Soc. Chim. Belg.* **1984**, 93, 1009.

²²³See Alt; Cook, Ref. 216, pp. 204-215.

²²⁴Stork; Dowd *J. Am. Chem. Soc.* **1963**, 85, 2178.

²²⁵Stork; Benaim *J. Am. Chem. Soc.* **1971**, 93, 5938.

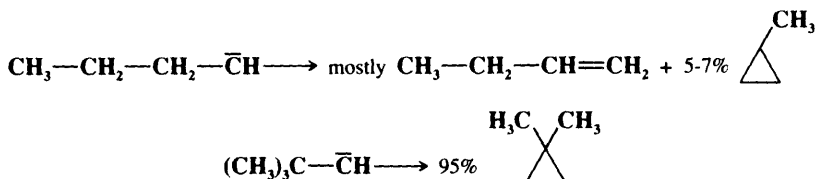
²²⁶Curphey; Hung; Chu *J. Org. Chem.* **1975**, 40, 607. See also Ho; Wong *Synth. Commun.* **1974**, 4, 147.

²²⁷For reviews, see N6agr6adi *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.

²²⁸First 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.

²²⁹Terao; Shida *Bull. Chem. Soc. Jpn.* **1964**, 37, 687.

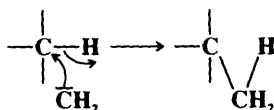
carbenes usually rearrange rather than give insertion (p. 201), but, when this is impossible, *intramolecular* insertion²³⁰ is found rather than intermolecular.²³¹



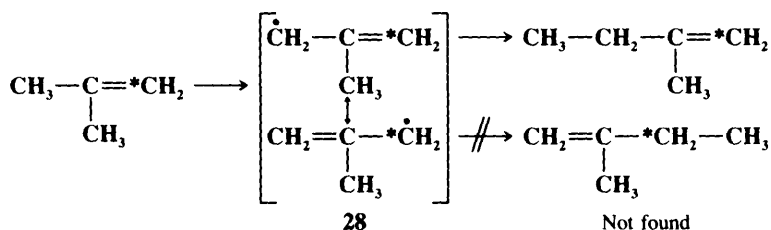
CH_2 generated by photolysis of CH_2N_2 in the liquid phase is indiscriminate—totally non-selective—in its reactivity (p. 199). CH_2 generated in other ways and other carbenes are less reactive and insert in the order tertiary > secondary > primary.²³² Halocarbenes insert much less readily, though a 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 mechanism²³⁵ 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-1-¹⁴C 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:



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

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

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

²³³For 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.

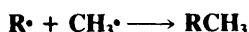
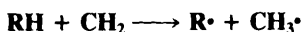
²³⁴For some examples of intramolecular carbene insertions used synthetically, see Gilbert; Giamalva; Weerasooriya *J. Org. Chem.* **1983**, *48*, 5251; Taber; Ruckle *J. Am. Chem. Soc.* **1986**, *108*, 7686; Paquette; Kobayashi; Gallucci *J. Am. Chem. Soc.* **1988**, *110*, 1305; Adams; Poupart; Grenier;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

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

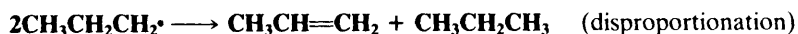
²³⁶Doering; Prinzbach *Tetrahedron* **1959**, *6*, 24.

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

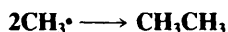
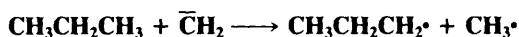
2. A free-radical process in which the carbene directly abstracts a hydrogen from the substrate to generate a pair of free radicals:



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



and



That this mechanism can take place under suitable conditions has been demonstrated by isotopic labeling²³⁹ 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 suggested²⁴² 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 signals²⁴³ (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, $\text{RCHO} + \text{CH}_2\text{N}_2 \rightarrow \text{RCOCH}_3$, while apparently similar, does not involve a free carbene intermediate. It is considered in Chapter 18 (8-9).

OS VII, 200.

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

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

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

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

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

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

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

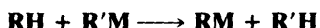
²⁴⁴Roth *J. Am. Chem. Soc.* **1972**, 94, 1761. See also Closs; Closs *J. Am. Chem. Soc.* **1969**, 91, 4549; Bethell; McDonald *J. Chem. Soc., Perkin Trans. 2* **1977**, 671.

²⁴⁵See 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



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*-BuOK²⁴⁸ 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 $\text{Me}_3\text{SiCH}_2\text{K}$ 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 $\text{Li}_3\text{CC}\equiv\text{CLi}$ 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 $\text{R}-\text{C}\equiv\text{C}-\text{H} \rightarrow \text{R}-\text{C}\equiv\text{C}-\text{MgX}$. This is the best method for the preparation of alkynyl Grignard reagents.²⁵⁸

²⁴⁶For 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; *Ducept Org. React.* **1982**, 27, 1-344; Gschwend; *Rodriguez Org. React.* **1979**, 26, 1-360; Mallan; *Bebb Chem. Rev.* **1969**, 69, 693-755.

²⁴⁷For 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.

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

²⁴⁹Eberhardt; 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.

²⁵⁰For 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.

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

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

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

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

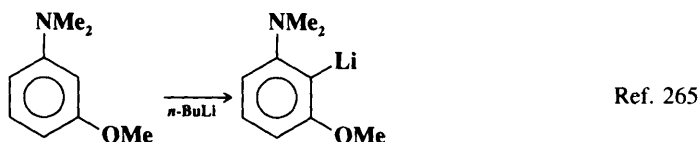
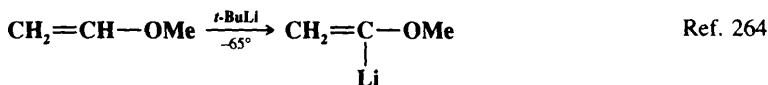
²⁵⁵Kaiser; Solter; Schwartz; Beard; Hauser *J. Am. Chem. Soc.* **1971**, 93, 4237. See also Kowalski; O'Dowd; Burke; Fields *J. Am. Chem. Soc.* **1980**, 102, 5411.

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

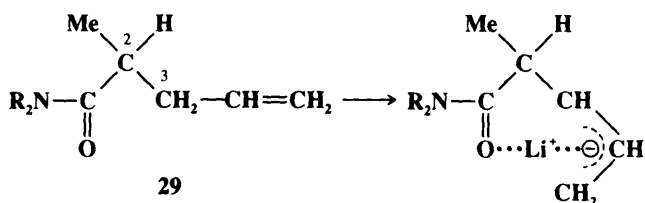
²⁵⁷For examples, see Broadbudd; Logan; Flaatt *J. Org. Chem.* **1963**, 28, 1174; Finnegan; McNees *J. Org. Chem.* **1964**, 29, 3234; Shirley; Hendrix *J. Organomet. Chem.* **1968**, 11, 217.

²⁵⁸For 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



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 $(\text{R}_2\text{N})_2\text{Mg}$.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

²⁵⁹For 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.

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

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

²⁶²For 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.

²⁶³For 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.

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

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

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

²⁶⁷Beak; 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.

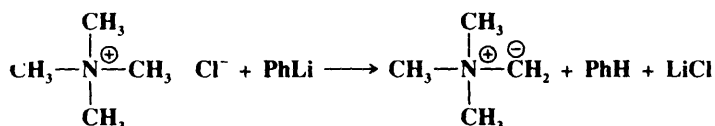
²⁶⁸Eaton; Lee; Xiong *J. Am. Chem. Soc.* **1989**, *111*, 8016.

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

R is aryl, OMe and CF₃ 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.

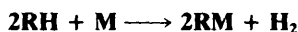
A closely related reaction is formation of nitrogen ylides from quaternary ammonium salts (see 7-7):



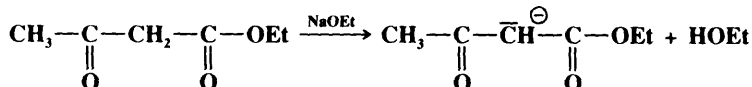
Phosphonium salts undergo a similar reaction (see 6-47).

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



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-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

²⁷⁰Bryce-Smith *J. Chem. Soc.* **1963**, 5983; Benkeser; Hooz; Liston; Trevillyan *J. Am. Chem. Soc.* **1963**, 85, 3984.

²⁷¹Bryce-Smith; Gold; Satchell *J. Chem. Soc.* **1954**, 2743; Pocker; Exner *J. Am. Chem. Soc.* **1968**, 90, 6764.

²⁷²West; Waack; Purmort *J. Am. Chem. Soc.* **1970**, 92, 840.

²⁷³For 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.

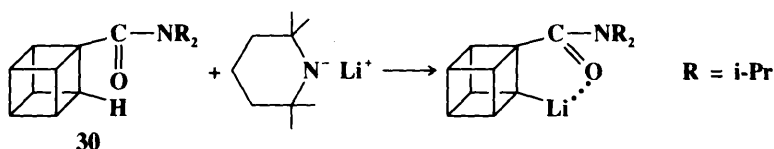
²⁷⁴For a review, see Caine, Ref. 185, vol. 1, pp. 95-145, 284-291.

²⁷⁵For a review, see Ziegenbein, in *Viehe Acetylenes*; Marcel Dekker: New York, 1969, pp. 170-185. For an improved method, see Fisch; Coisne; Figey *Synthesis* **1982**, 211.

²⁷⁶The alkali metal hydrides, LiH, NaH, and KH, when prepared in a special way, are very rapid metallation agents: Klusener; Brandsma; Verkruissje; Schleyer; Friedl; Pi *Angew. Chem. Int. Ed. Engl.* **1986**, 25, 465 [*Angew. Chem.* 98, 458].

²⁷⁷For example, see Comins; Killpack *J. Org. Chem.* **1987**, 52, 104.

²⁷⁸Eaton; Castaldi *J. Am. Chem. Soc.* **1985**, 107, 724; Jayasuriya; Alster; Politzer *J. Org. Chem.* **1987**, 52, 2306.

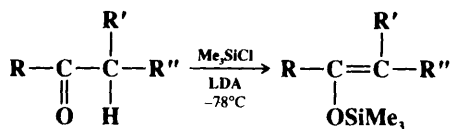


Mercuration of aromatic compounds²⁷⁹ can be accomplished with mercuric salts, most often $\text{Hg}(\text{OAc})_2$ ²⁸⁰ or $\text{Hg}(\text{ClO}_4)_2$ (to give ArHgOAc or ArHgClO_4 , respectively). This is ordinary electrophilic aromatic substitution and takes place by the arenium ion mechanism (p. 501).²⁸¹ Aromatic compounds can also be converted to arylthallium bis(trifluoroacetates) $\text{ArTl}(\text{OOCF}_3)_2$ by treatment with thallium (III) trifluoroacetate²⁸² 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

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

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

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

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

²⁸³McKillop; 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 Ussatinskii; Bregadze *Russ. Chem. Rev.* **1988**, *57*, 1054-1068; Uemura, in Hartley; Patai, Ref. 1, vol. 4, pp. 473-538.

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

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

²⁸⁶For 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.

²⁸⁷For 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.

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

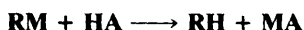
for **112** on p. 452) also give the reaction. The reaction can be applied to aldehydes by the use of the base KH in 1,2-dimethoxyethane.²⁸⁹ A particularly mild method for conversion of ketones or aldehydes to silyl enol ethers uses Me₃SiI and the base hexamethyldisilazane (Me₃Si)₂NH.²⁹⁰ Cyclic ketones can be converted to silyl enol ethers in the presence of acyclic ketones, by treatment with Me₃SiBr, tetraphenylstibonium bromide Ph₄SbBr, 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

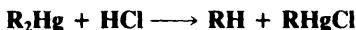
A. Hydrogen as the Electrophile

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



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 $\text{RX} \rightarrow \text{RMgX} \rightarrow \text{RH}$.

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, R₂Zn compounds react explosively with water, R₂Cd slowly, and R₂Hg 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, BR₃ compounds are completely inert to water, and GaR₃ at room temperature cleave just one R group, but AlR₃ react violently with water. However, BR₃ 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,



Organometallic compounds of less active metals and metalloids, such as silicon,²⁹⁴ antimony, bismuth, etc., are quite inert to water. Organomercury compounds (RHgX or R₂Hg) can be reduced to RH by H₂, NaBH₄, or other reducing agents.²⁹⁵ The reduction with NaBH₄

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

²⁹⁰Miller; 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.

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

²⁹²For 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.

²⁹³Brown; 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.

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

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

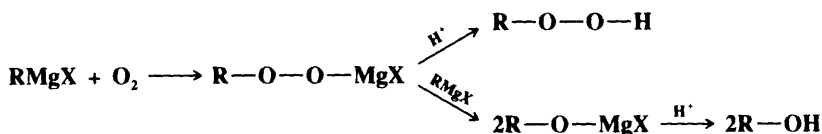
takes place by a free-radical mechanism.²⁹⁶ Alkyl-silicon bonds can be cleaved by H₂SO₄, e.g., HOOCCH₂CH₂SiMe₃ → 2CH₄ + (HOOCCH₂CH₂SiMe₂)₂O.²⁹⁷

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 Oxygen²⁹⁸ 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 H₂O₂ in acetic acid²⁹⁹ (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 RBCl₂ 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-dimetallc compounds R₂C(SnMe₃)ZnBr were oxidized by dry air at -10 to 0°C in the presence of Me₃SiCl to give aldehydes or ketones R₂C=O.³⁰⁴

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

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

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

²⁹⁸For 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.

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

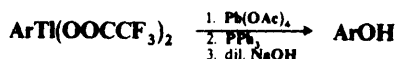
³⁰⁰Parker; Koziski *J. Org. Chem.* **1987**, 52, 674. For other reagents, see Taddei; Ricci *Synthesis* **1986**, 633; Einhorn; Luche; Demerseman *J. Chem. Soc., Chem. Commun.* **1988**, 1350.

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

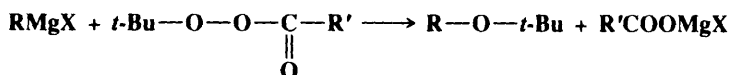
³⁰²Moersch; Zwiesler *Synthesis* **1971**, 647; Adam; Cueto *J. Org. Chem.* **1977**, 42, 38.

³⁰³Lamb; 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.

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

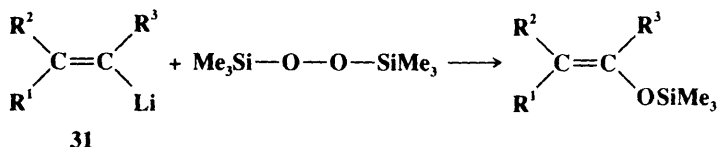
2-26 Conversion of Arylthallium Compounds to Phenols**Hydroxy-de-(bistrifluoroacetoxy)thallation**

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 $\text{ArH} \rightarrow \text{ArOH}$. Diarylthallium trifluoroacetates undergo the same reaction.³⁰⁶

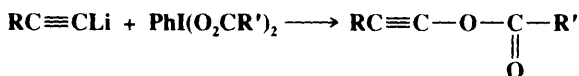
2-27 Reaction Between Organometallic Reagents and Peroxides***t*-Butoxy-de-metallation**

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



(**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



OS V, 642, 924.

³⁰⁵Taylor; Altland; Danforth; McGillivray; McKillop *J. Am. Chem. Soc.* **1970**, 92, 3520.

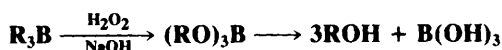
³⁰⁶Taylor; Altland; McKillop *J. Org. Chem.* **1975**, 40, 2351.

³⁰⁷Lawesson; 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.

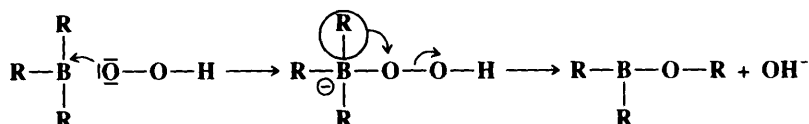
³⁰⁸Longone; Miller *Tetrahedron Lett.* **1967**, 4941.

³⁰⁹Davis; Lal; Wei *Tetrahedron Lett.* **1988**, 29, 4269.

³¹⁰Stang; Boeshar; Wingert; Kitamura *J. Am. Chem. Soc.* **1988**, 110, 3272.

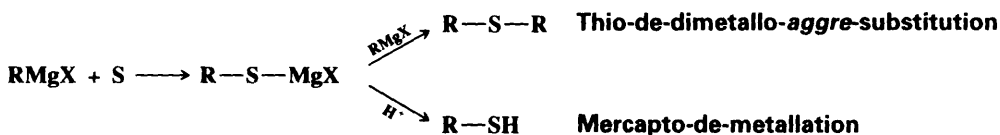
2-28 Oxidation of Trialkylboranes to Borates

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

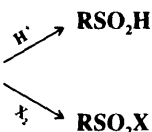
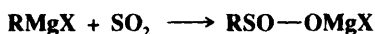
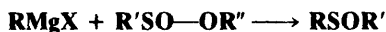


The other two R groups then similarly migrate. Retention of configuration is observed in R. Boranes can also be oxidized to borates in good yields with oxygen,³¹² with sodium perborate NaBO_3 ,³¹³ with sodium percarbonate ($\text{Na}_2\text{CO}_3 \cdot \frac{3}{2}\text{H}_2\text{O}_2$),³¹⁴ and with trimethylamine oxide, either anhydrous³¹⁵ 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



³¹¹For 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.

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

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

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

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

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

³¹⁷Mirviss *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.

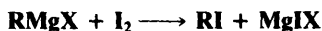
³¹⁸For reviews of the reactions in this section, see Wardell; Paterson, Ref. 298, pp. 316-323; Wardell, in Patai *The Chemistry of the Thiol Group*, pt. 1; Wiley: New York, 1974, pp. 211-215; Wakefield, Ref. 273, pp. 135-142.

and other organometallic compounds³¹⁹ react with sulfonyl chloride to give sulfonyl chlorides,³²⁰ with esters of sulfinic acids to give (stereospecifically) sulfoxides,³²¹ with disulfides to give sulfides,³²² and with SO₂ to give sulfinic acid salts³²³ 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



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 Cl₂ 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 FClO₃³²⁶ (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 $\text{RC}\equiv\text{CH} \rightarrow \text{RC}\equiv\text{CX}$. Trialkylboranes react rapidly with I₂³²⁹ or Br₂³³⁰ in the presence of NaOMe in methanol, or with FeCl₃ or other reagents³³¹ 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 catecholborane³³³ (5-12) followed by hydrolysis, react with I₂ in the presence of NaOH at 0°C in ethereal solvents to give *trans* vinylic iodides.³³⁴ This is an indirect way of accom-

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

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

³²¹Harrp; Vines; Montillier; Chan *J. Org. Chem.* **1976**, *41*, 3987.

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

³²³For a review of the reactions of organometallic compounds with SO₂, see Kitching; Fong *Organomet. Chem. Rev., Sect. A* **1970**, *5*, 281-321.

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

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

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

³²⁷For 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.

³²⁸For 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; Verkruisje *Synthesis* **1990**, 984.

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

³³⁰Brown; 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.

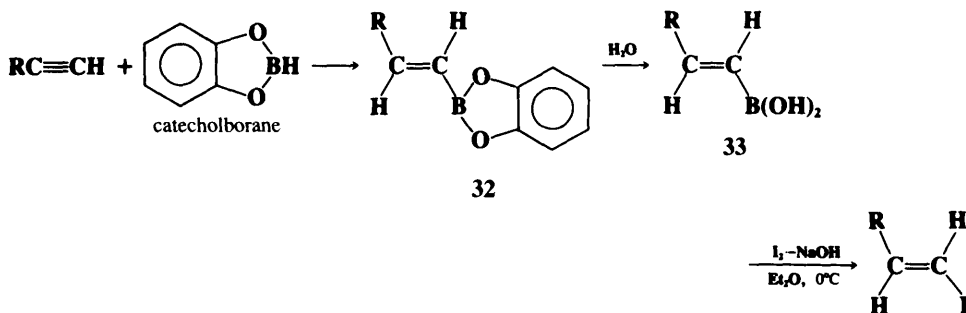
³³¹Nelson; Soundararajan *J. Org. Chem.* **1988**, *53*, 5664. For other reagents, see Jigajinni; Paget; Smith *J. Chem. Res., (S)* **1981**, 376; Brown; De Lue *Tetrahedron* **1988**, *44*, 2785.

³³²Suzuki; 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.

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

³³⁴Brown; 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 silanes³³⁸ and from vinylic aluminum³³⁹ 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 iodides³⁴² and fluorides can be prepared from arylthallium bis(trifluoroacetates) (see 2-22), indirectly achieving the conversions $\text{ArH} \rightarrow \text{ArI}$ and $\text{ArH} \rightarrow \text{ArF}$. 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 $\text{ArPb}(\text{OAc})_3$ 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

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

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

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

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

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

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

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

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

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

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

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

³⁴⁶Adam; 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.

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

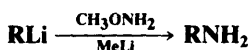
³⁴⁸For reviews of the mechanisms, see Abraham; Grellier, Ref. 327; Abraham, Ref. 2, pp. 135-177; Jensen; Rickborn, Ref. 2, pp. 75-97.

inversion of configuration (see p. 572), indicating an S_N2 (back) mechanism, while in other cases retention of configuration has been shown,³⁴⁹ implicating an S_N2 (front) or S_Ni 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



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 $\text{CH}_3\text{ONHR}'$.³⁵⁴ There is evidence³⁵⁵ that the mechanism involves the direct displacement of OCH_3 by R on an intermediate $\text{CH}_2\text{ONR}'^-$ ($\text{CH}_3\text{ONR}'^- \text{Li}^+ + RLi \rightarrow \text{CH}_3\text{OLi} + \text{RNR}'^- \text{Li}^+$). 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 initial product is a triazene (in this case $\text{ArNH}=\text{NHCH}_2\text{SPh}$ 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



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

³⁵⁰See, 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.

³⁵¹For a review of methods for achieving the conversion $\text{RM} \rightarrow \text{RNH}_2$, see Erdik; Ay *Chem. Rev.* **1989**, 89, 1947-1980.

³⁵²For 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.

³⁵³Beak; 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.

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

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

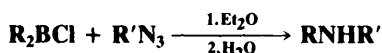
³⁵⁶See, for example, Spagnolo; Zanirato; Gronowitz *J. Org. Chem.* **1982**, 47, 3177; Reed; Snieckus *Tetrahedron Lett.* **1983**, 24, 3795. For other azides, see Hassner; Munger; Belinka *Tetrahedron Lett.* **1982**, 23, 699; Mori; Aoyama; Shioiri *Tetrahedron Lett.* **1984**, 25, 429.

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

³⁵⁸Kabalka; Sastry; McCollum; Yoshioka *J. Org. Chem.* **1981**, 46, 4296; Kabalka; Wang; Goudgaon *Synth. Commun. Organometallics* **1989**, 8, 1093; *Synth. Commun.* **1990**, 20, 231.

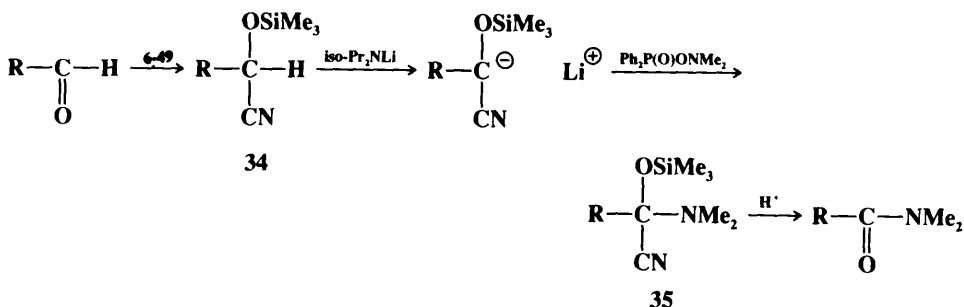
³⁵⁹Brown; Heydkamp; Breuer; Murphy *J. Am. Chem. Soc.* **1964**, 86, 3565.

hydroxylamine-O-sulfonic acid in diglyme,³⁶⁰ and trimethylsilyl azide³⁶¹ 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 prepared³⁶² by the treatment of alkyl- or aryldichloroboranes or dialkylchloroboranes with alkyl or aryl azides.



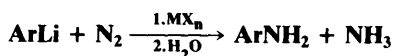
The use of an optically active RBCl_2 gave secondary amines of essentially 100% optical purity.³⁶³ In other methods, trialkylboranes R_3B gave secondary amines $\text{RR}'\text{NH}$ upon treatment with N-chloroamines $\text{R}'\text{NHCl}$,³⁶⁴ and aryllead triacetates $\text{ArPb}(\text{OAc})_3$ give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



OS VI, 943.

³⁶⁰Rathke; 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.

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

³⁴²Brown; Midland; Levy; Suzuki; Sono; Itoh *Tetrahedron* **1987**, 43, 4079; Carboni; Vaultier; Courgeon; Carrié *Bull. Soc. Chim. Fr.* **1989**, 844.

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

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

³⁴⁶Barton; Donnelly; Finet; Guiry *Tetrahedron Lett.* **1989**, 30, 1377.

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

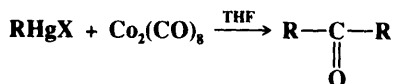
³⁶⁷Yamamoto; Maruoka *J. Org. Chem.* **1980**, *45*, 2739.

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

³⁰ Dodonov; Gushchin; Brilkina Zh. *Obshch. Khim.* **1985**, 55, 466 [*Chem. Abstr.* 107, 22218z]; Barton; Finet; Khamsi *Tetrahedron Lett.* **1986**, 27, 3615; Barton; Yadav-Bhatnagar; Finet; Khamsi *Tetrahedron Lett.* **1987**, 28, 3111.

³⁷⁰Vol'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.

Symmetrical ketones³⁷¹ can be prepared in good yields by the reaction of organomercuric halides³⁷² 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 $\text{Co}_2(\text{CO})_8$ reaction, though the $\text{Ni}(\text{CO})_4$ reaction seems to be free from such rearrangements.³⁷⁴ Divinyl 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 $\text{Ar}'\text{I}$, unsymmetrical diaryl ketones can be obtained.³⁷⁴ In a more general synthesis of unsymmetrical ketones, tetraalkyltin compounds R_4Sn are treated with a halide $\text{R}'\text{X}$ ($\text{R}' = \text{aryl, vinylic, benzylic}$), CO, and a Pd complex catalyst.³⁷⁶ Similar reactions use Grignard reagents, $\text{Fe}(\text{CO})_5$, 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 alkyl lithium 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-

³⁷¹For 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.

³⁷²For 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].

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

³⁷⁴Hirota; 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.

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

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

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

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

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

³⁸⁰Sato; 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.

³⁸¹Ryang; 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.

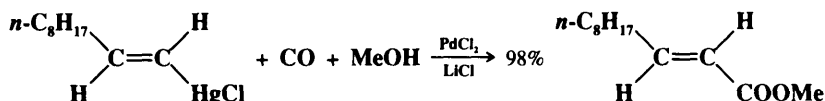
³⁸²Ryang; Tsutsumi *Bull. Chem. Soc. Jpn.* **1962**, 35, 1121; Ryang; Sawa; Hasimoto; Tsutsumi *Bull. Chem. Soc. Jpn.* **1964**, 37, 1704; Trzupek; Newirth; Kelly; Sbarbati; Whitesides *J. Am. Chem. Soc.* **1973**, 95, 8118.

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

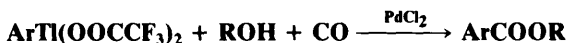
³⁸⁴Zweifel; Lynd *Synthesis* **1976**, 625.

³⁸⁵Miyaura; 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

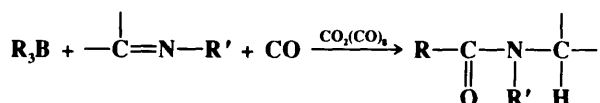


Arylthallium bis(trifluoroacetates) (see 2-22) can be carbonylated with CO, an alcohol, and a PdCl₂ catalyst to give esters:³⁸⁷



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

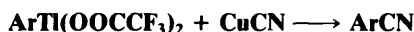


In another method for the conversion $\text{RM} \rightarrow \text{RCONR}'_2$, Grignard reagents and organolithium compounds are treated with a formamide HCONR'_2 to give the intermediate $\text{RCH}(\text{OM})\text{NR}'_2$, which is not isolated, but treated with PhCHO or Ph_2CO to give the product RCONR'_2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

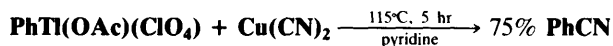
See also reactions 0-102, 5-21, 6-70, and 8-24 to 8-26.

OS 68, 116.

2-33 Cyano-de-metallation



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 $\text{ArTl}(\text{CN})_3^-$ in the presence of excess KCN.³⁰⁵ Alternatively, arylthallium acetates react with $\text{Cu}(\text{CN})_2$ or CuCN to give aryl nitriles, e.g.³⁹³



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

³⁸⁶Larock *J. Org. Chem.* **1975**, *40*, 3237.

³⁸⁷Larock; Fellows *J. Am. Chem. Soc.* **1982**, *104*, 1900.

³⁸⁸Baird; Hartgerink; Surridge *J. Org. Chem.* **1985**, *50*, 4601.

³⁸⁹Yamashita; Suemitsu *Tetrahedron Lett.* **1978**, 1477.

³⁹⁰Alper; Amaratunga *J. Org. Chem.* **1982**, *47*, 3593.

³⁹¹Screttas; Steele *J. Org. Chem.* **1988**, *53*, 5151.

³⁹²Taylor; Katz; McKillop *Tetrahedron Lett.* **1984**, *25*, 5473.

³⁹³Uemura; Ikeda; Ichikawa *Tetrahedron* **1972**, *28*, 3025.

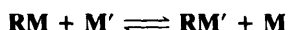
³⁹⁴Westmijze; Vermeer *Synthesis* **1977**, 784.

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 $RM \rightarrow RC$, see 0-86 to 0-107, which are discussed under nucleophilic substitutions in Chapter 10. See also 6-69.

G. Metal Electrophiles

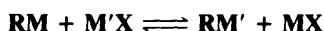
2-34 Transmetallation with a Metal Metallo-de-metallation



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 alkyls³⁷² 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



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,

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

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

³⁹⁷For 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.

³⁹⁸BuNa 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.

³⁹⁹For 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.

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

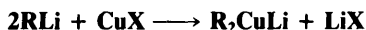
⁴⁰¹For a review of the use of activated zinc, see Erdik *Tetrahedron* **1987**, 43, 2203-2212.

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

⁴⁰³For 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



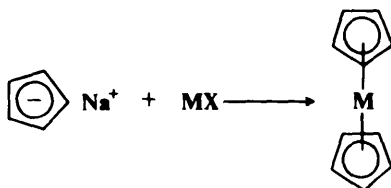
Another way is to dissolve an alkylcopper compound in an alkyllithium solution.

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.,



However, it is not always possible: $\text{RMgX} + \text{BF}_3$ 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:



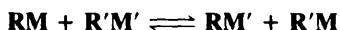
Among others, metallocenes of Sc, Ti, V, Cr, Mn, Fe, Co, and Ni have been prepared in this manner.⁴⁰⁷

Metal nitrates are sometimes used instead of halides.

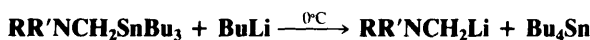
OS **I**, 231, 550; **III**, 601; **IV**, 258, 473, 881; **V**, 211, 496, 727, 918, 1001; **VI**, 776, 875, 1033; **VII**, 236, 290, 524; **65**, 61, 108; **67**, 20, 86, 125; **68**, 104, 182. Also see OS **IV**, 476

2-36 Transmetalation with an Organometallic Compound

Metallo-de-metalation



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 vinyl lithium from phenyllithium and tetravinyltin and the formation of α -dialkylamino organolithium compounds from the corresponding organotin compounds⁴⁰⁹



⁴⁰⁴For 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.

⁴⁰⁵For 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.

⁴⁰⁶House; 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.

⁴⁰⁷For 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.

⁴⁰⁸For 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.

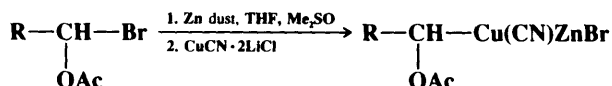
⁴⁰⁹Peterson *J. Am. Chem. Soc.* **1971**, *93*, 4027; Peterson; Ward *J. Organomet. Chem.* **1974**, *66*, 209; Pearson; Lindbeck *J. Org. Chem.* **1989**, *54*, 5651.

The reaction has also been used to prepare 1,3-dilithiopropanes⁴¹⁰ and 1,1-dilithio-methylenecyclohexane⁴¹¹ 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 S_Ei 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



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

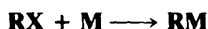
A. Hydrogen as the Electrophile

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



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 $\text{I} > \text{Br} > \text{Cl}$. 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

⁴¹⁰Seetz; Schat; Akkerman; Bickelhaupt *J. Am. Chem. Soc.* **1982**, 104, 6848.

⁴¹¹Maercker; Dujardin *Angew. Chem. Int. Ed. Engl.* **1984**, 23, 224 [*Angew. Chem.* 96, 222].

⁴¹²Seyferth; Vaughan *J. Am. Chem. Soc.* **1964**, 86, 883; Sawyer; Kucerozy; Macdonald; McGarvey *J. Am. Chem. Soc.* **1988**, 110, 842.

⁴¹³Dessy; Kaplan; Coe; Salinger *J. Am. Chem. Soc.* **1963**, 85, 1191.

⁴¹⁴Behling; Babiak; Ng; Campbell; Moretti; Koerner; Lipshutz *J. Am. Chem. Soc.* **1988**, 110, 2641.

⁴¹⁵Chou; Knochel *J. Org. Chem.* **1990**, 55, 4791.

⁴¹⁶For reviews, see Massey; Humphries *Aldrichimica Acta* **1989**, 22, 31-38; Negishi, Ref. 1, pp. 30-37; Rochow *J. Chem. Educ.* **1966**, 43, 58-62.

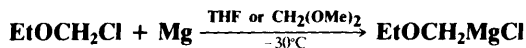
⁴¹⁷For reviews, see Raston; Salem, in Hartley; Patai, Ref. 1, vol. 4, pp. 159-306, pp. 162-175; Kharasch; Reinmuth, Ref. 404, pp. 5-91.

⁴¹⁸Pearson; 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.

Dihalides⁴²⁴ 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., $\text{BrMg}(\text{CH}_2)_4\text{MgBr}$.⁴²⁵ 1,2-Dihalides give elimination⁴²⁶ 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 $\text{CH}_2(\text{MgBr})_2$, 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 $\text{C}=\text{O}$, $\text{C}\equiv\text{N}$, 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 ethers⁴³⁰ can only be formed in THF or dimethoxymethane at a low temperature, e.g.,⁴³¹



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

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

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

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

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

⁴²³Baker; 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.

⁴²⁴For 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].

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

⁴²⁶For 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].

⁴²⁷For 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.

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

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

⁴³⁰For 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.

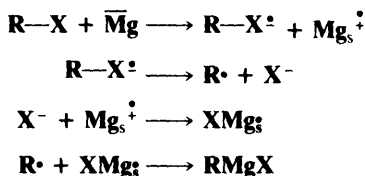
⁴³¹For example, see Normant; Castro, *C. R. Acad. Sci.* **1963**, 257, 2115, **1964**, 259, 830; Castro *Bull. Soc. Chim. Fr.* **1967**, 1533, 1540, 1547; Taeger; Kahlert; Walter *J. Prakt. Chem.* **1965**, [4] 28, 13.

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-dioxahexyl)amine $\text{N}(\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3)_3$.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 vapor⁴³⁶ 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 CIDNP⁴⁴⁴ (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



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

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

⁴³⁴Boudin; Cerveau; Chuit; Corriu; Rey *Tetrahedron* **1989**, 45, 171.

⁴³⁵For 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.

⁴³⁶For 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.

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

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

⁴³⁹Rieke; 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.

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

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

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

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

⁴⁴⁴Bodewitz; 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.

⁴⁴⁵See, 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.

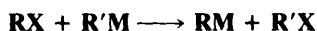
⁴⁴⁶Root; Hill; Lawrence; Whitesides *J. Am. Chem. Soc.* **1989**, 111, 5405.

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

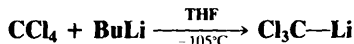
The species $R-X^\bullet$ and Mg^\bullet are radical ions.⁴⁴⁸ The subscript "s" is meant to indicate that the species so marked are bound to the surface of the magnesium. It has been suggested that some of the R^\bullet radicals diffuse from the magnesium surface into the solution and then return to the surface to react with the XMg^\bullet . There is evidence both for⁴⁴⁹ and against⁴⁵⁰ this suggestion. Another proposal is that the fourth step is not the one shown here, but that the R^\bullet 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.

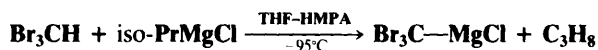
2-39 Replacement of a Halogen by a Metal from an Organometallic Compound Metallo-de-halogenation



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



Such compounds can also be prepared by hydrogen-metal exchange, e.g.,⁴⁵⁸



⁴⁴⁸For 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.

⁴⁴⁹Garst; 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.

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

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

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

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

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

⁴⁵⁵For 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.

⁴⁵⁶For 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.

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

⁴⁵⁸Villieras *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 ($\sim -100^\circ\text{C}$) 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 -magnesium sulfones $\text{ArSO}_2\text{CH}(\text{Cl})\text{MgBr}$ 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 mechanism⁴⁶¹ of the reaction of alkyllithium compounds with alkyl and aryl iodides involves free radicals.⁴⁶²



Solvent cage

Among the evidence is the obtention of coupling and disproportionation products from $\text{R}\cdot$ and $\text{R}'\cdot$ and the observation of CIDNP.⁴⁶³ However, in the degenerate exchange between PhI and PhLi the ate complex $\text{Ph}_2\text{I}^- \text{Li}^+$ 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.,



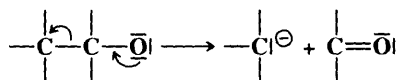
Most of the evidence is in accord with a free radical mechanism involving electron transfer, though an $\text{S}_\text{N}2$ mechanism can compete under some conditions.⁴⁶⁶

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 ($\text{S}_\text{E}1$). 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; Bowersdorf *J. Chem. Soc., Chem. Commun.* **1991**, 195; Schmidt; Köbrich; Hoffmann *Chem. Ber.* **1991**, 124, 1253; Hoffmann; Bowersdorf *Chem. Ber.* **1991**, 124, 1259.

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

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

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

⁴⁶²Ward; 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.

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

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

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

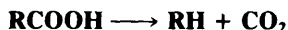
⁴⁶⁶See San Filippo; Silbermann *J. Am. Chem. Soc.* **1982**, 104, 2831; Ashby; Su; Pham *Organometallics* **1985**, 4, 1493; Alnajjar; Kuivila *J. Am. Chem. Soc.* **1985**, 107, 416.

⁴⁶⁷For 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



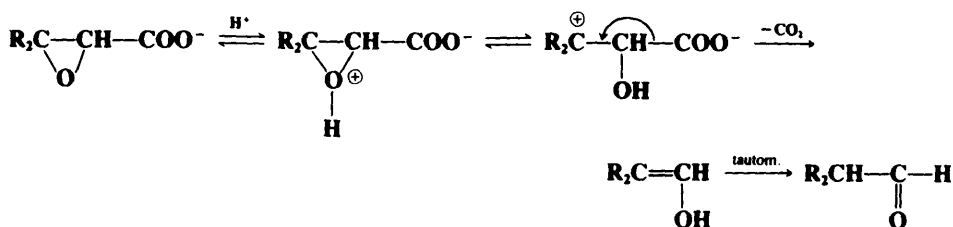
Many carboxylic acids can be successfully decarboxylated, either as the free acid or in the salt form, but not simple fatty acids.⁴⁶⁸ An exception is acetic acid, which as the acetate, heated with base, gives good yields of methane. Aliphatic acids that do undergo successful decarboxylation have certain 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	$\text{HOOC}-\underset{\textstyle }{\text{C}}-\text{COOH}$	$\text{HOOC}-\underset{\textstyle }{\text{C}}-\text{H}$
α -Cyano	$\text{NC}-\underset{\textstyle }{\text{C}}-\text{COOH}$	$\text{NC}-\underset{\textstyle }{\text{C}}-\text{H}$ or $\text{HOOC}-\underset{\textstyle }{\text{C}}-\text{H}$
α -Nitro	$\text{O}_2\text{N}-\underset{\textstyle }{\text{C}}-\text{COOH}$	$\text{O}_2\text{N}-\underset{\textstyle }{\text{C}}-\text{H}$
α -Aryl	$\text{Ar}-\underset{\textstyle }{\text{C}}-\text{COOH}$	$\text{Ar}-\underset{\textstyle }{\text{C}}-\text{H}$
α,α,α -Trihalo	$\text{X}_3\text{C}-\text{COOH}$	X_3CH
β -Keto	$\begin{array}{c} \text{---C---C---COOH} \\ \quad \\ \text{O} \end{array}$	$\begin{array}{c} \text{---C---C---H} \\ \quad \\ \text{O} \end{array}$
β,γ -Unsaturated	$\begin{array}{c} \text{---C=C---C---COOH} \\ \quad \quad \end{array}$	$\begin{array}{c} \text{---C=C---C---H} \\ \quad \quad \end{array}$

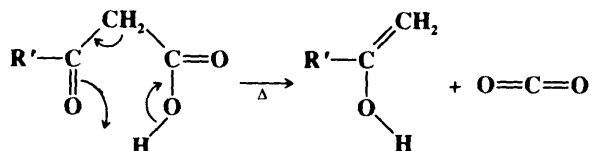
⁴⁶⁸March J. *Chem. Educ.* **1963**, 40, 212.

⁴⁶⁹Singh; Kagan J. *Org. Chem.* **1970**, 35, 2203.

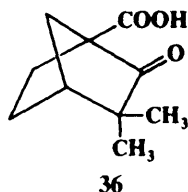


The direct product is an enol that tautomerizes to the aldehyde.⁴⁷⁰ This is the usual last step in the Darzens reaction (6-45).

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 S_E1 or S_E2. In the case of the S_E1 mechanism, the reaction is of course aided by the presence of electron-withdrawing groups, which stabilize the carbanion.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 acids⁴⁷⁶ 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



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

⁴⁷¹For 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.

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

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

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

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

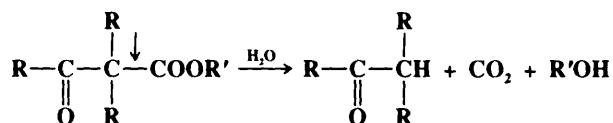
⁴⁷⁶Bigley; Clarke *J. Chem. Soc., Perkin Trans. 2* **1982**, *1*, and references cited therein. For a review, see Smith; Kelly, *Prog. Phys. Org. Chem.* **1971**, *8*, 75-234, pp. 150-153.

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

⁴⁷⁸Wasserman, 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 S_E1 or S_E2 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 water⁴⁸¹), and is not subject to acid catalysis.⁴⁸² The rate of decarboxylation of a β,γ-unsaturated acid was increased about 10⁵-10⁶ times by introduction of a β-methoxy group, indicating that the cyclic transition state has dipolar character.⁴⁸³

β-Keto acids⁴⁸⁴ 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 CR₂ group (2-43). β-Keto esters can be decarbalkoxylated without passing through the free-acid stage by treatment with boric anhydride B₂O₃ 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, Na₃PO₄, 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 Bu₃SnH.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 + CO₂.⁴⁹¹

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

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

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

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

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

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

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

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

⁴⁸⁷For 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; Dehmloew; Kunesch *Synthesis* **1985**, 320; Taber; Amedio; Gulino *J. Org. Chem.* **1989**, 54, 3474.

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

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

⁴⁹⁰See 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.

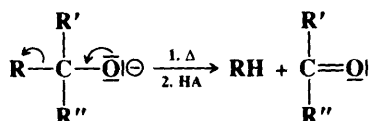
⁴⁹¹For reviews, see Deacon *Organomet. Chem. Rev. A* **1970**, 355-372; Deacon; Faulks; Pain *Adv. Organomet. Chem.* **1986**, 25, 237-276.

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

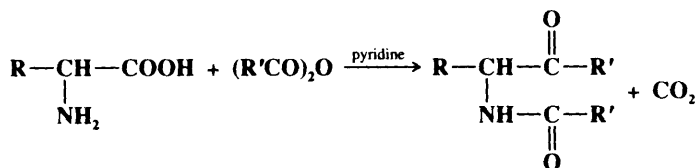


Alkoxides of tertiary alcohols can be cleaved in a reaction that is essentially the reverse of addition of carbanions to ketones (**6-29**).⁴⁹² The reaction is unsuccessful when the R groups are simple unbranched alkyl groups, e.g., the alkoxide of triethylcarbinol. Cleavage is accomplished with branched 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



⁴⁹²Zook; 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.

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

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

⁴⁹⁵Partington; Watt *J. Chem. Soc., Perkin Trans. 2* **1988**, 983.

⁴⁹⁶Tumas; Foster; Brauman *J. Am. Chem. Soc.* **1988**, *110*, 2714; Ibrahim; Watt; Wilson; Moore *J. Chem. Soc., Chem. Commun.* **1989**, 161.

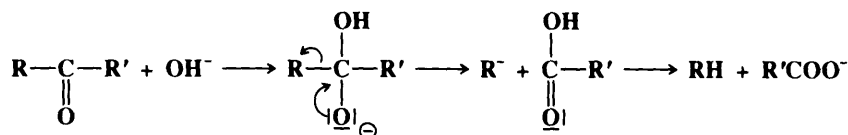
⁴⁹⁷Paquette; Gilday; Maynard *J. Org. Chem.* **1989**, *54*, 5044; Paquette; Maynard *J. Org. Chem.* **1989**, *54*, 5054.

⁴⁹⁸See 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 $\text{RCH}(\text{NHR}')\text{COOH}$ give the corresponding N-alkylated products.

OS IV, 5; V, 27.

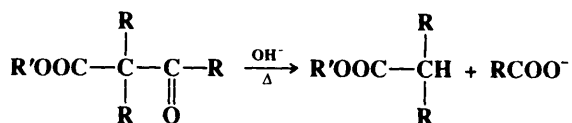
B. Acyl Cleavages. In these reactions (2-43 to 2-46) a carbonyl group is attacked by a hydroxide ion (or amide ion), giving an intermediate that undergoes cleavage to a carboxylic acid (or an amide). With respect to the leaving group, this is nucleophilic substitution at a carbonyl group and the mechanism is the tetrahedral one discussed in Chapter 10.



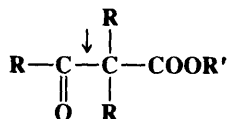
With respect to R this is of course electrophilic substitution. The mechanism is usually SE_1 .

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

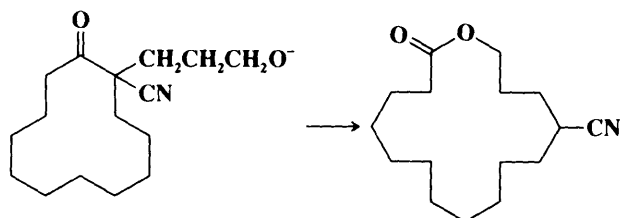


products are a carboxylic ester and the salt of an acid. However, the utility of the reaction is somewhat limited by the fact that decarboxylation is a side reaction, even under basic conditions. β -Diketones behave similarly to give a ketone and the salt of a carboxylic acid. With both β -keto esters 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

⁴⁹⁹For a review, see Buchanan *Chem. Soc. Rev.* **1988**, 17, 91-109.

⁵⁰⁰Allinger; Wang; Dewhurst *J. Org. Chem.* **1974**, 39, 1730.

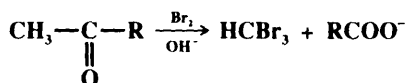
cyclic α -cyano ketones, in an intramolecular fashion, has been used to effect a synthesis of macrocyclic lactones, e.g.,⁵⁰¹



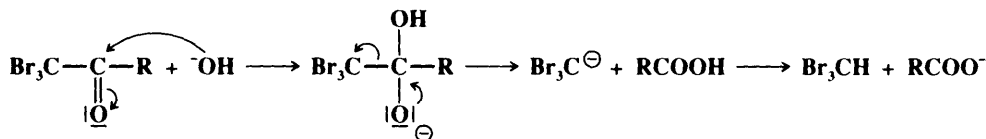
Activated F^- (from KF and a crown ether) has been used as the base to cleave an α -cyano ketone.⁵⁰²

OS II, 266, 531; III, 379; IV, 415, 957; V, 179, 187, 277, 533, 747, 767.

2-44 Haloform Reaction



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

⁵⁰¹Milenkov; Hesse *Helv. Chim. Acta* **1987**, 70, 308. For a similar preparation of lactams, see Wälschli; Bienz; Hesse *Helv. Chim. Acta* **1985**, 68, 484.

⁵⁰²Beletskaya; Gulyukina; Borodkin; Solov'yanov; Reutov *Doklad. Chem.* **1984**, 276, 202. See also Mignani; Morel; Grass *Tetrahedron Lett.* **1987**, 28, 5505.

⁵⁰³For 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.

⁵⁰⁴For 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.

⁵⁰⁵Pocker *Chem. Ind. (London)* **1959**, 1383.

⁵⁰⁶Levine; Stephens *J. Am. Chem. Soc.* **1950**, 72, 1642.

⁵⁰⁷See Hudlicky *Chemistry of Organic Fluorine Compounds*, 2nd ed.; Ellis Horwood: Chichester, 1976, pp. 276-278.

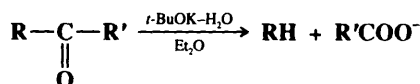
⁵⁰⁸Guthrie; Cossar *Can. J. Chem.* **1990**, 68, 1640.

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

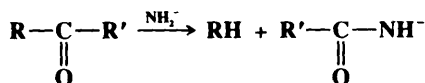


Ordinary ketones are generally much more difficult to cleave than trihalo ketones or β -diketones, because the carbanion intermediates in these cases are more stable than simple carbanions. However, nonenolizable ketones can be cleaved by treatment with a 10:3 mixture of $t\text{-BuOK}-\text{H}_2\text{O}$ in an aprotic solvent such as ether, dimethyl sulfoxide, 1,2-dimethoxyethane (glyme), etc.,⁵¹⁰ or with solid $t\text{-BuOK}$ 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 strain).⁵¹² In certain cases, cyclic ketones can be cleaved by base treatment, even if they are enolizable.⁵¹³

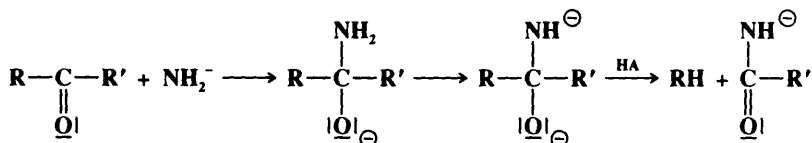
OS VI, 625. See also OS VII, 297.

2-46 The Haller-Bauer Reaction

Hydro-de-acylation



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



OS V, 384, 1074.

⁵⁰⁹Nikishin; Elinson; Makhova *Tetrahedron* **1991**, 47, 895.

⁵¹⁰Swan *J. Chem. Soc.* **1948**, 1408; Gassman; Lumb; Zalar *J. Am. Chem. Soc.* **1967**, 89, 946.

⁵¹¹March; Plankl *J. Chem. Soc., Perkin Trans. I* **1977**, 460.

⁵¹²Davies; Derenberg; Hodge *J. Chem. Soc. C* **1971**, 455; Ref. 511.

⁵¹³For example, see Swaminathan; Newman *Tetrahedron* **1958**, 2, 88; Hoffman; Cram, Ref. 25.

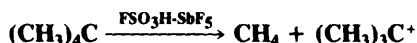
⁵¹⁴For a review, see Gilday; Paquette *Org. Prep. Proced. Int.* **1990**, 22, 167-201. For an improved procedure, see Kaiser; Warner *Synthesis* **1975**, 395.

⁵¹⁵Impastato; Walborsky *J. Am. Chem. Soc.* **1962**, 84, 4838; Paquette; Gilday *J. Org. Chem.* **1988**, 53, 4972; Paquette; Ra *J. Org. Chem.* **1988**, 53, 4978.

⁵¹⁶Bunnett; Hrutford *J. Org. Chem.* **1962**, 27, 4152.

C. Other Cleavages

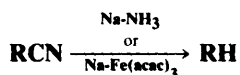
2-47 The Cleavage of Alkanes

Hydro-de-*t*-butylation, etc.

The C—C bonds of alkanes can be cleaved by treatment with super acids⁴⁴ (p. 249). For example, neopentane in $\text{FSO}_3\text{H-SbF}_5$ 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 \gg 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., $\text{R-R}' + \text{H}_2 \rightarrow \text{RH} + \text{R}'\text{H}$), but methyl and ethyl groups have been cleaved from substituted adamantanes by hydrogenation with a $\text{Ni-Al}_2\text{O}_3$ catalyst at about 250°C .⁵¹⁷ Certain C—C bonds have been cleaved by alkali metals.⁵¹⁸

2-48 Decyanation or Hydro-de-cyanation



The cyano group of alkyl nitriles can be removed⁵¹⁹ by treatment with metallic sodium, either in liquid ammonia,⁵²⁰ or together with tris(acetylacetonato)iron(III) $\text{Fe}(\text{acac})_3$,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 $\text{Na-Fe}(\text{acac})_3$ procedure. Sodium in liquid ammonia is known to be a source of solvated electrons, and the reaction may proceed through the free radical $\text{R}\cdot$ which would then be reduced to the carbanion R^- , which by abstraction of a proton from the solvent, would give RH. The mechanism with $\text{Fe}(\text{acac})_3$ 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 $\text{RCH}(\text{CN})\text{NR}'_2$ and $\text{RCH}(\text{CN})\text{NHCOR}'$ can be decyanated in high yield by treatment with NaBH_4 .⁵²⁴

⁵¹⁷Grubmüller; Schleyer; McKervey *Tetrahedron Lett.* **1979**, 181.

⁵¹⁸For examples and references, see Grovenstein; Bhatti; Quest; Sengupta; VanDerveer *J. Am. Chem. Soc.* **1983**, 105, 6290.

⁵¹⁹For a list of procedures, with references, see Ref. 52, pp. 42-43.

⁵²⁰Büchner; 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.

⁵²¹Van Tamelen; Rudler; Bjorklund *J. Am. Chem. Soc.* **1971**, 93, 7113.

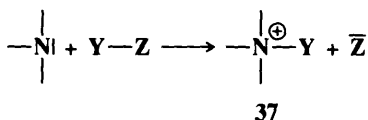
⁵²²For other procedures, see Cuvigny; Larcheveque; Normant *Bull. Soc. Chim. Fr.* **1973**, 1174; Berkoff; Rivard; Kirkpatrick; Ives *Synth. Commun.* **1980**, 10, 939; Savoia; Tagliavini; Trombini; Umani-Ronchi *J. Org. Chem.* **1980**, 45, 3227; Ozawa; Iri; Yamamoto *Chem. Lett.* **1982**, 1707.

⁵²³Ohisawa; Kobayashi; Mizuguchi; Saitoh; Oishi *Tetrahedron Lett.* **1985**, 26, 6103.

⁵²⁴Yamada; 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:

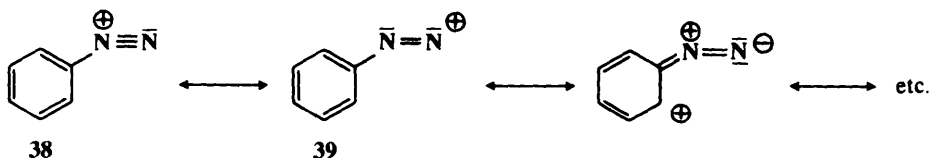


Further reaction of **37** depends on the nature of Y and of the other groups attached to the nitrogen.

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:



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

⁵²⁵For 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.

⁵²⁶For a review of diazonium salt structures, see Sorriso, in Patai *The Chemistry of Diazonium and Diazo Groups*, pt. 1, Ref. 525, pp. 95-105.

⁵²⁷Rømming *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.

⁵²⁸For a review of reactions of diazonium salts, see Wulfman, in Patai, Ref. 526, pt. 1, pp. 247-339.

⁵²⁹Korzeniowski; 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.

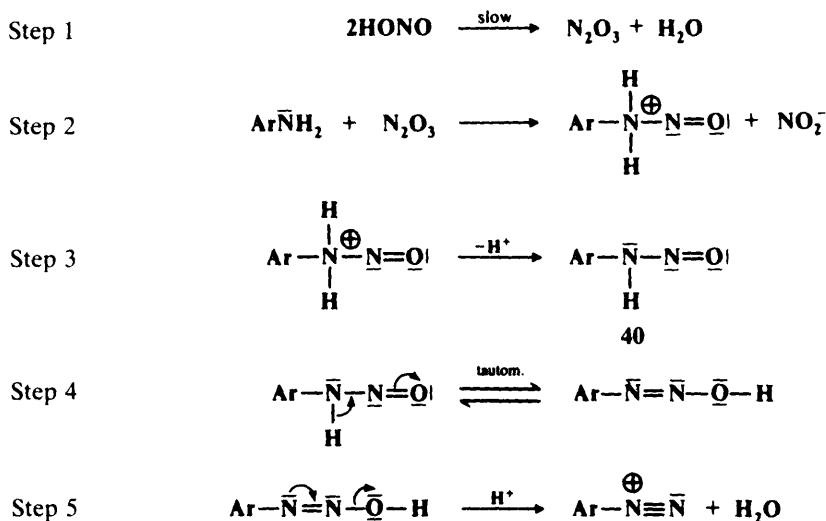
below a pH of about 3, it is even possible, by working at a pH of about 1, to diazotize an aromatic amine without disturbing an aliphatic amino group in the same molecule.⁵³⁰

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



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



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., $\text{HNO}_2 + \text{Cl}^- + \text{H}^+ \rightarrow \text{NOCl} + \text{H}_2\text{O}$.⁵³⁷

⁵³⁰Kornblum; Iffland *J. Am. Chem. Soc.* **1949**, *71*, 2137.

⁵³¹For 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.

⁵³²Takamura; Mizoguchi; Koga; Yamada *Tetrahedron* **1975**, *31*, 227.

⁵³³Butler, Ref. 525.

⁵³⁴Challis; Ridd *J. Chem. Soc.* **1962**, 5197, 5208; Challis; Larkworthy; Ridd *J. Chem. Soc.* **1962**, 5203.

⁵³⁵Hughes; Ingold; Ridd *J. Chem. Soc.* **1958**, 58, 65, 77, 88; Hughes; Ridd *J. Chem. Soc.* **1958**, 70, 82.

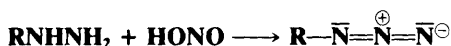
⁵³⁶For discussions, see Ref. 157, pp. 95-109; Ridd, Ref. 540, pp. 422-424.

⁵³⁷Ref. 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



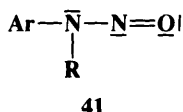
Monosubstituted hydrazines treated with nitrous acid give azides in a reaction exactly analogous to the formation of aliphatic diazo compounds mentioned in 2-49. Among other reagents used for this conversion have been N_2O_4 ⁵³⁸ and nitrosyl tetrafluoroborate NOBF_4 .⁵³⁹ OS III, 710; IV, 819; V, 157.

2-51 N-Nitrosation or N-Nitroso-de-hydrogenation



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: $\text{RCONHR}' + \text{HONO} \rightarrow \text{RCON}(\text{NO})\text{R}'$.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



⁵³⁸Kim; Kim; Shim *Tetrahedron Lett.* **1986**, 27, 4749.

⁵³⁹Pozsgay; Jennings *Tetrahedron Lett.* **1987**, 28, 5091.

⁵⁴⁰For 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.

⁵⁴¹For a discussion of the mechanism with amides, see Castro; Iglesias; Leis; Peña; Tato *J. Chem. Soc., Perkin Trans. 2* **1986**, 1725.

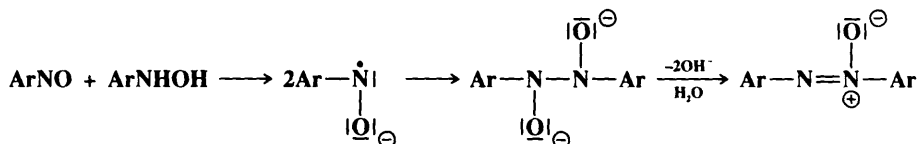
⁵⁴²Hein *J. Chem. Educ.* **1963**, 40, 181. See also Verardo; Giumanini; Strazzolini *Tetrahedron* **1990**, 46, 4303.

⁵⁴³Challis; Kyrtopoulos *J. Chem. Soc., Perkin Trans. 1* **1979**, 299.

⁵⁴⁴Casado; Castro; Lorenzo; Meijide *Monatsh. Chem.* **1986**, 117, 335.

⁵⁴⁵Challis; Yousaf *J. Chem. Soc., Chem. Commun.* **1990**, 1598.

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 obtained⁵⁵⁷ 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 ($\text{ArNO} + \text{Ar'NHOH} \rightarrow \text{Ar'NO} + \text{ArNHOH}$).⁵⁵⁸ The mechanism⁵⁵⁹ 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, ¹⁸O and ¹⁵N labeling show that the two nitrogens and the two oxygens become equivalent.⁵⁶¹ Unsymmetrical azoxy compounds can be prepared⁵⁶² 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 $\text{ArN}(\text{MgBr})_2$.⁵⁶³

2-54 N-Halogenation or N-Halo-de-hydrogenation



Treatment with sodium hypochlorite or hypobromite converts primary amines into N-halo- or N,N-dihaloamines. Secondary amines can be converted to N-halo secondary amines. Similar reactions can be carried out on unsubstituted and N-substituted amides and on sulfonamides. With unsubstituted amides the N-halogen product is seldom isolated but usually rearranges (see **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 $\text{PhCH}_2\text{NMe}_3^+ \text{Br}_3^-$,⁵⁶⁶ and N-chlorosuccinimide.⁵⁶⁷ The mechanisms of these reactions⁵⁶⁸ involve attack by a positive halogen and are probably

⁵⁵⁶Boyer, Ref. 554.

⁵⁵⁷See, for example, Ogata; Tsuchida; Takagi *J. Am. Chem. Soc.* **1957**, 79, 3397.

⁵⁵⁸Knight; Saville *J. Chem. Soc., Perkin Trans. 2* **1973**, 1550.

⁵⁵⁹For 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.

⁵⁶⁰Russell; Geels; Smentowski; Chang; Reynolds; Kaupp *J. Am. Chem. Soc.* **1967**, 89, 3821.

⁵⁶¹Shemyakin; Maimind; Vaichunaite *Izv. Akad. Nauk SSSR, Ser. Khim.* **1957**, 1260; Oae; Fukumoto; Yamagami *Bull. Chem. Soc. Jpn.* **1963**, 36, 728.

⁵⁶²Zawalski; Kovacic *J. Org. Chem.* **1979**, 44, 2130. For another method, see Moriarty; Hopkins; Prakash; Vaid; *Synth. Commun.* **1990**, 20, 2353.

⁵⁶³Okubo; Matsuo; Yamauchi *Bull. Chem. Soc. Jpn.* **1989**, 62, 915, and other papers in this series.

⁵⁶⁴Altenkirk; Isrealstam *J. Org. Chem.* **1962**, 27, 4532.

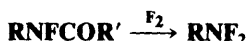
⁵⁶⁵Kajigaeshi; Nakagawa; Fujisaki *Chem. Lett.* **1984**, 2045.

⁵⁶⁶Kajigaeshi; Murakawa; Asano; Fujisaki; Kakinami *J. Chem. Soc., Perkin Trans. 1* **1989**, 1702.

⁵⁶⁷See Deno; Fishbein; Wyckoff *J. Am. Chem. Soc.* **1971**, 93, 2065; Guillemin; Denis *Synthesis* **1985**, 1131.

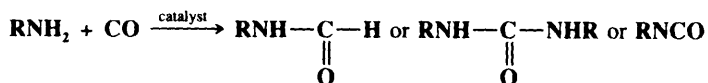
⁵⁶⁸For a study of the mechanism, see Matte; Solastiouk; Merlin; Deglise *Can. J. Chem.* **1989**, 67, 786.

similar to those of **2-49** and **2-51**.⁵⁶⁹ N-Fluorination can be accomplished by direct treatment of amines⁵⁷⁰ or amides⁵⁷¹ with F₂. Fluorination of N-alkyl-N-fluoro amides results in cleavage to N,N-difluoroamines.⁵⁷²



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.



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, Me₃N-H₂Se, 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 selenium⁵⁷⁴ or sulfur.⁵⁷⁵ R can be alkyl or aryl. The same thing can be done with secondary amines, by using Pd(OAc)₂-I₂-K₂CO₃.⁵⁷⁶ (3) When PdCl₂ is the catalyst, primary amines yield isocyanates.⁵⁷⁷ Isocyanates can also be obtained by treatment of CO with azides: RN₃ + CO → 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, O₂, 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 R₂C=CHRCHRN'R'₂ are treated with CO and a palladium-phosphine catalyst, the CO inserts to produce the β,γ-unsaturated amides R₂C=CHRCHRCONR'₂ in good yields.⁵⁸³ See also **6-19**.

⁵⁶⁹For studies of reactivity in this reaction, see Thomm; Wayman *Can. J. Chem.* **1969**, 47, 3289; Higuchi; Hussain; Pitman *J. Chem. Soc. B* **1969**, 626.

⁵⁷⁰Sharts *J. Org. Chem.* **1968**, 33, 1008.

⁵⁷¹Grakauskas; Baum *J. Org. Chem.* **1969**, 34, 2840, **1970**, 35, 1545.

⁵⁷²Ref. 571. See also Wiesboeck; Ruff *Tetrahedron* **1970**, 26, 837; Barton; Hesse; Klose; Pechet *J. Chem. Soc., Chem. Commun.* **1975**, 97.

⁵⁷³See 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.

⁵⁷⁴Sonoda; Yasuhara; Kondo; Ikeda; Tsutsumi *J. Am. Chem. Soc.* **1971**, 93, 6344.

⁵⁷⁵Franz; Applegath; Morriss; Baiocchi; Bolze *J. Org. Chem.* **1961**, 26, 3309.

⁵⁷⁶Pri-Bar; Alper *Can. J. Chem.* **1990**, 68, 1544.

⁵⁷⁷Stern; Spector *J. Org. Chem.* **1966**, 31, 596.

⁵⁷⁸Bennett; Hardy *J. Am. Chem. Soc.* **1968**, 90, 3295.

⁵⁷⁹Unverferth; 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.

⁵⁸⁰Fukuoka; 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.

⁵⁸¹Alper; Vasapollo *Tetrahedron Lett.* **1987**, 28, 6411.

⁵⁸²Cenini; Crotti; Pizzotti; Porta *J. Org. Chem.* **1988**, 53, 1243.

⁵⁸³Murahashi; Imada; Nishimura *J. Chem. Soc., Chem. Commun.* **1988**, 1578.

13

AROMATIC NUCLEOPHILIC SUBSTITUTION

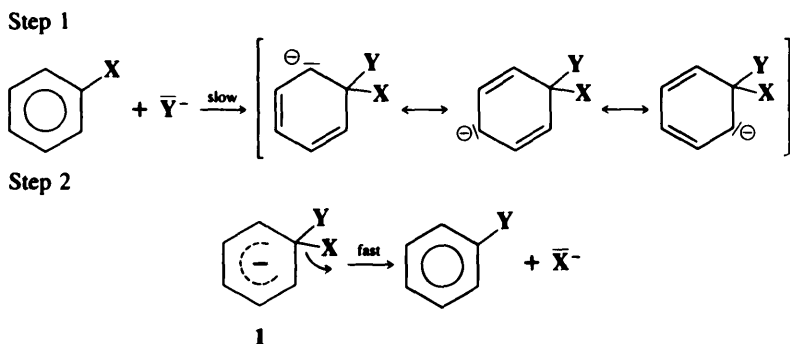
On p. 341 it was pointed out that nucleophilic substitutions proceed so slowly at an aromatic carbon that the reactions of Chapter 10 are not feasible for aromatic substrates. There are, however, exceptions to this statement, and it is these exceptions that form the subject of this chapter.¹ Reactions that *are* successful at an aromatic substrate are largely of four kinds: (1) reactions activated by electron-withdrawing groups ortho and para to the leaving group; (2) reactions catalyzed by very strong bases and proceeding through arynes intermediates; (3) reactions initiated by electron donors; and (4) reactions in which the nitrogen of a diazonium salt is replaced by a nucleophile. However, not all the reactions discussed in this chapter fit into these categories.

MECHANISMS

There are four principal mechanisms for aromatic nucleophilic substitution.² Each of the four is similar to one of the aliphatic nucleophilic substitution mechanisms discussed in Chapter 10.

The S_NAr Mechanism

By far the most important mechanism for aromatic nucleophilic substitution consists of two steps:

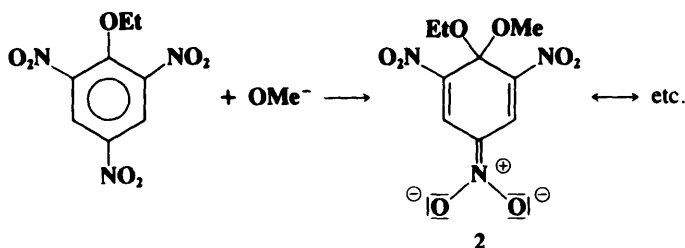


¹For a review of aromatic nucleophilic substitution, see Zoltewicz *Top. Curr. Chem.* **1975**, 59, 33-64.

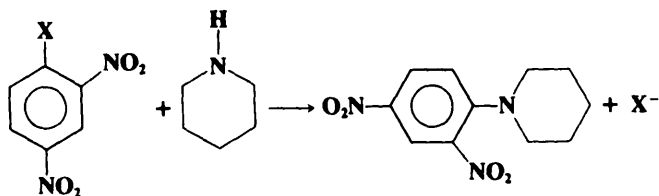
²For a monograph on aromatic nucleophilic substitution mechanisms, see Miller *Aromatic Nucleophilic Substitution*; Elsevier: New York, 1968. For reviews, see Bernasconi *Chimia* **1980**, 34, 1-11, *Acc. Chem. Res.* **1978**, 11, 147-152; Bunnett *J. Chem. Educ.* **1974**, 51, 312-315; Ross, in Bamford; Tipper *Comprehensive Chemical Kinetics*, vol. 13; Elsevier: New York, 1972, pp. 407-431; Buck *Angew. Chem. Int. Ed. Engl.* **1969**, 8, 120-131 [*Angew. Chem.* 81, 136-148]; Bunce; Norris; Russell *Q. Rev., Chem. Soc.* **1968**, 22, 123-146; Ref. 1.

The first step is usually, but not always, rate-determining. It can be seen that this mechanism greatly resembles the tetrahedral mechanism discussed in Chapter 10 and, in another way, the arenium ion mechanism of electrophilic aromatic substitution. In all three cases, the attacking species forms a bond with the substrate, giving an intermediate, and then the leaving group departs. We refer to this mechanism as the S_NAr mechanism.³ The IUPAC designation is $A_N + D_N$ (the same as for the tetrahedral mechanism; compare the designation $A_E + D_E$ for the arenium ion mechanism). This mechanism is generally found where activating groups are present on the ring (see p. 649).

There is a great deal of evidence for the mechanism; we shall discuss only some of it.² Probably the most convincing evidence was the isolation, as long ago as 1902, of the intermediate **2** in the reaction between ethyl picrate and methoxide ion.⁴ Intermediates of this



type are stable salts, called *Meisenheimer* or *Meisenheimer-Jackson salts*, and many more have been isolated since 1902.⁵ The structures of several of these intermediates have been proved by nmr⁶ and by x-ray crystallography.⁷ Further evidence comes from studies of the effect of the leaving group on the reaction. If the mechanism were similar to either the S_N1 or S_N2 mechanisms described in Chapter 10, the $Ar-X$ bond would be broken in the rate-determining step. In the S_NAr mechanism this bond is not broken until after the rate-determining step (that is, if step 1 is rate-determining). We would predict from this that if the S_NAr mechanism is operating, a change in leaving group should not have much effect on the reaction rate. In the reaction



³The mechanism has also been called by other names, including the S_N2Ar , the addition-elimination, and the intermediate complex mechanism.

⁴Meisenheimer *Liebigs Ann. Chem.* **1902**, 323, 205. Similar salts were isolated even earlier by Jackson; see Jackson; Gazzolo *Am. Chem. J.* **1900**, 23, 376; Jackson; Earle *Am. Chem. J.* **1903**, 29, 89.

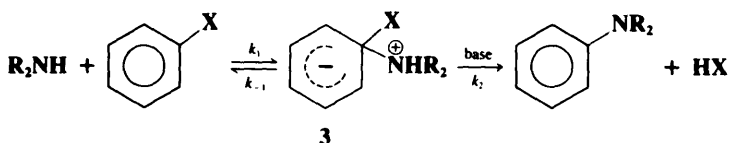
⁵For a monograph on Meisenheimer salts and on this mechanism, see Buncel; Crampton; Strauss; Terrier *Electron Deficient Aromatic- and Heteroaromatic-Base Interactions*; Elsevier: New York, 1984. For reviews of structural and other studies, see Illuminati; Stegel *Adv. Heterocycl. Chem.* **1983**, 34, 305-444; Artamkina; Egorov; Beletskaya *Chem. Rev.* **1982**, 82, 427-459; Terrier *Chem. Rev.* **1982**, 82, 77-152; Strauss *Chem. Rev.* **1970**, 70, 667-712. *Acc. Chem. Res.* **1974**, 7, 181-188; Hall; Poranski, in Feuer *The Chemistry of the Nitro and Nitroso Groups*, pt. 2; Wiley: New York, 1970, pp. 329-384; Crampton, *Adv. Phys. Org. Chem.* **1969**, 7, 211-257; Foster; Fyfe *Rev. Pure Appl. Chem.* **1966**, 16, 61-82.

⁶First done by Crampton; Gold *J. Chem. Soc.* **1964**, 4293, *J. Chem. Soc. B* **1966**, 893. A good review of spectral studies is found in Buncel et al., Ref. 5, pp. 15-133.

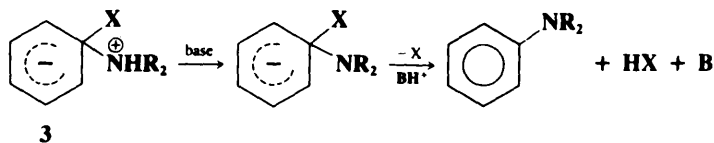
⁷Destro; Gramaccioli; Simonetta *Acta Crystallogr.* **1968**, 24, 1369; Ueda; Sakabe; Tanaka; Furusaki *Bull. Chem. Soc. Jpn.* **1968**, 41, 2866; Messmer; Palenik *Chem. Commun.* **1969**, 470.

when X was Cl, Br, I, SPh, SO₂Ph, or *p*-nitrophenoxy, the rates differed only by a factor of about 5.⁸ This behavior would not be expected in a reaction in which the Ar—X bond is broken in the rate-determining step. We do not expect the rates to be *identical*, because the nature of X affects the rate at which Y attacks. An increase in the electronegativity of X causes a decrease in the electron density at the site of attack, resulting in a faster attack by a nucleophile. Thus, in the reaction just mentioned, when X = F, the relative rate was 3300 (compared with I = 1). The very fact that fluoro is the best leaving group among the halogens in most aromatic nucleophilic substitutions is good evidence that the mechanism is different from the S_N1 and S_N2 mechanisms, where fluoro is by far the poorest leaving group of the halogens. This is an example of the element effect (p. 336).

The pattern of base catalysis of reactions with amine nucleophiles provides additional evidence. These reactions are catalyzed by bases only when a relatively poor leaving group (such as OR) is present (not Cl or Br) and only when relatively bulky amines are nucleophiles.⁹ Bases could not catalyze step 1, but if amines are nucleophiles, bases can catalyze step 2. Base catalysis is found precisely in those cases where the amine moiety cleaves easily



but X does not, so that k_{-1} is large and step 2 is rate-determining. This is evidence for the S_NAr mechanism because it implies two steps. Furthermore, in cases where bases *are* catalysts, they catalyze only at low base concentrations: a plot of the rate against the base concentration shows that small increments of base rapidly increase the rate until a certain concentration of base is reached, after which further base addition no longer greatly affects the rate. This behavior, based on a partitioning effect (see p. 503), is also evidence for the S_NAr mechanism. At low base concentration, each increment of base, by increasing the rate of step 2, increases the fraction of intermediate that goes to product rather than reverting to reactants. At high base concentration the process is virtually complete: there is very little reversion to reactants and the rate becomes dependent on step 1. Just how bases catalyze step 2 has been investigated. For protic solvents two proposals have been presented. One is that step 2 consists of two steps: rate-determining deprotonation of **3** followed by rapid loss of X, and that bases catalyze the reaction by increasing the rate of the deprotonation



step.¹⁰ According to the other proposal, loss of X assisted by BH⁺ is rate-determining.¹¹ Two mechanisms, both based on kinetic evidence, have been proposed for aprotic solvents

⁸Bunnett; Garbisch; Pruitt *J. Am. Chem. Soc.* **1957**, 79, 385.

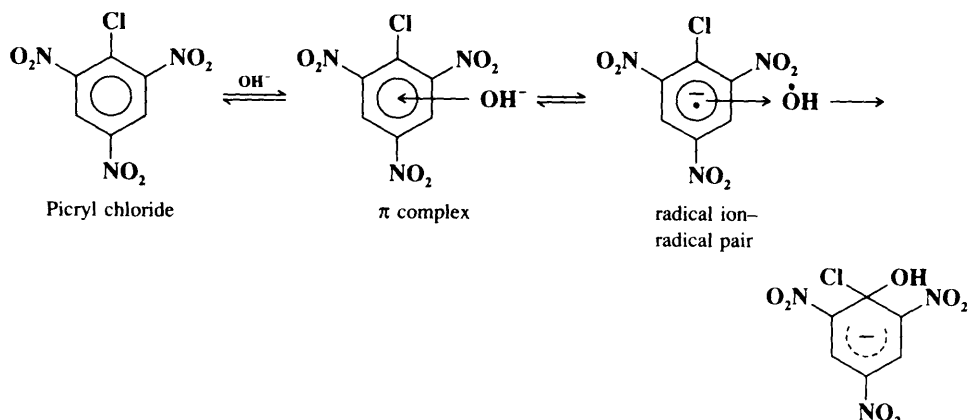
⁹Kirby; Jencks *J. Am. Chem. Soc.* **1965**, 87, 3217; Bunnett; Garst *J. Am. Chem. Soc.* **1965**, 87, 3875, 3879, *J. Org. Chem.* **1968**, 33, 2320; Bunnett; Bernasconi *J. Org. Chem.* **1970**, 35, 70; Bernasconi; Schmid *J. Org. Chem.* **1967**, 32, 2953; Bernasconi; Zollinger *Helv. Chim. Acta* **1966**, 49, 103, **1967**, 50, 1; Pietra; Vitali *J. Chem. Soc. B* **1968**, 1200; Chiacchiera; Singh; Anunziata; Silber *J. Chem. Soc., Perkin Trans. 2* **1987**, 987.

¹⁰Bernasconi; de Rossi; Schmid *J. Am. Chem. Soc.* **1977**, 99, 4090, and references cited therein.

¹¹Bunnett; Sekiguchi; Smith *J. Am. Chem. Soc.* **1981**, 103, 4865, and references cited therein.

such as benzene. In both proposals the ordinary S_NAr mechanism operates, but in one the attacking species involves two molecules of the amine (the *dimer mechanism*),¹² while in the other there is a cyclic transition state.¹³ Further evidence for the S_NAr mechanism has been obtained from $^{18}O/^{16}O$ and $^{15}N/^{14}N$ isotope effects.¹⁴

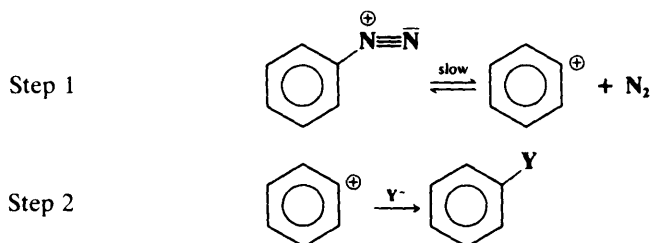
Step 1 of the S_NAr mechanism has been studied for the reaction between picryl chloride (as well as other substrates) and OH^- ions (3-1), and spectral evidence has been reported¹⁵ for two intermediates, one a π complex (p. 505), and the other a radical ion–radical pair:



As with the tetrahedral mechanism at an acyl carbon, nucleophilic catalysis (p. 334) has been demonstrated with an aryl substrate, in certain cases.¹⁶

The S_N1 Mechanism

For aryl halides and sulfonates, even active ones, a unimolecular S_N1 mechanism (IUPAC: $D_N + A_N$) is very rare; it has only been observed for aryl triflates in which both ortho positions contain bulky groups (*t*-butyl or SiR_3).¹⁷ It is in reactions with diazonium salts that this mechanism is important.¹⁸



¹²For a review of this mechanism, see Nudelman *J. Phys. Org. Chem.* **1989**, 2, 1-14. See also Nudelman; Montserrat *J. Chem. Soc., Perkin Trans. 2* **1990**, 1073.

¹³Banjoko; Ezeani *J. Chem. Soc., Perkin Trans. 2* **1986**, 531; Banjoko; Bayeroju *J. Chem. Soc., Perkin Trans. 2* **1988**, 1853; Jain; Gupta; Kumar *J. Chem. Soc., Perkin Trans. 2* **1990**, 11.

¹⁴Hart; Bourns *Tetrahedron Lett.* **1966**, 2995; Ayrey; Wylie *J. Chem. Soc. B* **1970**, 738.

¹⁵Bacaloglu; Blaskó; Bunton; Dorwin; Ortega; Zucco *J. Am. Chem. Soc.* **1991**, 113, 238, and references cited therein. For earlier reports, based on kinetic data, of complexes with amine nucleophiles, see Forlani *J. Chem. Res. (S)* **1984**, 260; Hayami; Otani; Yamaguchi; Nishikawa *Chem. Lett.* **1987**, 739; Crampton; Davis; Greenhalgh; Stevens *J. Chem. Soc., Perkin Trans. 2* **1989**, 675.

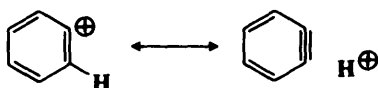
¹⁶See Muscio; Rutherford *J. Org. Chem.* **1987**, 52, 5194.

¹⁷Himeshima; Kobayashi; Sonoda *J. Am. Chem. Soc.* **1985**, 107, 5286.

¹⁸Aryl iodonium salts Ar_2I^+ also undergo substitutions by this mechanism (and by a free-radical mechanism).

Among the evidence for the S_N1 mechanism¹⁹ with aryl cations as intermediates,²⁰ is the following:²¹

1. The reaction rate is first order in diazonium salt and independent of the concentration of Y.
2. When high concentrations of halide salts are added, the product is an aryl halide but the rate is independent of the concentration of the added salts.
3. The effects of ring substituents on the rate are consistent with a unimolecular rate-determining cleavage.²²
4. When reactions were run with substrate deuterated in the ortho position, isotope effects of about 1.22 were obtained.²³ It is difficult to account for such high secondary isotope effects in any other way except that an incipient phenyl cation is stabilized by hyperconjugation,²⁴ which is reduced when hydrogen is replaced by deuterium.



5. That the first step is reversible cleavage²⁵ was demonstrated by the observation that when $\text{Ar}^{15}\text{N}\equiv\text{N}$ was the reaction species, recovered starting material contained not only $\text{Ar}^{15}\text{N}\equiv\text{N}$ but also $\text{ArN}\equiv^{15}\text{N}$.²⁶ This could arise only if the nitrogen breaks away from the ring and then returns. Additional evidence was obtained by treating $\text{PhN}\equiv^{15}\text{N}$ with unlabeled N_2 at various pressures. At 300 atm the recovered product had lost about 3% of the labeled nitrogen, indicating that PhN_2^+ was exchanging with atmospheric N_2 .²⁷

There is kinetic and other evidence²⁸ that step 1 is more complicated and involves two steps, both reversible:



4

4, which is probably some kind of tight ion-molecule pair, has been trapped with carbon monoxide.²⁹

¹⁹For additional evidence, see Lorand *Tetrahedron Lett.* **1989**, 30, 7337.

²⁰For a review of aryl cations, see Ambroz; Kemp *Chem. Soc. Rev.* **1979**, 8, 353-365. Also see Ref. 51 in Chapter 5.

²¹For a review, see Zollinger *Angew. Chem. Int. Ed. Engl.* **1978**, 17, 141-150 [*Angew. Chem.* 90, 151-160]. For discussions, see Swain; Sheats; Harbison *J. Am. Chem. Soc.* **1975**, 97, 783, 796; Burri; Wahl; Zollinger *Helv. Chim. Acta* **1974**, 57, 2099; Richey; Richey, in Olah; Schleyer *Carbonium Ions*, vol. 2; Wiley: New York, 1970, pp. 922-931; Zollinger *Azo and Diazo Chemistry*; Wiley: New York, 1961, pp. 138-142; Miller, Ref. 2, pp. 29-40.

²²Lewis; Miller *J. Am. Chem. Soc.* **1953**, 75, 429.

²³Swain; Sheats; Gorenstein; Harbison *J. Am. Chem. Soc.* **1975**, 97, 791.

²⁴See Apeloig; Arad *J. Am. Chem. Soc.* **1985**, 107, 5285.

²⁵For discussions, see Williams; Buncl *Isot. Org. Chem.* **1980**, 147-230, pp. 212-221; Zollinger *Pure Appl. Chem.* **1983**, 55, 401-408.

²⁶Lewis; Insole *J. Am. Chem. Soc.* **1964**, 86, 32; Lewis; Kotcher *Tetrahedron* **1969**, 25, 4873; Lewis; Holliday *J. Am. Chem. Soc.* **1969**, 91, 426; Ref. 27; Tröndlin; Medina; Rüchardt *Chem. Ber.* **1979**, 112, 1835.

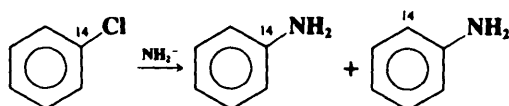
²⁷Bergstrom; Landells; Wahl; Zollinger *J. Am. Chem. Soc.* **1976**, 98, 3301.

²⁸Maurer; Szele; Zollinger *Helv. Chim. Acta* **1979**, 62, 1079; Szele; Zollinger *Helv. Chim. Acta* **1981**, 64, 2728.

²⁹Ravenscroft; Skrabal; Weiss; Zollinger *Helv. Chim. Acta* **1988**, 71, 515.

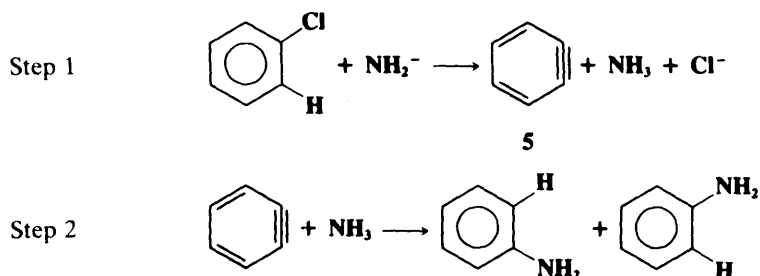
The Benzyne Mechanism³⁰

Some aromatic nucleophilic substitutions are clearly different in character from those that occur by the S_NAr mechanism (or the S_N1 mechanism). These substitutions occur on aryl halides that have no activating groups; bases are required that are stronger than those normally used; and most interesting of all, the incoming group does not always take the position vacated by the leaving group. That the latter statement is true was elegantly demonstrated by the reaction of 1-¹⁴C-chlorobenzene with potassium amide:



The product consisted of almost equal amounts of aniline labeled in the 1 position and in the 2 position.³¹

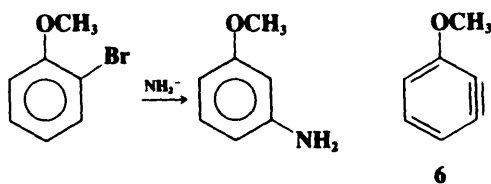
A mechanism that can explain all these facts involves elimination followed by addition:



The symmetrical intermediate **5** can be attacked by the NH_3 at either of two positions, which explains why about half of the aniline produced from the radioactive chlorobenzene was labeled at the 2 position. The fact that the 1 and 2 positions were not labeled equally is the result of a small isotope effect. Other evidence for this mechanism is the following:

1. If the aryl halide contains two ortho substituents, the reaction should not be able to occur. This is indeed the case.³¹

2. It had been known many years earlier that aromatic nucleophilic substitution occasionally results in substitution at a different position. This is called *cine substitution* and can



³⁰For a monograph, see Hoffmann *Dehydrobenzene and Cycloalkynes*; Academic Press: New York, 1967. For reviews, see Gilchrist, in Patai; Rappaport *The Chemistry of Functional Groups, Supplement C*, pt. 1; Wiley: New York, 1983, pp. 383-419; Bryce; Vernon *Adv. Heterocycl. Chem.* **1981**, 28, 183-229; Levin *React. Intermed. (Wiley)* **1985**, 3, 1-18, **1981**, 2, 1-14, **1978**, 1, 1-26; Nefedov; D'yachenko; Prokof'ev *Russ. Chem. Rev.* **1977**, 46, 941-966; Fields, in McManus *Organic Reactive Intermediates*; Academic Press: New York, 1973, pp. 449-508; Heaney *Fortschr. Chem. Forsch.* **1970**, 16, 35-74, *Essays Chem.* **1970**, 1, 95-115; Hoffmann, in Viehe *Acetylenes*; Marcel Dekker: New York, 1969, pp. 1063-1148; Fields; Meyerson *Adv. Phys. Org. Chem.* **1968**, 6, 1-61; Wittig *Angew. Chem. Int. Ed. Engl.* **1965**, 4, 731-737 [*Angew. Chem.* 77, 752-759].

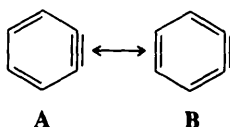
³¹Roberts; Semenov; Simmons; Carlsmith *J. Am. Chem. Soc.* **1965**, 78, 601.

be illustrated by the conversion of *o*-bromoanisole to *m*-aminoanisole.³² In this particular case, only the meta isomer is formed. The reason a 1:1 mixture is not formed is that the intermediate **6** is not symmetrical and the methoxy group directs the incoming group meta but not ortho (see p. 651). However, not all cine substitutions proceed by this kind of mechanism (see 3-25).

3. The fact that the order of halide reactivity is $\text{Br} > \text{I} > \text{Cl} > \text{F}$ (when the reaction is performed with KNH_2 in liquid NH_3) shows that the $\text{S}_{\text{N}}\text{Ar}$ mechanism is not operating here.³¹

In the conversion of the substrate to **6**, either proton removal or subsequent loss of halide ion can be rate-determining. In fact, the unusual leaving-group order just mentioned ($\text{Br} > \text{I} > \text{Cl}$) stems from a change in the rate-determining step. When the leaving group is Br or I, proton removal is rate-determining and the rate order for this step is $\text{F} > \text{Cl} > \text{Br} > \text{I}$. When Cl or F is the leaving group, cleavage of the C—X bond is rate-determining and the order for this step is $\text{I} > \text{Br} > \text{Cl} > \text{F}$. Confirmation of the latter order was found in a direct competitive study. *meta*-Dihalobenzenes in which the two halogens are different were treated with NH_2^- .³³ In such compounds, the most acidic hydrogen is the one between the two halogens; when it leaves, the remaining anion can lose either halogen. Therefore a study of which halogen is preferentially lost provides a direct measure of leaving-group ability. The order was found to be $\text{I} > \text{Br} > \text{Cl}$.³³

Species such as **5** and **6** are called *benzynes* (sometimes *dehydrobenzenes*), or more generally, *arynes*, and the mechanism is known as the *benzyne mechanism*. Benzynes are very reactive. Neither benzyne nor any other aryne has yet been isolated under ordinary conditions,³⁴ but benzyne has been isolated in an argon matrix at 8 K,³⁵ where its ir spectrum could be observed. In addition, benzynes can be trapped; e.g., they undergo the Diels–Alder reaction (see 5-47). It should be noted that the extra pair of electrons does not affect the aromaticity. The original sextet still functions as a closed ring, and the two additional electrons are merely located in a π orbital that covers only two carbons. Benzynes do not have a formal triple bond, since two canonical forms (**A** and **B**) contribute to the hybrid.



The ir spectrum, mentioned above, indicates that **A** contributes more than **B**. Not only benzene rings but other aromatic rings³⁶ and even nonaromatic rings (p. 338) can react through this kind of intermediate. Of course, the nonaromatic rings do have a formal triple bond.

³²This example is from Gilman; Avakian *J. Am. Chem. Soc.* **1945**, 67, 349. For a table of many such examples, see Bunnett; Zahler *Chem. Rev.* **1951**, 49, 273-412, pp. 385-386.

³³Bunnett; Kearley *J. Org. Chem.* **1971**, 36, 184.

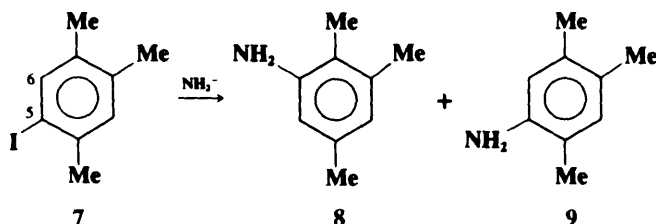
³⁴For the measurement of aryne lifetimes in solution, see Gaviña; Luis; Costero; Gil *Tetrahedron* **1986**, 42, 155.

³⁵Chapman; Mattes; McIntosh; Pacansky; Calder; Orr *J. Am. Chem. Soc.* **1973**, 95, 6134. For the ir spectrum of pyridyne trapped in a matrix, see Nam; Leroi *J. Am. Chem. Soc.* **1988**, 110, 4096. For spectra of transient arynes, see Berry; Spokes; Stiles *J. Am. Chem. Soc.* **1962**, 84, 3570; Brown; Godfrey; Rodler *J. Am. Chem. Soc.* **1986**, 108, 1296.

³⁶For reviews of *hetarynes* (benzyne intermediates in heterocyclic rings), see van der Plas; Roeterdink, in Patai; Rappoport, Ref. 30, pt. 1, pp. 421-511; Reinecke, *React. Intermed. (Plenum)* **1982**, 2, 367-526, *Tetrahedron* **1982**, 38, 427-498; den Hertog; van der Plas, in Viche, Ref. 30, pp. 1149-1197. *Adv. Heterocycl. Chem.* **1971**, 40, 121-144; Kauffmann; Wirthwein *Angew. Chem. Int. Ed. Engl.* **1971**, 10, 20-33 [*Angew. Chem.* 83, 21-34]; Kauffmann *Angew. Chem. Int. Ed. Engl.* **1965**, 4, 543-557 [*Angew. Chem.* 77, 557-571]; Hoffmann, *Dehydrobenzene and Cycloalkynes* Ref. 30, pp. 275-309.

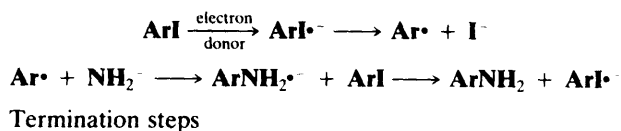
The SRN1 Mechanism

When 5-iodo-1,2,4-trimethylbenzene **7** was treated with KNH_2 in NH_3 , **8** and **9** were formed in the ratio 0.63:1. From what we have already seen, the presence of an unactivated substrate,



a strong base, and the occurrence of cine along with normal substitution would be strong indications of a benzyne mechanism. Yet if that were so, the 6-iodo isomer of **7** should have given **8** and **9** in the same ratio (because the same aryne intermediate would be formed in both cases), but in this case the ratio of **8** to **9** was 5.9:1 (the chloro and bromo analogs did give the same ratio, 1.46:1, showing that the benzyne mechanism may be taking place there).

To explain the iodo result, it has been proposed³⁷ that besides the benzyne mechanism, this free-radical mechanism is also operating here:



This is called the SRN1 mechanism,³⁸ and many other examples are known (see **3-4**, **3-5**, **3-7**, **3-14**). The IUPAC designation is T + D_N + A_N.³⁹ Note that the last step of the mechanism produces $\text{ArI}^{\bullet-}$ radical ions, so the process is a chain mechanism⁴⁰ (see p. 678). An electron donor is required to initiate the reaction. In the case above it was solvated electrons from KNH_2 in NH_3 . Evidence was that the addition of potassium metal (a good producer of solvated electrons in ammonia) completely suppressed the cine substitution. Further evidence for the SRN1 mechanism was that addition of radical scavengers (which would suppress a free-radical mechanism) led to **8**:**9** ratios much closer to 1.46:1. Numerous other observations of SRN1 mechanisms that were stimulated by solvated electrons and inhibited by radical scavengers have also been recorded.⁴¹ Further evidence for the SRN1 mechanism in the case above was that some 1,2,4-trimethylbenzene was found among the products. This could easily be formed by abstraction by Ar^{\bullet} of H from the solvent NH_3 . Besides initiation

³⁷Kim; Bunnett *J. Am. Chem. Soc.* **1970**, *92*, 7463, 7464. For an alternative proposal, in which the first step is the same, but the radical ion reacts directly with the nucleophile, see Denney; Denney *Tetrahedron* **1991**, *47*, 6577.

³⁸For a monograph, see Rossi; de Rossi *Aromatic Substitution by the SRN1 Mechanism*; American Chemical Society: Washington, 1983. For reviews, see Savéant *Adv. Phys. Org. Chem.* **1990**, *26*, 1-130; Russell *Adv. Phys. Org. Chem.* **1987**, *23*, 271-322; Norris, in Patai; Rappoport *The Chemistry of Functional Groups, Supplement D*, pt. 1; Wiley: New York, 1983, pp. 681-701; Chanon; Tobc *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 1-23 [*Angew. Chem.* **94**, 27-49]; Rossi *Acc. Chem. Res.* **1982**, *15*, 164-170; Beletskaya; Drozd *Russ. Chem. Rev.* **1979**, *48*, 431-448; Bunnett; *Acc. Chem. Res.* **1978**, *11*, 413-420; Wolfe; Carver *Org. Prep. Proced. Int.* **1978**, *10*, 225-253. For a review of this mechanism with aliphatic substrates, see Rossi; Pierini; Palacios *Adv. Free Radical Chem. (Greenwich, Conn.)* **1990**, *1*, 193-252.

³⁹The symbol T is used for electron transfer.

⁴⁰For a discussion, see Amatore; Pinson; Savéant; Thiébaud *J. Am. Chem. Soc.* **1981**, *103*, 6930.

⁴¹Bunnett, Ref. 38.

by solvated electrons, S_N1 reactions have been initiated photochemically,⁴² electrochemically,⁴³ and even thermally.⁴⁴

S_N1 reactions have a fairly wide scope. There is no requirement for activating groups or strong bases. Alkyl, alkoxy, aryl, and COO^- groups do not interfere, although Me_2N , O^- , and NO_2 groups do interfere. Cine substitution is not found.

Other Mechanisms

There is no clear-cut proof that a one-step S_N2 mechanism, so important at a saturated carbon, ever actually occurs with an aromatic substrate. The hypothetical aromatic S_N2 process is sometimes called the *one-stage* mechanism to distinguish it from the *two-stage* S_NAr mechanism. Some of the reactions in this chapter operate by still other mechanisms, among them an addition–elimination mechanism (see 3-17).

REACTIVITY

The Effect of Substrate Structure

In the discussion of electrophilic aromatic substitution (Chapter 11) equal attention was paid to the effect of substrate structure on reactivity (activation or deactivation) and on orientation. The question of orientation was important because in a typical substitution there are four or five hydrogens that could serve as leaving groups. This type of question is much less important for aromatic nucleophilic substitution, since in most cases there is only one potential leaving group in a molecule. Therefore attention is largely focused on the reactivity of one molecule compared with another and not on the comparison of the reactivity of different positions within the same molecule.

S_NAr mechanism These substitutions are accelerated by electron-withdrawing groups, especially in positions ortho and para to the leaving group⁴⁵ and hindered by electron-donating groups. This is, of course, opposite to the effects of these groups on electrophilic substitutions, and the reasons are similar to those discussed in Chapter 11 (p. 507). Table 13.1 contains a list of groups arranged approximately in order of activating or deactivating ability.⁴⁶ Hetero nitrogen atoms are also strongly activating (especially to the α and γ positions) and are even more so when quaternized.⁴⁷ Thus 2- and 4-chloropyridine, for example, are often used as substrates. Heterocyclic N-oxides are readily attacked by nucleophiles in the 2 and 4 positions, but the oxygen is generally lost in these reactions.⁴⁸ The most highly activating group, N_2^+ , is seldom deliberately used to activate a reaction, but it

⁴²For reviews of photochemical aromatic nucleophilic substitutions, see Cornelisse, de Gunst, Havinga *Adv. Phys. Org. Chem.* **1975**, *11*, 225-266; Cornelisse *Pure Appl. Chem.* **1975**, *41*, 433-453; Pietra *Q. Rev. Chem. Soc.* **1969**, *23*, 504-521, pp. 519-521.

⁴³For a review, see Savéant *Acc. Chem. Res.* **1980**, *13* 323-329. See also Alam; Amatore; Combéllas; Thiébaud; Verpeaux *J. Org. Chem.* **1990**, *55*, 6347.

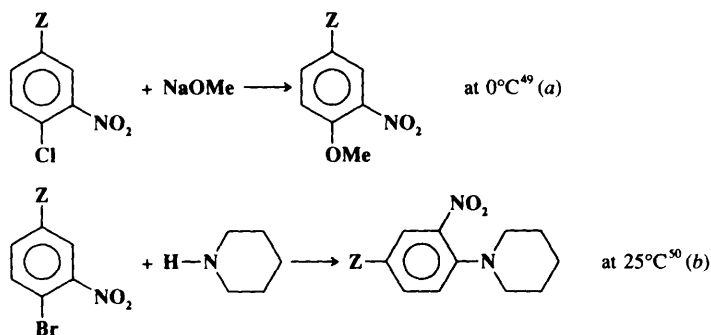
⁴⁴Swartz; Bunnett *J. Org. Chem.* **1979**, *44*, 340, and references cited therein.

⁴⁵The effect of meta substituents has been studied much less, but it has been reported that here too, electron-withdrawing groups increase the rate: See Nurgatin; Sharnin; Ginzburg *J. Org. Chem. USSR* **1983**, *19*, 343.

⁴⁶For additional tables of this kind, see Miller, Ref. 2, pp. 61-136.

⁴⁷For reviews of reactivity of nitrogen-containing heterocycles, see Illuminati *Adv. Heterocycl. Chem.* **1964**, *3*, 285-371; Shepherd; Fedrick *Adv. Heterocycl. Chem.* **1965**, *4*, 145-423.

⁴⁸For reviews, see Albini; Pietra *Heterocyclic N-Oxides*; CRC Press: Boca Raton, FL, 1991, pp. 142-180; Katritzky; Lagowski *Chemistry of the Heterocyclic N-Oxides*; Academic Press: New York, 1971, pp. 258-319, 550-553.

TABLE 13.1 Groups listed in approximate descending order of activating ability in the S_NAr mechanism⁴⁶

For reaction (a) the rates are relative to **H**; for (b) they are relative to **NH₂**

	Group Z	Relative rate of reaction	
		(a) H = 1 ⁴⁹	(b) NH ₂ = 1 ⁵⁰
Activates halide exchange at room temperature	N ₂ ⁺		
Activates reaction with strong nucleophiles at room temperature	N ⁺ —R (heterocyclic)		
Activate reactions with strong nucleophiles at 80–100°C	NO NO ₂ N (heterocyclic)	5.22 × 10 ⁶ 6.73 × 10 ⁵	Very fast
With nitro also present, activate reactions with strong nucleophiles at room temperature	SO ₂ Me NMe ₃ ⁺ CF ₃ CN CHO COR	3.81 × 10 ⁴ 2.02 × 10 ⁴	
With nitro also present, activate reactions with strong nucleophiles at 40–60°C	COOH SO ₃ [−] Br Cl I COO [−] H F CMe ₃ Me OMe NMe ₂ OH NH ₂		6.31 × 10 ⁴ 4.50 × 10 ⁴ 4.36 × 10 ⁴ 2.02 × 10 ⁴ 8.06 × 10 ³ 2.10 × 10 ³ 1.37 × 10 ³ 1.17 × 10 ³ 145 9.77 4.70 1

The comments on the left are from Bunnett and Zahler, Ref. 31, p. 308.

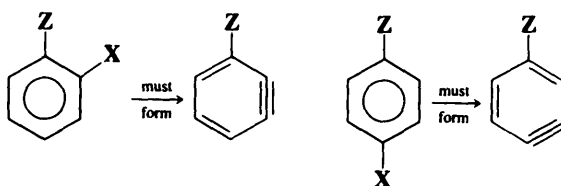
⁴⁶Miller; Parker *Aust. J. Chem.* **1958**, *11*, 302.

⁵⁰Berliner; Monack *J. Am. Chem. Soc.* **1952**, *74*, 1574.

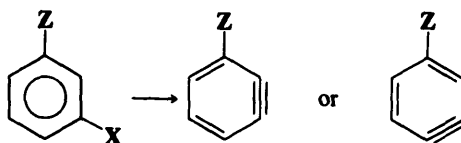
sometimes happens that in the diazotization of a compound such as *p*-nitroaniline or *p*-chloroaniline the group para to the diazonium group is replaced by OH from the solvent or by X from $\text{ArN}_2^+ \text{X}^-$, to the surprise and chagrin of the investigator, who was trying only to replace the diazonium group and to leave the para group untouched. By far the most common activating group is the nitro group and the most common substrates are 2,4-dinitrophenyl halides and 2,4,6-trinitrophenyl halides (also called picryl halides).⁵¹ Polyfluorobenzenes,⁵² e.g., C_6F_6 , also undergo aromatic nucleophilic substitution quite well.⁵³ Benzene rings that lack activating substituents are generally not useful substrates for the $\text{S}_{\text{N}}\text{Ar}$ mechanism, because the two extra electrons in **1** are in an antibonding orbital (p. 27). Activating groups, by withdrawing electron density, are able to stabilize the intermediates and the transition states leading to them. Reactions taking place by the $\text{S}_{\text{N}}\text{Ar}$ mechanism are also accelerated when the aromatic ring is coordinated with a transition metal (e.g., **7** in Chapter 3).⁵⁴

Just as electrophilic aromatic substitutions were found more or less to follow the Hammett relationship (with σ^+ instead of σ ; see p. 518), so do nucleophilic substitutions, with σ^- instead of σ for electron-withdrawing groups.⁵⁵

Benzyne mechanism Two factors affect the positions of the incoming group, the first being the direction in which the aryne forms.⁵⁶ When there are groups ortho or para to the leaving group, there is no choice:



but when a meta group is present, the aryne can form in two different ways:



In such cases, the more acidic hydrogen is removed. Since acidity is related to the field effect of Z, it can be stated that an electron-attracting Z favors removal of the ortho hydrogen while an electron-donating Z favors removal of the para hydrogen. The second factor is that the aryne, once formed, can be attacked at two positions. The favored position for nucleophilic attack is the one that leads to the more stable carbanion intermediate, and this

⁵¹For a review of the activating effect of nitro groups, see de Boer; Dirkx, in Feuer, Ref. 5, pt. 1, pp. 487-612.

⁵²Fluorine significantly activates ortho and meta positions, and slightly deactivates (see Table 13.1) para positions: Chambers; Seabury; Williams; Hughes *J. Chem. Soc., Perkin Trans. 1* **1988**, 255.

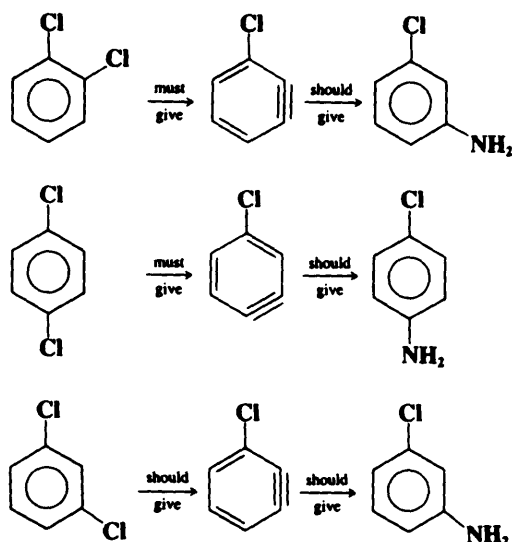
⁵³For reviews, see Yakobson; Vlasov *Synthesis* **1976**, 652-672; Kobrina *Fluorine Chem. Rev.* **1974**, 7, 1-114.

⁵⁴For a review, see Balas; Jhurry; Latxague; Grelier; Morel; Hamdani; Ardoin; Astruc *Bull. Soc. Chim. Fr.* **1990**, 401-426.

⁵⁵For a discussion of linear free-energy relationships in this reaction, see Bartoli; Todesco *Acc. Chem. Res.* **1977**, 10, 125-132. For a list of σ^- values, see Table 9.4.

⁵⁶This analysis is from Roberts; Vaughan; Carlsmith; Semenov *J. Am. Chem. Soc.* **1956**, 78, 611. For a discussion, see Hoffmann *Dehydrobenzene and Cycloalkynes*, Ref. 30, pp. 134-150.

in turn also depends on the field effect of Z. For $-I$ groups, the more stable carbanion is the one in which the negative charge is closer to the substituent. These principles are illustrated by the reaction of the three dichlorobenzenes with alkali-metal amides. The predicted products are



In each case the predicted product was the one chiefly formed.⁵⁷ The obtention of *m*-aminoanisole, mentioned on p. 647, is also in accord with these predictions.

The Effect of the Leaving Group⁵⁸

The common leaving groups in aliphatic nucleophilic substitution (halide, sulfate, sulfonate, NR_3^+ , etc.) are also common leaving groups in aromatic nucleophilic substitutions, but the groups NO_2 , OR, OAr, SO_2R ,⁵⁹ and SR, which are not generally lost in aliphatic systems, are leaving groups when attached to aromatic rings. Surprisingly, NO_2 is a particularly good leaving group.⁶⁰ An approximate order of leaving-group ability is⁶¹ $\text{F} > \text{NO}_2 > \text{OTs} > \text{SOPh} > \text{Cl}, \text{Br}, \text{I} > \text{N}_3 > \text{NR}_3^+ > \text{OAr}, \text{OR}, \text{SR}, \text{NH}_2$. However, this depends greatly on the nature of the nucleophile, as illustrated by the fact that $\text{C}_6\text{Cl}_5\text{OCH}_3$ treated with NH_2 gives mostly $\text{C}_6\text{Cl}_5\text{NH}_2$; i.e., one methoxy group is replaced in preference to five chlorines.⁶² As usual, OH can be a leaving group if it is converted to an inorganic ester. Among the halogens, fluoro is generally a much better leaving group than the other halogens, which have reactivities fairly close together. The order is usually $\text{Cl} > \text{Br} > \text{I}$, but not always.⁶³

⁵⁷Wotiz; Huba *J. Org. Chem.* **1959**, *24*, 595. Eighteen other reactions also gave products predicted by these principles. See also Caubere; Lalloz *Bull. Soc. Chim. Fr.* **1974**, 1983, 1989, 1996; Biehl; Razzuk; Jovanovic; Khanapure *J. Org. Chem.* **1986**, *51*, 5157.

⁵⁸For a review, see Miller, Ref. 2, pp. 137-179.

⁵⁹See, for example Furukawa; Ogawa; Kawai; Oae *J. Chem. Soc., Perkin Trans. 1* **1984**, 1839.

⁶⁰For a review, see Beck *Tetrahedron* **1978**, *34*, 2057-2068. See also Effenberger; Koch; Streicher *Chem. Ber.* **1991**, *24*, 163.

⁶¹Loudon; Shulman *J. Chem. Soc.* **1941**, 772; Suhr *Chem. Ber.* **1963**, *97*, 3268.

⁶²Kobrina; Yakobson *J. Gen. Chem. USSR* **1963**, *33*, 3238.

⁶³Reinheimer; Taylor; Rohrbaugh *J. Am. Chem. Soc.* **1961**, *83*, 835; Ross *J. Am. Chem. Soc.* **1959**, *81*, 2113; Bunnett; Garbisch; Pruitt *J. Am. Chem. Soc.* **1957**, *79*, 385; Parker; Read *J. Chem. Soc.* **1962**, *9*, 3149; Litvinenko; Shpan'ko; Korostylev *Doklad. Chem.* **1982**, *266*, 309.

The leaving-group order is quite different from that for the S_N1 or S_N2 mechanisms. The most likely explanation is that the first step of the S_NAr mechanism is usually rate determining, and this step is promoted by groups with strong $-I$ effects. This would explain why fluoro and nitro are such good leaving groups when this mechanism is operating. Fluoro is the poorest leaving group of the halogens when the second step of the S_NAr mechanism is rate-determining or when the benzyne mechanism is operating. The four halogens, as well as SPh , NMe_3^+ , and $OPO(OEt)_2$, have been shown to be leaving groups in the $S_{RN}1$ mechanism.⁴¹ The only important leaving group in the S_N1 mechanism is N_2^+ .

The Effect of the Attacking Nucleophile⁶⁴

It is not possible to construct an invariant nucleophilicity order because different substrates and different conditions lead to different orders of nucleophilicity, but an overall approximate order is $NH_2^- > PH_3C^- > PhNH^-$ (aryne mechanism) $> ArS^- > RO^- > R_2NH > ArO^- > OH^- > ArNH_2 > NH_3 > I^- > Br^- > Cl^- > H_2O > ROH$.⁶⁵ As with aliphatic nucleophilic substitution, nucleophilicity is generally dependent on base strength and nucleophilicity increases as the attacking atom moves down a column of the periodic table, but there are some surprising exceptions, e.g., OH^- , a stronger base than ArO^- , is a poorer nucleophile.⁶⁶ In a series of similar nucleophiles, such as substituted anilines, nucleophilicity is correlated with base strength. Oddly, the cyanide ion is not a nucleophile for aromatic systems, except for sulfonic acid salts (3-12) and in the von Richter (3-25) and Rosenmund-von Braun (3-11) reactions, which are special cases.

REACTIONS

In the first part of this section, reactions are classified according to attacking species, with all leaving groups considered together, except for hydrogen and N_2^+ , which are treated subsequently. Finally, a few rearrangement reactions are discussed.

All Leaving Groups except Hydrogen and N_2^+

A. Oxygen Nucleophiles

3-1 Hydroxy-de-halogenation



Aryl halides can be converted to phenols only if activating groups are present or if exceedingly strenuous conditions are employed.⁶⁷ Other leaving groups, including nitro,⁶⁸ azide, NR_3^+ , etc., can also be replaced by OH groups. When the reaction is carried out at high

⁶⁴For a review, see Miller, Ref. 2, pp. 180-233.

⁶⁵This list is compiled from data in Bunnett; Zahler, Ref. 32, p. 340; Bunnett *Q. Rev. Chem. Soc.* **1958**, *12*, 1-16, p. 13; Sauer; Huisgen *Angew. Chem.* **1960**, *72*, 294-315, p. 311; Bunnett *Annu. Rev. Phys. Chem.* **1963**, *14*, 271-290.

⁶⁶For studies of nucleophilicity in the $S_{RN}1$ mechanism, see Amatore; Combellas; Robveille; Savéant; Thiébaud *J. Am. Chem. Soc.* **1986**, *108*, 4754, and references cited therein.

⁶⁷For a review of OH^- and OR^- as nucleophiles in aromatic substitution, see Fyfe, in Patai *The Chemistry of the Hydroxyl Group*, pt. 1; Wiley: New York, 1971, pp. 83-124.

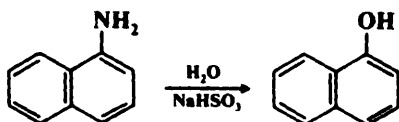
⁶⁸For a convenient way of achieving this conversion, see Knudsen; Snyder *J. Org. Chem.* **1974**, *39*, 3343.

temperatures, cine substitution is observed, indicating a benzyne mechanism.⁶⁹ Phenols have been obtained from unactivated aryl halides by treatment with borane and a metal such as lithium, followed by oxidation with alkaline H_2O_2 .⁷⁰

OS I, 455; II, 451; V, 632. Also see OS V, 918.

3-2 Replacement of an Amino Group by a Hydroxyl Group

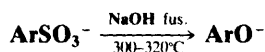
Hydroxy-de-amination



The amino group of naphthylamines can be replaced by a hydroxyl group by treatment with aqueous bisulfite.⁷¹ The scope is greatly limited; the amino group (which may be NH_2 or NHR) must be on a naphthalene ring, with very few exceptions. The reaction is reversible (see 3-7), and both the forward and reverse reactions are called the *Bucherer reaction*. The mechanism is completely different from any outlined in the first section of this chapter and is discussed at 3-7.

3-3 Alkali Fusion of Sulfonate Salts

Oxido-de-sulfonato-substitution



Aryl sulfonic acids can be converted, through their salts, to phenols, by alkali fusion. In spite of the extreme conditions, the reaction gives fairly good yields, except when the substrate contains other groups that are attacked by alkali at the fusion temperatures. Milder conditions can be used when the substrate contains activating groups, but the presence of deactivating groups hinders the reaction. The mechanism is obscure, but a benzyne intermediate has been ruled out by the finding that cine substitution does not occur.⁷²

OS I, 175; III, 288.

3-4 Replacement by OR or OAr

Alkoxy-de-halogenation



This reaction is similar to 3-1 and, like that one, generally requires activated substrates.⁶⁷ With unactivated substrates, side reactions predominate, though aryl methyl ethers have been prepared from unactivated chlorides by treatment with MeO^- in HMPA.⁷³ This reaction gives better yields than 3-1 and is used more often. A good solvent is liquid ammonia. NaOMe reacted with *o*- and *p*-fluoronitrobenzenes about 10^9 times faster in NH_3 at -70°C

⁶⁹The benzyne mechanism for this reaction is also supported by ^{14}C labeling experiments: Bottini; Roberts *J. Am. Chem. Soc.* **1957**, *79*, 1458; Dalman; Neumann *J. Am. Chem. Soc.* **1968**, *90*, 1601.

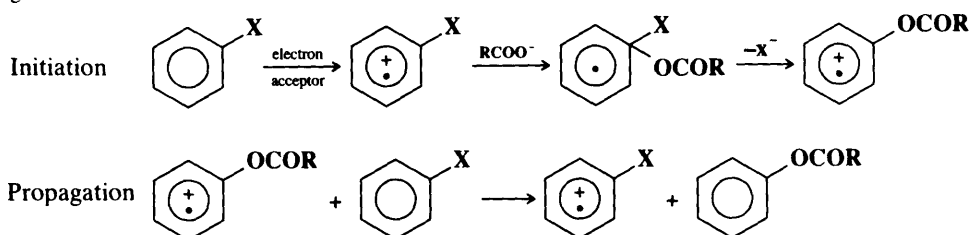
⁷⁰Pickles; Thorpe *J. Organomet. Chem.* **1974**, *76*, C23.

⁷¹For reviews, see Secbooth *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 307-317 [*Angew. Chem.* *79*, 329-340]; Gilbert *Sulfonation and Related Reactions*; Wiley: New York, 1965, pp. 166-169.

⁷²Buzbee *J. Org. Chem.* **1966**, *31*, 3289; Oae; Furukawa; Kise; Kawanishi *Bull. Chem. Soc. Jpn.* **1966**, *39*, 1212.

⁷³Shaw; Kuncerth; Swanson *J. Org. Chem.* **1976**, *41*, 732; Testaferri; Tiecco; Tingoli; Chianelli; Montanucci *Tetrahedron* **1983**, *39*, 193.

than in MeOH.⁷⁴ Phase transfer catalysis has also been used.⁷⁵ In addition to halides, leaving groups can be nitro, NR_3^+ , other OR, etc., even OH.⁷⁶ Acid salts, RCOO^- , are sometimes used as nucleophiles. Good yields of aryl benzoates can be obtained by the treatment of aryl halides with cuprous benzoate in diglyme or xylene at 140 to 160°C.⁷⁷ Unactivated substrates have been converted to carboxylic esters in low-to-moderate yields under oxidizing conditions.⁷⁸ The following chain mechanism, called the $\text{S}_{\text{N}}2$ mechanism,⁷⁹ has been suggested:⁷⁸



For aroxide nucleophiles, the reaction is promoted by copper salts,⁸⁰ and when these are used, activating groups need not be present. This method of preparation of diaryl ethers is called the *Ullmann ether synthesis*⁸¹ and should not be confused with the Ullmann biaryl synthesis (3-16). The reactivity order is typical of nucleophilic substitutions, despite the presence of the copper salts.⁸² Because aryloxy copper(I) reagents ArOCu react with aryl halides to give ethers, it has been suggested that they are intermediates in the Ullmann ether synthesis.⁸³ Indeed, high yields of ethers can be obtained by reaction of ROCu or ArOCu with aryl halides.⁸⁴ Unactivated substrates also react with phenoxide ion with electrochemical catalysis in liquid $\text{NH}_3\text{-Me}_2\text{SO}$, to give diaryl ethers, presumably by the $\text{S}_{\text{RN}}1$ mechanism.⁸⁵ Diaryl ethers can be prepared from activated aryl halides by treatment with triaryl phosphate $(\text{ArO})_3\text{PO}$.⁸⁶

OS I, 219; II, 445; III, 293, 566; V, 926; VI, 150.

B. Sulfur Nucleophiles

3-5 Replacement by SH or SR



Mercapto-de-halogenation



Alkylthio-de-halogenation

Aryl thiols and thioethers can be prepared in reactions similar to 3-1 and 3-4.⁸⁷ Activated aryl halides generally give good results, but side reactions are occasionally important. Diaryl

⁷⁴Kizner; Shteingarts *J. Org. Chem. USSR* **1984**, 20, 991.

⁷⁵Artamanova; Seregina; Shner; Salov; Kokhlova; Zhdamarova *J. Org. Chem. USSR* **1989**, 25, 554.

⁷⁶Oac; Kiritani *Bull. Chem. Soc. Jpn.* **1964**, 37, 770, **1966**, 39, 611.

⁷⁷Cohen; Lewin *J. Am. Chem. Soc.* **1966**, 88, 4521; Cohen; Wood; Dietz *Tetrahedron Lett.* **1974**, 3555.

⁷⁸Ebersson; Jönsson; Wistrand *Tetrahedron* **1982**, 38, 1087; Jönsson; Wistrand *J. Org. Chem.* **1984**, 49, 3340.

⁷⁹First proposed by Alder *J. Chem. Soc., Chem. Commun.* **1980**, 1184.

⁸⁰For a review of copper-assisted aromatic nucleophilic substitution, see Lindley *Tetrahedron* **1984**, 40, 1433-1456.

⁸¹For a review of the Ullmann ether synthesis, see Moroz; Shvartsberg *Russ. Chem. Rev.* **1974**, 43, 679-689.

⁸²Weingarten *J. Org. Chem.* **1964**, 29, 977, 3624.

⁸³Kawaki; Hashimoto *Bull. Chem. Soc. Jpn.* **1972**, 45, 1499.

⁸⁴Whitesides; Sadowski; Lilburn *J. Am. Chem. Soc.* **1974**, 96, 2829.

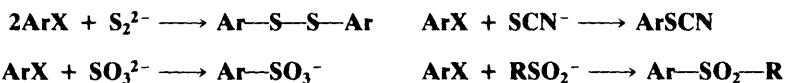
⁸⁵Alam; Amatore; Combéllas; Pinson; Savéant; Thiébaud; Verpeaux *J. Org. Chem.* **1988**, 53, 1496.

⁸⁶Ohta; Iwasaki; Akita *Synthesis* **1982**, 828. For other procedures, see Bates; Janda *J. Org. Chem.* **1982**, 47, 4374; Sammes; Thetford; Voyle *J. Chem. Soc., Perkin Trans. 1* **1988**, 3229.

⁸⁷For a review of sulfur nucleophiles in aromatic substitution, see Peach, in Patai *The Chemistry of the Thiol Group*, pt. 2; Wiley: New York, 1974, pp. 735-744.

sulfides can be prepared by the use of SAr^- . Even unactivated aryl halides react with SAr^- if polar aprotic solvents, e.g., DMF,⁸⁸ Me_2SO ,⁸⁹ tetraglyme,⁹⁰ 1-methyl-2-pyrrolidinone,⁹¹ or HMPA,⁹² are used, though the mechanisms are still mostly or entirely nucleophilic substitution. Unactivated aryl halides also give good yields of sulfides on treatment with SAr^- or SR^- in the presence of a catalytic amount of $(\text{Ph}_3\text{P})_4\text{Pd}$.⁹³ Copper catalysts have also been used.⁹⁴ Diaryl sulfides can also be prepared (in high yields) by treatment of unactivated aryl iodides with ArS^- in liquid ammonia under irradiation.⁹⁵ The mechanism in this case is probably SRN1 . The reaction (with unactivated halides) has also been carried out electrolytically, with a nickel complex catalyst.⁹⁶

Other sulfur nucleophiles also react with activated aryl halides:



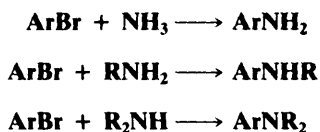
Unactivated thiocyanation has been accomplished with charcoal supported copper (I) thiocyanate.⁹⁷

OS I, 220; III, 86, 239, 667; V, 107, 474; VI, 558, 824. Also see OS V, 977.

C. Nitrogen Nucleophiles

3-6 Replacement by NH_2 , NHR , or NR_2

Amino-de-halogenation



Activated aryl halides react quite well with ammonia and with primary and secondary amines to give the corresponding arylamines. Primary and secondary amines usually give better results than ammonia, with piperidine especially reactive. Picryl chloride (2,4,6-trinitrochlorobenzene) is often used to form amine derivatives. 2,4-Dinitrofluorobenzene is used to tag the amino end of a peptide or protein chain. Other leaving groups in this reaction may be NO_2 , N_3 , OSO_2R , OR , SR , $\text{N}=\text{NAr}$ (where Ar contains electron-withdrawing groups)⁹⁸ and even NR_2 .⁹⁹ Activated halides can be converted to diethylamino compounds $\text{ArX} \rightarrow \text{ArNMe}_2$ by treatment with HMPA.¹⁰⁰

⁹⁸Campbell *J. Org. Chem.* **1964**, 29, 1830; Testaferri; Tiecco; Tingoli; Chianelli; Montanucci *Synthesis* **1983**, 751. For the extension of this to selenides, see Tiecco; Testaferri; Tingoli; Chianelli; Montanucci *J. Org. Chem.* **1983**, 48, 4289.

⁹⁹Bradshaw; South; Hales *J. Org. Chem.* **1972**, 37, 2381.

¹⁰⁰Pastor; Hessel *J. Org. Chem.* **1985**, 50, 4812; Pastor *Helv. Chim. Acta* **1988**, 71, 859.

¹⁰¹Caruso; Colley; Bryant *J. Org. Chem.* **1991**, 56, 862; Shaw *J. Org. Chem.* **1991**, 56, 3728.

¹⁰²Cogolli; Maiolo; Testaferri; Tingoli; Tiecco *J. Org. Chem.* **1979**, 44, 2642. See also Testaferri; Tingoli; Tiecco *Tetrahedron Lett.* **1980**, 21, 3099; Suzuki; Abe; Osuka *Chem. Lett.* **1980**, 1363.

¹⁰³Migita; Shimizu; Asami; Shiobara; Kato; Kosugi *Bull. Chem. Soc. Jpn.* **1980**, 53, 1385.

¹⁰⁴Bowman; Heaney; Smith *Tetrahedron Lett.* **1984**, 25, 5821; Yamamoto; Sekine *Can. J. Chem.* **1984**, 62, 1544. For other catalysts, see Cristau; Chabaud; Chêne; Christol *Synthesis* **1981**, 892; Takagi *Chem. Lett.* **1985**, 1307. **1986**, 1379. **1987**, 2221.

¹⁰⁵Bunnett; Creary *J. Org. Chem.* **1974**, 39, 3173, 3611.

¹⁰⁶Meyer; Troupel *J. Organomet. Chem.* **1988**, 354, 249.

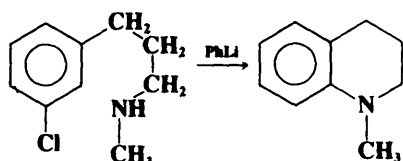
¹⁰⁷Clark; Jones; Duke; Miller *J. Chem. Soc., Chem. Commun.* **1989**, 81.

¹⁰⁸Kazankov; Ginodman *J. Org. Chem. USSR* **1975**, 11, 451.

¹⁰⁹Sekiguchi; Horie; Suzuki *J. Chem. Soc., Chem. Commun.* **1988**, 698.

¹¹⁰See, for example, Gup-ton; Idoux; Baker; Colon; Crews; Jurss; Rampi *J. Org. Chem.* **1983**, 48, 2933.

Unactivated aryl halides can be converted to amines by the use of NaNH_2 , NaNHR , or NaNR_2 .¹⁰¹ With these reagents, the benzyne mechanism generally operates, so cine substitution is often found. Ring closure has been effected by this type of reaction,¹⁰² e.g.,



It has also proved possible to close larger rings in this manner: eight- and even twelve-membered. Triarylamines have been prepared in a similar manner from ArI and Ar_2NLi , even with unactivated ArI .¹⁰³ In the *Goldberg reaction*, an aryl bromide reacts with an acetanilide in the presence of K_2CO_3 and CuI to give an N-acetyldiarylamine, which can be hydrolyzed to a diarylamine: $\text{ArBr} + \text{Ar}'\text{NHAc} \rightarrow \text{ArAr}'\text{NAc}$.¹⁰⁴

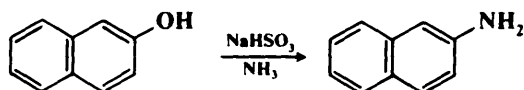
The reaction with ammonia or amines, which undoubtedly proceeds by the $\text{S}_{\text{N}}\text{Ar}$ mechanism, is catalyzed by copper⁸⁰ and nickel¹⁰⁵ salts, though these are normally used only with rather unreactive halides.¹⁰⁶ This reaction, with phase transfer catalysis, has been used to synthesize triarylamines.¹⁰⁷ Copper ion catalysts (especially cuprous oxide or iodide) also permit the Gabriel synthesis (0-58) to be applied to aromatic substrates. Aryl bromides or iodides are refluxed with potassium phthalimide and Cu_2O or CuI in dimethylacetamide to give N-aryl phthalimides, which can be hydrolyzed to primary aryl amines.¹⁰⁸

In certain cases the $\text{S}_{\text{RN}}1$ mechanism has been found (p. 648). When the substrate is a heterocyclic aromatic nitrogen compound, still a different mechanism [the $\text{S}_{\text{N}}(\text{ANRORC})$ mechanism], involving opening and reclosing of the aromatic ring, has been shown to take place.¹⁰⁹

OS I, 544; II, 15, 221, 228; III, 53, 307, 573; IV, 336, 364; V, 816, 1067; VII, 15.

3-7 Replacement of a Hydroxy Group by an Amino Group

Amino-de-hydroxylation



The reaction of naphthols with ammonia and sodium bisulfite is the reverse of 3-2 and has a similar scope.⁷¹ It is also called the *Bucherer reaction*. Primary amines can be used instead

¹⁰¹For a review, see Heaney *Chem. Rev.* **1962**, 62, 81-97, pp. 83-89.

¹⁰²Huisgen; König; Lepley *Chem. Ber.* **1960**, 93, 1496; Bunnett; Hrutfiord *J. Am. Chem. Soc.* **1961**, 83, 1691. For a review of ring closures by the benzyne mechanism, see Hoffmann *Dehydrobenzene and Cycloalkynes*, Ref. 30, pp. 150-164.

¹⁰³Neunhoeffer; Heitmann *Chem. Ber.* **1961**, 94, 2511.

¹⁰⁴See Freeman; Butler; Freedman, *J. Org. Chem.* **1978**, 43, 4975; Renger *Synthesis* **1985**, 856.

¹⁰⁵See Cramer; Coulson *J. Org. Chem.* **1975**, 40, 2267.

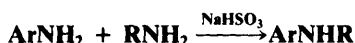
¹⁰⁶For discussions of the mechanism, see Bethell; Jenkins; Quan *J. Chem. Soc., Perkin Trans. 1* **1985**, 1789; Tuong; Hida *J. Chem. Soc., Perkin Trans. 2* **1974**, 676; Kondratov; Shein *J. Org. Chem. USSR* **1979**, 15, 2160; Paine *J. Am. Chem. Soc.* **1987**, 109, 1496.

¹⁰⁷Gauthier; Fréchet *Synthesis* **1987**, 383.

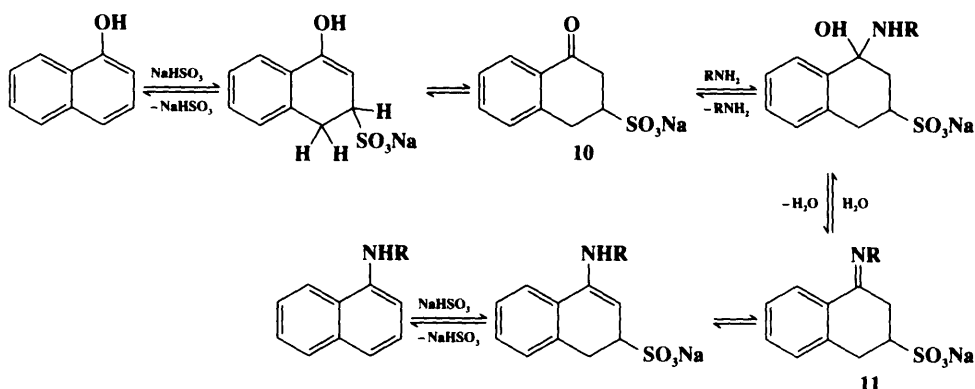
¹⁰⁸Bacon; Karim *Chem. Commun.* **1969**, 578; *J. Chem. Soc., Perkin Trans. 1* **1973**, 272, 278; Sato; Ebine; Akabori *Synthesis* **1981**, 472. See also Yamamoto; Kurata *Can. J. Chem.* **1983**, 61, 86.

¹⁰⁹For reviews, see van der Plas *Tetrahedron* **1985**, 41, 237-281, *Acc. Chem. Res.* **1978**, 11, 462-468.

of ammonia, in which case N-substituted naphthylamines are obtained. In addition, primary naphthylamines can be converted to secondary, by a transamination reaction:

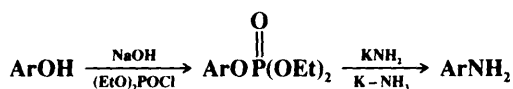


The mechanism of the Bucherer reaction amounts to a kind of overall addition-elimination:¹¹⁰



The first step in either direction consists of addition of NaHSO_3 to one of the double bonds of the ring, which gives an enol (or enamine) that tautomerizes to the keto (or imine) form. The conversion of **10** to **11** (or vice versa) is an example of **6-14** (or **6-2**). Evidence for this mechanism was the isolation of **10**¹¹¹ and the demonstration that for β -naphthol treated with ammonia and HSO_3^- , the rate of the reaction depends only on the substrate and on HSO_3^- , indicating that ammonia is not involved in the rate-determining step.¹¹² If the starting compound is a β -naphthol, the intermediate is a 2-keto-4-sulfonic acid compound, so the sulfur of the bisulfite in either case attacks meta to the OH or NH_2 .¹¹³

Hydroxy groups on benzene rings can be replaced by NH_2 groups if they are first converted to aryl diethyl phosphates. Treatment of these with KNH_2 and potassium metal in liquid



ammonia gives the corresponding primary aromatic amines.¹¹⁴ The mechanism of the second step is SRN1 .¹¹⁵

OS III, 78.

¹¹⁰Rieche: Seeboth *Liebigs Ann. Chem.* **1960**, 638, 66.

¹¹¹Rieche: Seeboth *Liebigs Ann. Chem.* **1960**, 638, 43, 57.

¹¹²Kozlov: Vesclovskaja *J. Gen. Chem. USSR* **1958**, 28, 3359.

¹¹³Rieche: Seeboth *Liebigs Ann. Chem.* **1960**, 638, 76.

¹¹⁴Rossi: Bunnett *J. Org. Chem.* **1972**, 37, 3570.

¹¹⁵For another method of converting phenols to amines, see Scherrer: Beatty *J. Org. Chem.* **1972**, 37, 1681.

D. Halogen Nucleophiles

3-8 The Introduction of Halogens

Halo-de-halogenation, etc.



It is possible to replace a halogen on a ring by another halogen¹¹⁶ if the ring is activated. There is an equilibrium, but it is usually possible to shift this in the desired direction by the use of an excess of added halide ion.¹¹⁷ Another common leaving group is nitro, which can be replaced with chloro by use of NH_4Cl , PCl_5 , SOCl_2 , HCl , Cl_2 , or CCl_4 . Some of these reagents operate only at high temperatures and the mechanism is not always nucleophilic substitution. Activated aromatic nitro compounds can be converted to fluorides with F^- .¹¹⁸

A phenolic hydroxy group can be replaced by chloro with PCl_5 or POCl_3 , but only if activated. Unactivated phenols give phosphates when treated with POCl_3 : $3\text{ArOH} + \text{POCl}_3 \rightarrow (\text{ArO})_3\text{PO}$. Phenols, even unactivated ones, can be converted to aryl bromides by treatment with Ph_3PBr_2 ¹¹⁹ (see 0-66) and to aryl chlorides by treatment with PhPCl_4 .¹²⁰

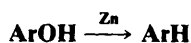
Halide exchange is particularly useful for putting fluorine into a ring, since there are fewer alternate ways of doing this than for the other halogens. Activated aryl chlorides give fluorides when treated with KF in DMF , Me_2SO , or dimethyl sulfone.¹²¹ Halide exchange can also be accomplished with copper halides. Since the leaving-group order in this case is $\text{I} > \text{Br} > \text{Cl} \gg \text{F}$ (which means that iodides cannot normally be made by this method), the $\text{S}_{\text{N}}\text{Ar}$ mechanism is probably not operating.¹²² However, aryl iodides have been prepared from bromides, by the use of Cu supported on charcoal or Al_2O_3 ,¹²³ and by treatment with excess KI and a nickel catalyst.¹²⁴

OS III, 194, 272, 475; V, 142, 478; 67, 20.

E. Hydrogen as Nucleophile

3-9 Reduction of Phenols and Phenolic Esters and Ethers¹²⁵

Hydro-de-hydroxylation or Dehydroxylation, etc.



¹¹⁶For a list of reagents, with references, see Larock *Comprehensive Organic Transformations*; VCH: New York, 1989, p. 340.

¹¹⁷Sauer; Huisgen *Angew. Chem.* **1960**, 72, 294-315, p. 297.

¹¹⁸Attinà; Cacace; Wolf *J. Chem. Soc. Chem. Commun.* **1983**, 108; Clark; Smith *Tetrahedron Lett.* **1985**, 26, 2233; Suzuki; Yazawa; Yoshida; Furusawa; Kimura *Bull. Chem. Soc. Jpn.* **1990**, 63, 2010; Effenberger; Streicher *Chem. Ber.* **1991**, 124, 157.

¹¹⁹Wiley; Hershkowitz; Rein; Chung *J. Am. Chem. Soc.* **1964**, 86, 964; Wiley; Rein; Hershkowitz *Tetrahedron Lett.* **1964**, 2509; Schaefer; Higgins *J. Org. Chem.* **1967**, 32, 1607.

¹²⁰Bay; Bak; Timony; Leone-Bay *J. Org. Chem.* **1990**, 55, 3415.

¹²¹Starr; Finger *Chem. Ind. (London)* **1962**, 1328; Shiley; Dickerson; Finger *J. Fluorine Chem.* **1972**, 2, 19; Kimura; Suzuki *Tetrahedron Lett.* **1989**, 30, 1271. For the use of phase transfer catalysis in this reaction, see Yoshida; Kimura *Chem. Lett.* **1988**, 1355. For a review of the preparation of aryl fluorides by halogen exchange, see Dolby-Glover *Chem. Ind. (London)* **1986**, 518-523.

¹²²Bacon; Hill *J. Chem. Soc.* **1964**, 1097, 1108. See also Nefedov; Tarygina; Kryuchkova; Ryabokohylko *J. Org. Chem. USSR* **1981**, 17, 487; Suzuki; Kondo; Ogawa *Chem. Lett.* **1985**, 411; Liedholm; Nilsson *Acta Chem. Scand., Ser. B* **1988**, 42, 289; Clark; Jones; Duke; Miller *J. Chem. Res. (S)* **1989**, 238.

¹²³Clark; Jones *J. Chem. Soc., Chem. Commun.* **1987**, 1409.

¹²⁴Yang; Li; Cheng *J. Org. Chem.* **1987**, 52, 691.

¹²⁵For a list of reagents, with references, see Ref. 116, pp. 27-31ff.

Phenols can be reduced by distillation over zinc dust or with HI and red phosphorus, but these methods are quite poor and are seldom feasible. Catalytic hydrogenation has also been used, but the corresponding cyclohexanol (see 5-10) is a side product.¹²⁶

Much better results have been obtained by conversion of phenols to certain esters or ethers and reduction of the latter:



12

12 are prepared by treatment of phenols with 1-phenyl-5-chlorotetrazole in acetone containing K_2CO_3 .

OS **VI**, 150. See also OS **VII**, 476.

3-10 Reduction of Halides and Nitro Compounds

The reaction $\text{ArX} \rightarrow \text{ArH}$ is treated in Chapter 11 (reaction 1-42), although, depending on reagent and conditions, it can be nucleophilic or free-radical substitution, as well as electrophilic.

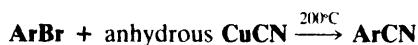
The nitro group of aromatic nitro compounds has been removed with sodium borohydride.¹³¹ This reaction involves an addition-elimination mechanism.

F. Carbon Nucleophiles^{131a}

Some formations of new aryl-carbon bonds formed from aryl substrates have been considered in Chapter 10 (see 0-87, 0-95, 0-102, 0-103).

3-11 The Rosenmund-von Braun Reaction

Cyano-de-halogenation



¹²⁶Shuikin; *Erivanskaya Russ. Chem. Rev.* **1960**, 29, 309-320, pp. 313-315. See also Bagnell; Jeffery *Aust. J. Chem.* **1981**, 34, 697.

¹²⁷Cacchi; Ciattini; Morera; Ortar *Tetrahedron Lett.* **1986**, 27, 5541. See also Peterson; Kunng; McCallum; Wulff *Tetrahedron Lett.* **1987**, 28, 1381; Chen; He *Synthesis* **1988**, 896; Cabri; De Bernardinis; Francalanci; Penco *J. Org. Chem.* **1990**, 55, 350.

¹²⁸Kenner; Murray *J. Chem. Soc.* **1949**, S178; Rottendorf; Sternhell *Aust. J. Chem.* **1963**, 16, 647.

¹²⁹Welch; Walters *J. Org. Chem.* **1978**, 43, 4797. See also Rossi; Bunnett *J. Org. Chem.* **1973**, 38, 2314.

¹³⁰Musliner; Gates *J. Am. Chem. Soc.* **1966**, 88, 4271; Hussey; Johnstone; Entwistle *Tetrahedron* **1982**, 38, 3775; Johnstone; Price *J. Chem. Soc., Chem. Commun.* **1984**, 845. For related methods, see Pailer; Gössinger *Monatsh. Chem.* **1969**, 100, 1613; van Muijlwijk; Kieboom; van Bekkum *Recl. Trav. Chim. Pays-Bas* **1974**, 93, 204.

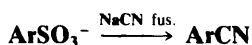
¹³¹Severin; Schmitz; Temme *Chem. Ber.* **1963**, 96, 2499; Kniel *Helv. Chim. Acta* **1968**, 51, 371. For another method, see Ono; Tamura; Kaji *J. Am. Chem. Soc.* **1983**, 105, 4017.

^{131a}For a review of many of these reactions, see Artamkina; Kovalenko; Beletskaya; Reutov *Russ. Chem. Rev.* **1990**, 59, 750-777.

The reaction between aryl halides and cuprous cyanide is called the *Rosenmund-von Braun reaction*.¹³² Reactivity is in the order $I > Br > Cl > F$, indicating that the S_NAr mechanism does not apply.¹³³ Other cyanides, e.g., KCN and NaCN, do not react with aryl halides, even activated ones. However, alkali cyanides do convert aryl halides to nitriles¹³⁴ in dipolar aprotic solvents in the presence of Pd(II) salts¹³⁵ or copper¹³⁶ or nickel¹³⁷ complexes. A nickel complex also catalyzes the reaction between aryl triflates and KCN to give aryl nitriles.¹³⁸ Aromatic ethers $ArOR$ ¹³⁹ and some nitro compounds $ArNO_2$ ¹⁴⁰ have been photochemically converted to $ArCN$.

OS III, 212, 631.

3-12 Cyanide Fusion of Sulfonate Salts Cyano-de-sulfonato-substitution

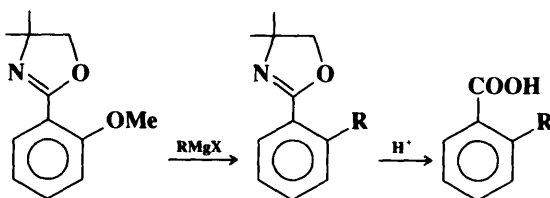


This reaction is very similar to 3-3. Yields are usually low.

3-13 Coupling of Organometallic Compounds with Aryl Halides, Ethers, and Carboxylic Esters Alkyl-de-halogenation, etc.



Aryl iodides, which need not be activated, couple with lithium dialkylcopper reagents. The reaction is discussed at 0-87. Aryl halides, even when activated, generally do not couple with Grignard reagents, though certain transition-metal catalysts do effect this reaction in variable yields.¹⁴¹ The reaction with Grignard reagents proceeds better when OR can be the leaving group, providing that activating groups are present in the ring. The oxazoline group activates *o*-methoxy and *o*-fluoro groups to reaction with Grignard reagents and organolithiums; the product can be hydrolyzed after coupling¹⁴² (see 0-98):



¹³²For a review of cyano-de-halogenation, see Ellis; Romney-Alexander *Chem. Rev.* **1987**, 87, 779-794.

¹³³For discussions of the mechanism, see Couture; Paine *Can. J. Chem.* **1985**, 63, 111; Connor; Leeming; Price *J. Chem. Soc., Perkin Trans. I* **1990**, 1127.

¹³⁴For a list of reagents that convert aryl halides to cyanides, with references, see Ref. 116, pp. 861-862.

¹³⁵Takagi; Okamoto; Sakakibara; Ohno; Oka; Hayama *Bull. Chem. Soc. Jpn.* **1975**, 48, 3298, **1976**, 49, 3177. See also Sekiya; Ishikawa *Chem. Lett.* **1975**, 277; Takagi; Sasaki; Sakakibara *Bull. Chem. Soc. Jpn.* **1991**, 64, 1118.

¹³⁶Connor; Gibson; Price *J. Chem. Soc., Perkin Trans. I* **1987**, 619.

¹³⁷Cassar; Foà; Montanari; Marinelli *J. Organomet. Chem.* **1979**, 173, 335; Sakakibara; Okuda; Shimobayashi; Kirino; Sakai; Uchino; Takagi *Bull. Chem. Soc. Jpn.* **1988**, 61, 1985.

¹³⁸Chambers; Widdowson *J. Chem. Soc., Perkin Trans. I* **1989**, 1365; Takagi; Sakakibara *Chem. Lett.* **1989**, 1957.

¹³⁹Letsinger; Colb *J. Am. Chem. Soc.* **1972**, 94, 3665.

¹⁴⁰See, for example, Vink; Verheijdt; Cornelisse; Havinga *Tetrahedron* **1972**, 28, 5081.

¹⁴¹See, for example, Sekiya; Ishikawa *J. Organomet. Chem.* **1976**, 118, 349, **1977**, 125, 281; Negishi; Matsushita; Kobayashi; Rand *Tetrahedron Lett.* **1983**, 24, 3823; Tiecco; Testaferri; Tingoli; Chianelli; Wenkert *Tetrahedron Lett.* **1982**, 23, 4629; Eapen; Dua; Tamborski *J. Org. Chem.* **1984**, 49, 478; Bell; Hu; Patel *J. Org. Chem.* **1987**, 52, 3847; Bumagin; Andryukhova; Beletskaya *Doklad. Chem.* **1987**, 297, 524; Ozawa; Kurihara; Fujimori; Hidaka; Toyoshima; Yamamoto *Organometallics* **1989**, 8, 180.

¹⁴²For a review of oxazolines in aromatic substitutions, see Reuman; Meyers *Tetrahedron* **1985**, 41, 837-860. For the similar use of oxazoles, see Cram; Bryant; Doxsee *Chem. Lett.* **1987**, 19.

Unactivated aryl halides couple with alkyllithium reagents in THF¹⁴³ and with organotin compounds and a Pd complex catalyst¹⁴⁴ to give moderate-to-good yields of alkyl arenes. Unactivated aryl triflates¹⁴⁵ $\text{ArOSO}_2\text{CF}_3$ react to give ArR in good yields when treated with $\text{R}_2\text{Cu}(\text{CN})\text{Li}_2$,¹⁴⁶ with RZnX ,¹⁴⁷ with R_3Al ,¹⁴⁸ or with R_3SnR and a Pd complex catalyst.¹⁴⁹ The coupling reaction between aryl halides and alkenes, with a Pd catalyst, is treated at 4-20.

Unactivated aryl halides react with copper acetylides to give good yields of arylacetylenes (*Stephens-Castro coupling*).¹⁵⁰

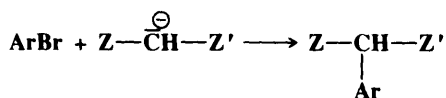


R may be alkyl or aryl. A wide variety of aryl iodides has been used and the reaction is of considerable synthetic importance.

Unactivated aryl iodides undergo the conversion $\text{ArI} \rightarrow \text{ArCH}_3$ when treated with tris(diethylamino)sulfonium difluorotrimethylsilicate and a palladium catalyst.¹⁵¹ A number of methods, all catalyzed by palladium complexes, have been used to prepare unsymmetrical biaryls (see also 3-16). In these methods, aryl bromides or iodides are coupled with aryl Grignard reagents,¹⁵² with arylboronic acids $\text{ArB}(\text{OH})_2$,¹⁵³ with aryltin compounds Ar-SnR_3 ,¹⁵⁴ and with arylmercury compounds.¹⁵⁵ Unsymmetrical binaphthyls were synthesized by photochemically stimulated reaction of naphthyl iodides with naphthoxide ions in an $\text{S}_{\text{RN}}1$ reaction.¹⁵⁶ Grignard reagents also couple with aryl halides without a palladium catalyst, by the benzyne mechanism.¹⁵⁷

OS VI, 916; 65, 108; 66, 67.

3-14 Arylation at a Carbon Containing Active Hydrogen Bis(ethoxycarbonyl)methyl-de-halogenation, etc.



¹⁴³Merrill; Negishi *J. Org. Chem.* **1974**, 39, 3452. For another method, see Hallberg; Westerlund *Chem. Lett.* **1982**, 1993.

¹⁴⁴Bumagin; Bumagina; Beletskaya *Doklad. Chem.* **1984**, 274, 39; Bumagin; Ponomarev; Beletskaya *J. Org. Chem. USSR* **1987**, 23, 1215, 1222; Kosugi; Sumiya; Ohhashi; Sano; Migita *Chem. Lett.* **1985**, 997; McKean; Parrinello; Renaldo; Stille *J. Org. Chem.* **1987**, 52, 422.

¹⁴⁵For another coupling reaction of aryl triflates, see Aoki; Fujimura; Nakamura; Kuwajima *J. Am. Chem. Soc.* **1988**, 110, 3296.

¹⁴⁶McMurry; Mohanraj *Tetrahedron Lett.* **1983**, 24, 2723.

¹⁴⁷Chen; He *Tetrahedron Lett.* **1987**, 28, 2387.

¹⁴⁸Hirota; Isobe; Maki *J. Chem. Soc., Perkin Trans. 1* **1989**, 2513.

¹⁴⁹Echevarren; Stille *J. Am. Chem. Soc.* **1987**, 109, 5478. For a similar reaction with aryl fluorosulfonates, see Roth; Fuller *J. Org. Chem.* **1991**, 56, 3493.

¹⁵⁰Castro; Stephens *J. Org. Chem.* **1963**, 28, 2163; Stephens; Castro *J. Org. Chem.* **1963**, 28, 3313; Sladkov; Ukhin; Korshak *Bull. Acad. Sci. USSR., Div. Chem. Sci.* **1963**, 2043. For a review, see Sladkov; Gol'ding *Russ. Chem. Rev.* **1979**, 48, 868-896. For an improved procedure, see Bumagin; Kalinovskii; Ponomarev; Beletskaya *Doklad. Chem.* **1982**, 265, 262.

¹⁵¹Hatanaka; Hiyama *Tetrahedron Lett.* **1988**, 29, 97.

¹⁵²Widdowson; Zhang *Tetrahedron* **1986**, 42, 2111. See also Ikoma; Taya; Ozaki; Higuchi; Naoi; Fuji-i *Synthesis* **1990**, 147.

¹⁵³Miyaura; Yanagi; Suzuki *Synth. Commun.* **1981**, 11, 513; Miller; Dugar *Organometallics* **1984**, 3, 1261; Sharp; Cheng; Snieckus *Tetrahedron Lett.* **1987**, 28, 5093; Cheng; Snieckus *Tetrahedron Lett.* **1987**, 28, 5097.

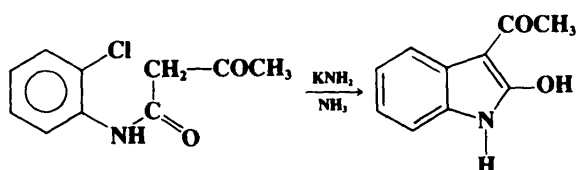
¹⁵⁴Bailey *Tetrahedron Lett.* **1986**, 27, 4407.

¹⁵⁵Bumagin; More; Beletskaya *J. Organomet. Chem.* **1989**, 364, 231.

¹⁵⁶Beugelmans; Bois-Choussy; Tang *Tetrahedron Lett.* **1988**, 29, 1705. For other preparations of biaryls via $\text{S}_{\text{RN}}1$ processes, see Alam; Amatore; Combéllas; Thiébaud; Verpeaux *Tetrahedron Lett.* **1987**, 28, 6171; Pierini; Baumgartner; Rossi *Tetrahedron Lett.* **1988**, 29, 3429.

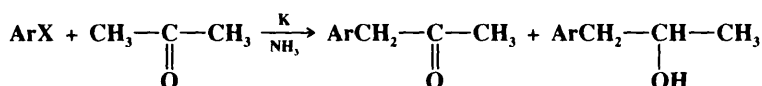
¹⁵⁷Du; Hart; Ng *J. Org. Chem.* **1986**, 51, 3162.

The arylation of compounds of the form ZCH_2Z' is analogous to **0-94**, and Z is as defined there. Activated aryl halides generally give good results.¹⁵⁸ Even unactivated aryl halides can be employed if the reaction is carried out in the presence of a strong base such as $NaNH_2$ ¹⁵⁹ or lithium diisopropylamide (LDA). Compounds of the form ZCH_2Z' and even simple ketones¹⁶⁰ and carboxylic esters have been arylated in this manner. The reaction with unactivated halides proceeds by the benzyne mechanism and represents a method for extending the malonic ester (and similar) syntheses to aromatic compounds. The base performs two functions: it removes a proton from ZCH_2Z' and catalyzes the benzyne mechanism. The reaction has been used for ring closure:¹⁶¹

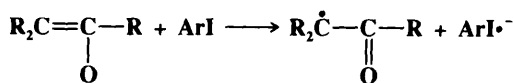


The reaction on unactivated halides can also be done with copper halide catalysts⁸⁰⁾ (the *Hurtley reaction*),¹⁶² and with palladium complex catalysts.¹⁶³

Compounds of the form CH_3Z can be arylated by treatment with an aryl halide in liquid ammonia containing Na or K, e.g.,¹⁶⁴



The same products are obtained (though in different proportions) when Na or K is omitted but the solution is irradiated with near-uv-light.¹⁶⁵ In either case other leaving groups can be used instead of halogens (e.g., NR_3^+ , SAr) and the mechanism is the $SRN1$ mechanism. Iron(II) salts have also been used to initiate this reaction.¹⁶⁶ The reaction can also take place without an added initiator: Enolate ions of ketones react with PhI in the dark.¹⁶⁷ In this case, it has been suggested¹⁶⁷ that initiation takes place by



¹⁵⁸ There is evidence for both $SNAr$ (see Leffek; Matinopoulos-Scordou *Can. J. Chem.* **1977**, *55*, 2656, 2664) and $SRN1$ (see Zhang; Yang; Liu; Chen; Cheng *Res. Chem. Intermed.* **1989**, *11*, 281) mechanisms.

¹⁵⁹ Leake; Levine *J. Am. Chem. Soc.* **1959**, *81*, 1169, 1627.

¹⁶⁰ For example, see Caubere; Guillaumet *Bull. Soc. Chim. Fr.* **1972**, 4643, 4649.

¹⁶¹ Bunnett; Hrutford *J. Am. Chem. Soc.* **1961**, *83*, 1691; Bunnett; Kato; Flynn; Skorcz *J. Org. Chem.* **1963**, *28*, 1. For reviews, see Bichl; Khanapure *Acc. Chem. Res.* **1989**, *22*, 275-281; Hoffmann, Ref. 102, pp. 150-164. See also Kessar, *Acc. Chem. Res.* **1978**, *11*, 283-288.

¹⁶² For discussions and procedures, see Bruggink; McKillop, *Tetrahedron* **1975**, *31*, 2607; McKillop; Rao *Synthesis* **1977**, 759; Setsune; Matsukawa; Wakemoto; Kitao *Chem. Lett.* **1981**, 367; Osuka; Kobayashi; Suzuki *Synthesis* **1983**, 67; Suzuki; Kobayashi; Yoshida; Osuka *Chem. Lett.* **1983**, 193; Aalten; van Koten; Vrieze; van der Kerk-van Hoof *Recl. Trav. Chim. Pays-Bas* **1990**, *109*, 46.

¹⁶³ Uno; Seto; Ueda; Masuda; Takahashi *Synthesis* **1985**, 506.

¹⁶⁴ Rossi; Bunnett *J. Am. Chem. Soc.* **1972**, *94*, 683; *J. Org. Chem.* **1973**, *38*, 3020; Bunnett; Gloor *J. Org. Chem.* **1973**, *38*, 4156, **1974**, *39*, 382.

¹⁶⁵ Rossi; Bunnett *J. Org. Chem.* **1973**, *38*, 1407; Hay; Hudlicky; Wolfe *J. Am. Chem. Soc.* **1975**, *97*, 374; Bunnett; Sundberg *J. Org. Chem.* **1976**, *41*, 1702; Rajan; Muralimohan *Tetrahedron Lett.* **1978**, 483; Rossi; de Rossi; Picrini *J. Org. Chem.* **1979**, *44*, 2662; Rossi; Alonso *J. Org. Chem.* **1980**, *45*, 1239; Beugelmans *Bull. Soc. Chim. Belg.* **1984**, *93*, 547.

¹⁶⁶ Galli; Bunnett *J. Org. Chem.* **1984**, *49*, 3041.

¹⁶⁷ Scamehorn; Bunnett *J. Org. Chem.* **1977**, *42*, 1449; Scamehorn; Hardacre; Lukanich; Sharpe *J. Org. Chem.* **1984**, *49*, 4881.

This is an SET mechanism (see p. 307). The photostimulated reaction has also been used for ring closure.¹⁶⁸ In certain instances of the intermolecular reaction there is evidence that the leaving group exerts an influence on the product ratios, even when it has already departed at the time that product selection takes place.¹⁶⁹ Malonic and β -keto esters can be arylated in high yields by treatment with aryllead tricarboxylates: $\text{RCOCHR}'\text{COOEt} + \text{ArPb}(\text{OAc})_3 \rightarrow \text{RCOArR}'\text{COOEt}$,¹⁷⁰ and with triphenylbismuth carbonate¹⁷¹ Ph_3BiCO_3 and other bismuth reagents.¹⁷² In a related process, manganese(III) acetate was used to convert a mixture of ArH and $\text{ZCH}_2\text{Z}'$ to ArCHZZ' .¹⁷³

OS V, 12, 263; VI, 36, 873, 928; VII, 229.

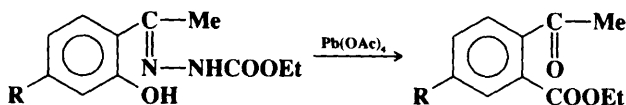
3-15 Conversion of Aryl Substrates to Carboxylic Acids, Their Derivatives, Aldehydes, and Ketones¹⁷⁴

Alkoxy carbonyl-de-halogenation, etc.



Aryl bromides and iodides, when treated with carbon monoxide, an alcohol ROH, a base, and a palladium complex catalyst, give carboxylic esters. The use of H_2O , RNH_2 , or an alkali metal or calcium carboxylate¹⁷⁵ instead of ROH, gives the carboxylic acid,^{175a} amide,¹⁷⁶ or mixed anhydride, respectively.¹⁷⁷ With certain palladium catalysts, aryl chlorides¹⁷⁸ and aryl triflates¹⁷⁹ can also be substrates. Other reagents used (instead of CO) have been nickel carbonyl $\text{Ni}(\text{CO})_4$ ¹⁸⁰ (see 0-103) and dicobalt octacarbonyl $\text{Co}_2(\text{CO})_8$.¹⁸¹ Aryl chlorides have been converted to carboxylic acids by an electrochemical synthesis,¹⁸² and aryl iodides to aldehydes by treatment with CO, Bu_3SnH , and $\text{NCCMe}_2\text{N}=\text{NCMe}_2\text{CN}$ (AIBN).¹⁸³

Lead tetraacetate has been used to convert phenols, with a hydrazone group in the ortho position, to carboxylic esters,¹⁸⁴ e.g.,



¹⁶⁸See Semmelhack; Bargar *J. Am. Chem. Soc.* **1980**, *102*, 7765; Bard; Bunnett *J. Org. Chem.* **1980**, *45*, 1546.

¹⁶⁹Bard; Bunnett; Creary; Tremelling *J. Am. Chem. Soc.* **1980**, *102*, 2852; Tremelling; Bunnett *J. Am. Chem. Soc.* **1980**, *102*, 7375.

¹⁷⁰Pinhey; Rowe *Aust. J. Chem.* **1980**, *33*, 113; Kopinski; Pinhey; Rowe *Aust. J. Chem.* **1984**, *37*, 1245; Kozyrod; Morgan; Pinhey *Aust. J. Chem.* **1991**, *44*, 369.

¹⁷¹For a review of these and related reactions, see Abramovitch; Barton; Finet *Tetrahedron* **1988**, *44*, 3039-3071.

¹⁷²Barton; Blazejewski; Charpiot; Finet; Motherwell; Papoula; Stanforth *J. Chem. Soc., Perkin Trans. 1* **1985**, 2667; O'Donnell; Bennett; Jacobsen; Ma *Tetrahedron Lett.* **1989**, *30*, 3913.

¹⁷³Citterio; Santi; Fiorani; Strologo *J. Org. Chem.* **1989**, *54*, 2703; Citterio; Fancelli; Finzi; Pesce; Santi *J. Org. Chem.* **1989**, *54*, 2713.

¹⁷⁴For a review, see Weil; Cassar; Foà, in Wender; Pino *Organic Synthesis Via Metal Carbonyls*, vol. 2; Wiley: New York, 1977, pp. 517-543.

¹⁷⁵Pri-Bar; Alper *J. Org. Chem.* **1989**, *54*, 36.

^{175a}For example, see Bumagin; Nikitin; Beletskaya *Doklad. Chem.* **1990**, *312*, 149.

¹⁷⁶For another reagent that also gives amides, see Bumagin; Gulevich; Beletskaya *J. Organomet. Chem.* **1985**, 285, 415.

¹⁷⁷For a review, see Heck *Palladium Reagents in Organic Synthesis*; Academic Press: New York, 1985, pp. 348-358.

¹⁷⁸Ben-David; Portnoy; Milstein *J. Am. Chem. Soc.* **1989**, *111*, 8742.

¹⁷⁹Cacchi; Ciattini; Morera; Ortar *Tetrahedron Lett.* **1986**, *27*, 3931.

¹⁸⁰Bauld *Tetrahedron Lett.* **1963**, 1841. See also Corey; Hegedus *J. Am. Chem. Soc.* **1969**, *91*, 1233; Nakayama; Mizoroki *Bull. Chem. Soc. Jpn.* **1971**, *44*, 508.

¹⁸¹Brunet; Sidot; Caubere *Tetrahedron Lett.* **1981**, *22*, 1013; *J. Org. Chem.* **1983**, *48*, 1166. See also Foà; Francalanci; Bencini; Gardano *J. Organomet. Chem.* **1985**, 285, 293; Kudo; Shibata; Kashimura; Mori; Sugita *Chem. Lett.* **1987**, 577.

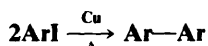
¹⁸²Hcintz; Sock; Saboureaux; Périchon *Tetrahedron* **1988**, *44*, 1631.

¹⁸³Ryu; Kusano; Masumi; Yamazaki; Ogawa; Sonoda *Tetrahedron Lett.* **1990**, *31*, 6887.

¹⁸⁴Katritzky; Kotali *Tetrahedron Lett.* **1990**, *31*, 6781.

The hydrazone group is hydrolyzed (6-2) during the course of the reaction. Yields are high. Aryl iodides are converted to unsymmetrical diaryl ketones on treatment with arylmercury halides and nickel carbonyl: $\text{ArI} + \text{Ar'HgX} + \text{Ni(CO)}_4 \rightarrow \text{ArCOAr'}$.¹⁸⁵

3-16 The Ullmann Reaction De-halogen-coupling



The coupling of aryl halides with copper is called the *Ullmann reaction*.¹⁸⁶ The reaction is of broad scope and has been used to prepare many symmetrical and unsymmetrical biaryls.¹⁸⁷ When a mixture of two different aryl halides is used, there are three possible products, but often only one is obtained. For example, picryl chloride and iodobenzene gave only 2,4,6-trinitrobiphenyl.¹⁸⁸ The best leaving group is iodo, and the reaction is most often done on aryl iodides, but bromides, chlorides, and even thiocyanates have been used.

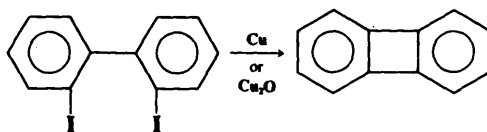
The effects of other groups on the ring are unusual. The nitro group is strongly activating, but only in the ortho (not meta or para) position.¹⁸⁹ R and OR are active in all positions. Not only do OH, NH₂, NHR, and NHCOR inhibit the reaction, as would be expected for aromatic nucleophilic substitution, but so do COOH (but not COOR), SO₂NH₂, and similar groups for which the reaction fails completely. These groups inhibit the coupling reaction by causing side reactions.

The mechanism is not known with certainty. It seems likely that it is basically a two-step process, similar to that of the Wurtz reaction (0-86), which can be represented schematically by:



Organocopper compounds have been trapped by coordination with organic bases.¹⁹⁰ In addition, arylcopper compounds (ArCu) have been independently prepared and shown to give biaryls (ArAr') when treated with aryl iodides Ar'I.¹⁹¹

A similar reaction has been used for ring closure:¹⁹²



¹⁸⁵Rhee; Ryang; Watanabe; Omura; Murai; Sonoda *Synthesis* **1977**, 776. For other acylation reactions, see Tanaka; *Synthesis* **1981**, 47, *Bull. Chem. Soc. Jpn.* **1981**, 54, 637; Bumagin; Ponomaryov; Beletskaya *Tetrahedron Lett.* **1985**, 26, 4819; Koga; Makinouchi; Okukado *Chem. Lett.* **1988**, 1141; Echavarren; Stille *J. Am. Chem. Soc.* **1988**, 110, 1557.

¹⁸⁶For reviews, see Fanta *Synthesis* **1974**, 9-21; Goshav; Otroshchenko; Sadykov *Russ. Chem. Rev.* **1972**, 41, 1046-1059.

¹⁸⁷For reviews of methods of aryl-aryl bond formation, see Bringmann; Walter; Weirich *Angew. Chem. Int. Ed. Engl.* **1990**, 29, 977-991 [*Angew. Chem.* **102**, 1006-1019]; Sainsbury *Tetrahedron* **1980**, 36, 3327-3359.

¹⁸⁸Rule; Smith *J. Chem. Soc.* **1937**, 1096.

¹⁸⁹Forrest *J. Chem. Soc.* **1960**, 592.

¹⁹⁰Lewin; Cohen *Tetrahedron Lett.* **1965**, 4531.

¹⁹¹For examples, see Nilsson *Tetrahedron Lett.* **1966**, 675; Cairncross; Sheppard *J. Am. Chem. Soc.* **1968**, 90, 2186; Ullenius *Acta Chem. Scand.* **1972**, 26, 3383; Mack; Suschitzky; Wakefield *J. Chem. Soc., Perkin Trans. 1* **1980**, 1682.

¹⁹²Salfeld; Baume *Tetrahedron Lett.* **1966**, 3365; Lothrop *J. Am. Chem. Soc.* **1941**, 63, 1187.

An important alternative to the Ullmann method is the use of certain nickel complexes.¹⁹³ This method has also been used intramolecularly.¹⁹⁴ Aryl halides ArX can also be converted to Ar—Ar¹⁹⁵ by treatment with activated Ni metal,¹⁹⁶ with Zn and nickel complexes,¹⁹⁷ with aqueous alkaline sodium formate, Pd—C, and a phase transfer catalyst,¹⁹⁸ and in an electrochemical process catalyzed by a nickel complex.¹⁹⁹

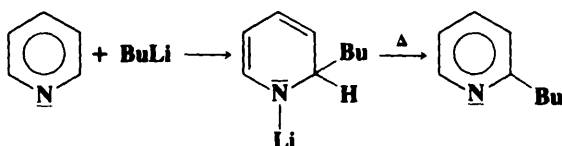
For other methods of coupling aromatic rings, see 3-13, 3-17, 4-18, 4-21, and 4-22.

OS III, 339; V, 1120.

Hydrogen as Leaving Group²⁰⁰

3-17 Alkylation and Arylation

Alkylation or **Alkyl-de-hydrogenation**, etc.



The alkylation of heterocyclic nitrogen compounds²⁰¹ with alkylolithiums is called *Ziegler alkylation*. Aryllithiums give arylation. The reaction occurs by an addition–elimination mechanism and the adduct can be isolated.²⁰² Upon heating of the adduct, elimination of LiH occurs (see 7-16) and an alkylated product is obtained. With respect to the 2-carbon the first step is the same as that of the S_NAr mechanism. The difference is that the unshared pair of electrons on the nitrogen combines with the lithium, so the extra pair of ring electrons has a place to go: it becomes the new unshared pair on the nitrogen.

The reaction has been applied to nonheterocyclic aromatic compounds: Benzene, naphthalene, and phenanthrene have been alkylated with alkylolithiums, though the usual reaction with these reagents is 2-21,²⁰³ and Grignard reagents have been used to alkylate naphthalene.²⁰⁴ The addition–elimination mechanism apparently applies in these cases too.

Aromatic nitro compounds can be methylated with dimethyloxosulfonium methylide²⁰⁵ or the methylsulfinyl carbanion (obtained by treatment of dimethyl sulfoxide with a strong base).²⁰⁶

¹⁹³See, for example Semmelhack; Helquist; Jones *J. Am. Chem. Soc.* **1971**, 93, 5908; Clark; Norman; Thomas *J. Chem. Soc., Perkin Trans. 1* **1975**, 121; Tsou; Kochi *J. Am. Chem. Soc.* **1979**, 101, 7547; Colon; Kelsey *J. Org. Chem.* **1986**, 51, 2627; Lourak; Vanderesse; Fort; Caubere *J. Org. Chem.* **1989**, 54, 4840, 4844; Iyoda; Otsuka; Sato; Nisato; Oda *Bull. Chem. Soc. Jpn.* **1990**, 63, 80. For a review of the mechanism, see Amatore; Jutand *Acta Chem. Scand.* **1990**, 44, 755-764.

¹⁹⁴See for example, Karimipour; Semones; Asleson; Heldrich *Synlett* **1990**, 525.

¹⁹⁵For a list of reagents, with references, see Ref. 116, pp. 46-47.

¹⁹⁶Inaba; Matsumoto; Rieck *Tetrahedron Lett.* **1982**, 23, 4215; Matsumoto; Inaba; Rieck *J. Org. Chem.* **1983**, 48, 840; Chao; Cheng; Chang *J. Org. Chem.* **1983**, 48, 4904.

¹⁹⁷Takagi; Hayama; Sasaki *Bull. Chem. Soc. Jpn.* **1984**, 57, 1887.

¹⁹⁸Bamfield; Quan *Synthesis* **1978**, 537.

¹⁹⁹Meyers; Rollin; Perichon *J. Organomet. Chem.* **1987**, 333, 263.

²⁰⁰For a review, see Chupakhin; Postovskii *Russ. Chem. Rev.* **1976**, 45, 454-468. For a review of reactivity and mechanism in these cases, see Chupakhin; Charushin; van der Plas *Tetrahedron* **1988**, 44, 1-34.

²⁰¹For a review of substitution by carbon groups on a nitrogen heterocycle, see Vorbrüggen; Maas *Heterocycles* **1988**, 27, 2659-2776. For a related review, see Comins; O'Connor *Adv. Heterocycl. Chem.* **1988**, 44, 199-267.

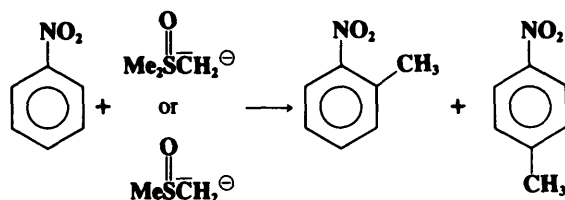
²⁰²See, for example, Armstrong; Mulvey; Barr; Snaith; Reed *J. Organomet. Chem.* **1988**, 350, 191.

²⁰³Dixon; Fishman *J. Am. Chem. Soc.* **1963**, 85, 1356; Eppley; Dixon *J. Am. Chem. Soc.* **1968**, 90, 1606.

²⁰⁴Bryce-Smith; Wakefield *Tetrahedron Lett.* **1964**, 3295.

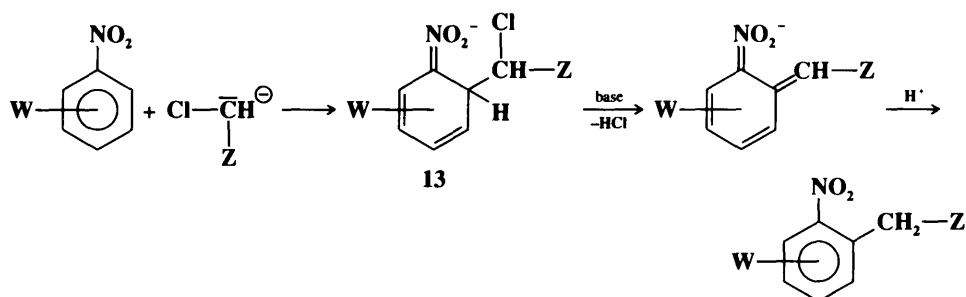
²⁰⁵Traynelis; McSwecney *J. Org. Chem.* **1966**, 31, 243.

²⁰⁶Russell; Weiner *J. Org. Chem.* **1966**, 31, 248.



The latter reagent also methylates certain heterocyclic compounds, e.g., quinoline, and certain fused aromatic compounds, e.g., anthracene, phenanthrene.²⁰⁷ The reactions with the sulfur carbanions are especially useful, since none of these substrates can be methylated by the Friedel–Crafts procedure (1-12). It has been reported²⁰⁸ that aromatic nitro compounds can also be alkylated, not only with methyl but with other alkyl and substituted alkyl groups as well, in ortho and para positions, by treatment with an alkylolithium compound (or, with lower yields, a Grignard reagent), followed by an oxidizing agent such as Br₂ or DDQ (p. 1163). Trinitrobenzene was alkylated (ArH → ArR) by treatment with a silane RSiMe₃ in the presence of KF and a crown ether.²⁰⁹ In this reaction, R was not a simple alkyl group, but a group such as CH₂COOMe, COMe, CH₂Ph, CH₂CH=CH₂, etc.

A different kind of alkylation of nitro compounds uses carbanion nucleophiles that have a chlorine at the carbanionic carbon. The following process takes place:²¹⁰



This type of process is called *vicarious nucleophilic substitution of hydrogen*.²¹¹ Z is an electron-withdrawing group such as SO₂R, SO₂OR, SO₂NR₂, COOR, or CN; it stabilizes the negative charge. The carbanion attacks the activated ring ortho or para to the nitro group. Hydride ion H⁻ is not normally a leaving group, but in this case the presence of the adjacent Cl allows the hydrogen to be replaced. Hence, Cl is a “vicarious” leaving group. Other leaving groups have been used, e.g., OMe, SPh, but Cl is generally the best. Many groups W in ortho, meta, or para positions do not interfere. The reaction is also successful for di- and trinitro compounds, for nitronaphthalenes,²¹² and for many nitro heterocycles.

Z—C⁻R—Cl may also be used.²¹³ When Br₃C⁻ or Cl₃C⁻ is the nucleophile the product is ArCHX₂, which can easily be hydrolyzed to ArCHO.²¹⁴ This is therefore an indirect way

²⁰⁷Ref. 206; Argabright; Hofmann; Schriesheim *J. Org. Chem.* **1965**, 30, 3233; Trost *Tetrahedron Lett.* **1966**, 5761; Yamamoto; Nisimura; Nozaki *Bull. Chem. Soc. Jpn.* **1971**, 44, 541.

²⁰⁸Kienle *Helv. Chim. Acta* **1978**, 61, 449.

²⁰⁹Artamkina; Kovalenko; Beletskaya; Reutov *J. Organomet. Chem.* **1987**, 329, 139, *J. Org. Chem. USSR* **1990**, 26, 801. See also RajanBabu; Reddy; Fukunaga *J. Am. Chem. Soc.* **1985**, 107, 5473.

²¹⁰In some cases intermediate 13 has been isolated: Stahly; Stahly; Maloney *J. Org. Chem.* **1988**, 53, 690.

²¹¹Goliński; Mąkosza *Tetrahedron Lett.* **1978**, 3495. For reviews, see Mąkosza *Synthesis* **1991**, 103-111, *Russ. Chem. Rev.* **1989**, 58, 747-757; Mąkosza; Winiarski *Acc. Chem. Res.* **1987**, 20, 282-289.

²¹²Mąkosza; Danikiewicz; Wojciechowski *Liebigs Ann. Chem.* **1987**, 711.

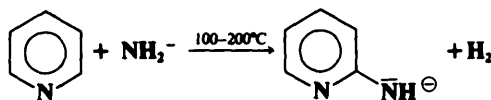
²¹³See Mudryk; Mąkosza *Tetrahedron* **1988**, 44, 209.

²¹⁴Mąkosza; Owczarczyk *J. Org. Chem.* **1989**, 54, 5094. See also Mąkosza; Winiarski *Chem. Lett.* **1984**, 1623.

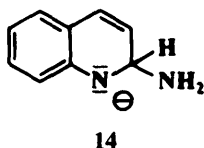
of formylating an aromatic ring containing one or more NO_2 groups, which cannot be done by any of the formylations mentioned in Chapter 11 (1-16 to 1-18).

For the introduction of CH_2SR groups into phenols, see 1-26. See also 4-23. OS II, 517.

3-18 Amination of Nitrogen Heterocycles Amination or Amino-de-hydrogenation



Pyridine and other heterocyclic nitrogen compounds can be aminated with alkali-metal amides in a process called the *Chichibabin reaction*.²¹⁵ The attack is always in the 2 position unless both such positions are filled, in which case the 4 position is attacked. Substituted alkali-metal amides, e.g., RNH^- and R_2N^- , have also been used. The mechanism is probably similar to that of 3-17. The existence of intermediate ions such as 14

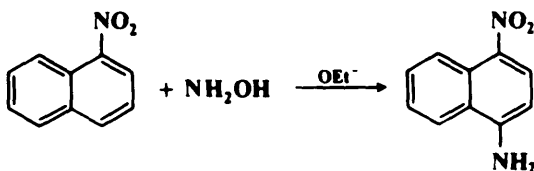


(from quinoline) has been demonstrated by nmr spectra.²¹⁶ A pyridyne type of intermediate was ruled out by several observations including the facts that 3-ethylpyridine gave 2-amino-3-ethylpyridine²¹⁷ and that certain heterocycles that cannot form an aryne could nevertheless be successfully aminated. Nitro compounds do not give this reaction,²¹⁸ but they have been aminated ($\text{ArH} \rightarrow \text{ArNH}_2$ or ArNHR) via the vicarious substitution principle (see 3-17), using 4-amino- or 4-alkylamino-1,2,4-triazoles as nucleophiles.²¹⁹ The vicarious leaving group in this case is the triazole ring.

Analogous reactions have been carried out with hydrazide ions, R_2NNH^- .²²⁰ For other methods of aminating aromatic rings, see 1-6 and 3-19.

There are no *Organic Syntheses* references, but see OS V, 977, for a related reaction.

3-19 Amination by Hydroxylamine Amination or Amino-de-hydrogenation



²¹⁵For reviews, see Vorbrüggen *Adv. Heterocycl. Chem.* **1990**, 49, 117-192; McGill; Rappa *Adv. Heterocycl. Chem.* **1988**, 44, 1-79; Pozharskii; Simonov; Doron'kin *Russ. Chem. Rev.* **1978**, 47, 1042-1060.

²¹⁶Zoltewicz; Helmick; Oestreich; King; Kandetzki *J. Org. Chem.* **1973**, 38, 1947; Woźniak; Baránski; Nowak; van der Plas *J. Org. Chem.* **1987**, 52, 5643.

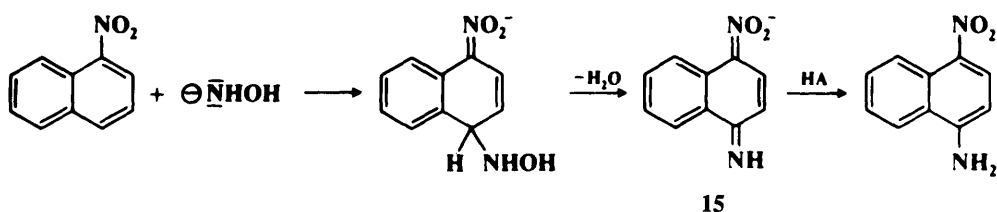
²¹⁷Ban; Wakamatsu *Chem. Ind. (London)* **1964**, 710.

²¹⁸See, for example, Levitt; Levitt *Chem. Ind. (London)* **1975**, 520.

²¹⁹Katritzky; Laurenzo *J. Org. Chem.* **1986**, 51, 5039. **1988**, 53, 3978.

²²⁰Kauffmann; Hansen; Kosel; Schoenck *Liebigs Ann. Chem.* **1962**, 656, 103.

Activated aromatic compounds can be directly aminated with hydroxylamine in the presence of strong bases.²²¹ Conditions are mild and yields are high. Ions of the type **15** are intermediates:

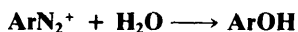


OS III, 664.

N_2^+ as Leaving Group

The diazonium group can be replaced by a number of groups.²²² Some of these are nucleophilic substitutions, with $\text{S}_{\text{N}}1$ mechanisms (p. 644), but others are free-radical reactions and are treated in Chapter 14. The solvent in all these reactions is usually water. With other solvents it has been shown that the $\text{S}_{\text{N}}1$ mechanism is favored by solvents of low nucleophilicity, while those of high nucleophilicity favor free-radical mechanisms.²²³ (For formation of diazonium ions, see **2-49**.) The N_2^+ group can be replaced by Cl^- , Br^- , and CN^- , by a nucleophilic mechanism (see OS IV, 182), but the Sandmeyer reaction is much more useful (**4-25** and **4-28**). As mentioned on p. 651 it must be kept in mind that the N_2^+ group can activate the removal of another group on the ring.

3-20 Hydroxy-de-diazonation



Water is usually present whenever diazonium salts are made, but at these temperatures (0 to 5°C) the reaction proceeds very slowly. When it is *desired* to have OH replace the diazonium group, the excess nitrous acid is destroyed and the solution is usually boiled. Some diazonium salts require even more vigorous treatment, e.g., boiling with aqueous sulfuric acid or with trifluoroacetic acid containing potassium trifluoroacetate.²²⁴ The reaction can be performed on solutions of any diazonium salts, but hydrogen sulfates are preferred to chlorides or nitrates, since in these cases there is competition from the nucleophiles Cl^- or NO_3^- . A better method, which is faster, avoids side reactions, takes place at room temperature, and gives higher yields consists of adding Cu_2O to a dilute solution of the diazonium salt dissolved in a solution containing a large excess of $\text{Cu}(\text{NO}_3)_2$.²²⁵ Aryl radicals are intermediates when this method is used. It has been shown that aryl radicals are at least partly involved when ordinary hydroxy-de-diazonation is carried out in weakly alkaline

²²¹See Chupakhin; Postovskii, Ref. 200, p. 456.

²²²For a review of such reactions, see Wulfman, in Patai *The Chemistry of Diazonium and Diazo Groups*, pt. 1; Wiley: New York, 1978, pp. 286-297.

²²³Szele; Zollinger *Helv. Chim. Acta* **1978**, 61, 1721.

²²⁴Horning; Ross; Muchowski *Can. J. Chem.* **1973**, 51, 2347.

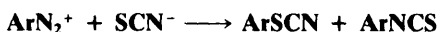
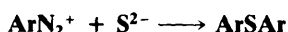
²²⁵Cohen; Dietz; Miscer *J. Org. Chem.* **1977**, 42, 2053.

aqueous solution.²²⁶ Decomposition of arenediazonium tetrafluoroborates in F_3CSO_2OH gives aryl triflates directly, in high yields.^{226a}

OS I, 404; III, 130, 453, 564; V, 1130.

3-21 Replacement by Sulfur-Containing Groups

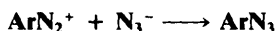
Mercapto-de-diazoniation, etc.



These reactions are convenient methods for putting sulfur-containing groups onto an aromatic ring. With $Ar'S^-$, diazosulfides $Ar-N=N-S-Ar'$ are intermediates,²²⁷ which can in some cases be isolated.²²⁸ Thiophenols can be made as shown above, but more often the diazonium ion is treated with $EtO-CSS^-$ or S_2^{2-} , which give the expected products, and these are easily convertible to thiophenols. See also 4-27.

OS II, 580; III, 809 (but see OS V, 1050). Also see OS II, 238.

3-22 Azido-de-diazoniation



Diazonium salts can be converted to aryl azides by the addition of sodium azide to the acidic diazonium salt solution.²²⁹

OS IV, 75; V, 829.

3-23 Iodo-de-diazoniation



One of the best methods for the introduction of iodine into aromatic rings is the reaction of diazonium salts with iodide ions. Analogous reactions with chloride, bromide, and fluoride ions give poorer results, and 4-25 and 3-24 are preferred for the preparation of aryl chlorides, bromides, and fluorides. However, when other diazonium reactions are carried out in the presence of these ions, halides are usually side products.

The actual attacking species is probably not only I^- , if it is I^- at all. The iodide ion is oxidized (by the diazonium ion, nitrous acid, or some other oxidizing agent) to iodine, which in a solution containing iodide ions is converted to I_3^- ; this is the actual attacking species, at least partly. This was shown by isolation of $ArN_2^+ I_3^-$ salts, which, on standing, gave ArI .²³⁰ From this, it can be inferred that the reason the other halide ions give poor results

²²⁶Dreher; Niederer; Rieker; Schwarz; Zollinger *Helv. Chim. Acta* **1981**, 64, 488.

^{226a}Yoneda; Fukuhara; Mizokami; Suzuki *Chem. Lett.* **1991**, 459.

²²⁷Abeywickrema; Beckwith *J. Am. Chem. Soc.* **1986**, 108, 8227, and references cited therein.

²²⁸See, for example Price; Tsunawaki *J. Org. Chem.* **1963**, 28, 1867.

²²⁹Smith; Brown *J. Am. Chem. Soc.* **1951**, 73, 2438. For a review, see Biffin; Miller; Paul, in Patai *The Chemistry of the Azido Group*; Wiley: New York, 1971, pp. 147-176.

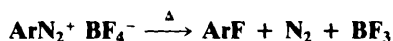
²³⁰Carey; Millar *Chem. Ind. (London)* **1960**, 97.

is not that they are poor nucleophiles but that they are poor reducing agents (compared with iodide). There is also evidence for a free radical mechanism.²³¹

OS II, 351, 355, 604; V, 1120.

3-24 The Schiemann Reaction

Fluoro-de-diazoniatio (overall transformation)



Heating of diazonium fluoroborates (the *Schiemann* or *Balz-Schiemann reaction*) is by far the best way of introducing fluorine into an aromatic ring.²³² In the most common procedure, the fluoroborate salts are prepared by diazotizing as usual with nitrous acid and HCl and then adding a cold aqueous solution of NaBF₄, HBF₄, or NH₄BF₄. A precipitate forms, which is dried, and the salt is heated in the dry state. These salts are unusually stable for diazonium salts, and the reaction is usually successful. In general, any aromatic amine that can be diazotized will form a BF₄⁻ salt, usually with high yields. The diazonium fluoroborates can be formed directly from primary aromatic amines with *t*-butyl nitrate and BF₃-etherate.²³³ The reaction has also been carried out on ArN₂⁺ PF₆⁻, ArN₂⁺ SbF₆⁻, and ArN₂⁺ AsF₆⁻ salts, in many cases with better yields.²³⁴ The reaction has been extended to ArN₂⁺ BCl₄⁻ and ArN₂⁺ BBr₄⁻,²³⁵ but aryl chlorides and bromides are more commonly prepared by the Sandmeyer reaction (4-25). In an alternative procedure, aryl fluorides have been prepared by treatment of aryltriazenes Ar—N=N—NR₂ with 70% HF in pyridine.²³⁶

The mechanism is of the S_N1 type. That aryl cations are intermediates was shown by the following experiments:²³⁷ aryl diazonium chlorides are known to arylate other aromatic rings by a free-radical mechanism (see 4-18). In radical arylation it does not matter whether the other ring contains electron-withdrawing or electron-donating groups; in either case a mixture of isomers is obtained, since the attack is not by a charged species. If an aryl radical were an intermediate in the Schiemann reaction and the reaction were run in the presence of other rings, it should not matter what kinds of groups were on these other rings: mixtures of biaryls should be obtained in all cases. But if an aryl cation is an intermediate in the Schiemann reaction, compounds containing meta-directing groups, i.e., meta-directing for *electrophilic* substitutions, should be meta-arylated and those containing ortho-para-directing groups should be ortho- and para-arylated, since an aryl cation should behave in this respect like any electrophile (see Chapter 11). Experiments are shown²³⁸ that such orientation is observed, demonstrating that the Schiemann reaction has a positively charged intermediate. The attacking species, in at least some instances, is not F⁻ but BF₄⁻.²³⁹

OS II, 188, 295, 299; V, 133.

²³¹Singh; Kumar *Aust. J. Chem.* **1972**, 25, 2133; Kumar; Singh *Tetrahedron Lett.* **1972**, 613; Meyer; Rössler; Stöcklin *J. Am. Chem. Soc.* **1979**, 101, 3121; Packer; Taylor *Aust. J. Chem.* **1985**, 38, 991; Abeywickrema; Beckwith *J. Org. Chem.* **1987**, 52, 2568.

²³²For a review, see Suschitzky *Adv. Fluorine Chem.* **1965**, 4, 1-30.

²³³Doyle; Bryker *J. Org. Chem.* **1979**, 44, 1572.

²³⁴Rutherford; Redmond; Rigamonti *J. Org. Chem.* **1961**, 26, 5149; Sellers; Suschitzky *J. Chem. Soc. C* **1968**, 2317.

²³⁵Olah; Tolgyesi *J. Org. Chem.* **1961**, 26, 2053.

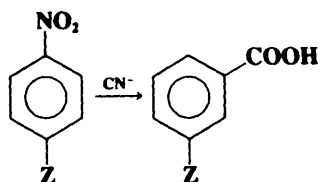
²³⁶Rosenfeld; Widdowson *J. Chem. Soc., Chem. Commun.* **1979**, 914. For another alternative procedure, see Yoneda; Fukuhara; Kikuchi; Suzuki *Synth. Commun.* **1989**, 19, 865.

²³⁷See also Swain; Sheats; Harbison, Ref. 21; Becker; Israel *J. Prakt. Chem.* **1979**, 321, 579.

²³⁸Makarova; Matveeva *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1958**, 548; Makarova; Matveeva; Gribchenko *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1958**, 1399.

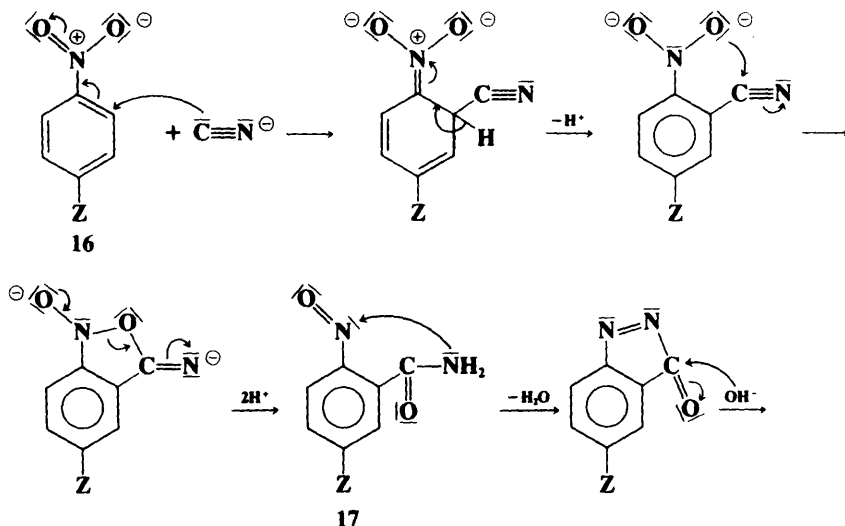
²³⁹Swain; Rogers *J. Am. Chem. Soc.* **1975**, 97, 799.

Rearrangements

3-25 The von Richter Rearrangement
Hydro-de-nitro-*cine*-substitution

When aromatic nitro compounds are treated with cyanide ion, the nitro group is displaced and a carboxyl group enters with *cine* substitution (p. 646), always ortho to the displaced group, never meta or para. The scope of this reaction, called the *von Richter rearrangement*, is variable.²⁴⁰ As with other nucleophilic aromatic substitutions, the reaction gives best results when electron-withdrawing groups are in ortho and para positions, but yields are low, usually less than 20% and never more than 50%.

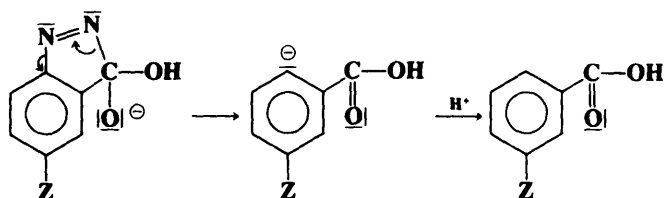
At one time it was believed that a nitrile, ArCN , was an intermediate, since cyanide is the reagent and nitriles are hydrolyzable to carboxylic acids under the reaction conditions (6-5). However, a remarkable series of results proved this belief to be in error. Bunnett and Rauhut demonstrated²⁴¹ that α -naphthyl cyanide is *not* hydrolyzable to α -naphthoic acid under conditions at which β -nitronaphthalene undergoes the von Richter rearrangement to give α -naphthoic acid. This proved that the nitrile cannot be intermediate. It was subsequently demonstrated that N_2 is a major product of the reaction.²⁴² It had previously been assumed that all the nitrogen in the reaction was converted to ammonia, which would be compatible with a nitrile intermediate, since ammonia is a hydrolysis product of nitriles. At the same time it was shown that NO_2^- is not a major product. The discovery of nitrogen indicated that a nitrogen-nitrogen bond must be formed during the course of the reaction. A mechanism in accord with all the facts was proposed by Rosenblum:²⁴²



²⁴⁰For a review, see Shine *Aromatic Rearrangements*; Elsevier: New York, 1967, pp. 326-335.

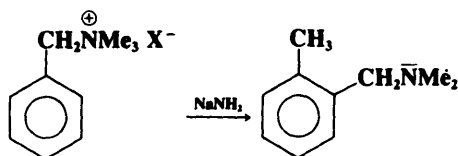
²⁴¹Bunnett; Rauhut *J. Org. Chem.* **1956**, *21*, 934, 944.

²⁴²Rosenblum *J. Am. Chem. Soc.* **1960**, *82*, 3796.



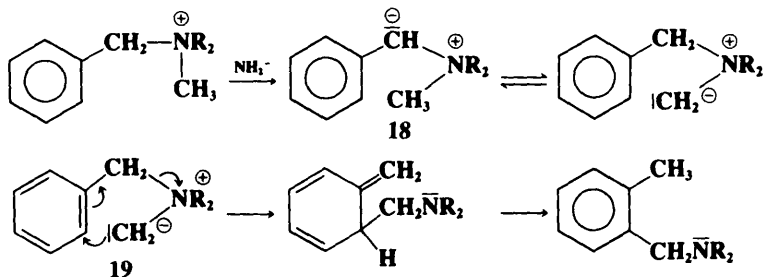
It may be noted that **17** are stable compounds; hence it should be possible to prepare them independently and to subject them to the conditions of the von Richter rearrangement. This was done and the correct products are obtained.²⁴³ Further evidence is that when **16** ($Z = \text{Cl}$ or Br) was treated with cyanide in H_2^{18}O , half the oxygen in the product was labeled, showing that one of the oxygens of the carboxyl group came from the nitro group and one from the solvent, as required by this mechanism.²⁴⁴

3-26 The Sommelet-Hauser Rearrangement



Benzylic quaternary ammonium salts, when treated with alkali-metal amides, undergo a rearrangement called the *Sommelet-Hauser rearrangement*.²⁴⁵ Since the product is a benzylic tertiary amine, it can be further alkylated and the product again subjected to the rearrangement. This process can be continued around the ring until an ortho position is blocked.²⁴⁶

The rearrangement occurs with high yields and can be performed with various groups present in the ring.²⁴⁷ The reaction is most often carried out with three methyl groups on the nitrogen, but other groups can also be used, though if a β hydrogen is present, Hofmann elimination (**7-6**) often competes. The Stevens rearrangement (**8-22**) is also a competing process.²⁴⁸ When both rearrangements are possible, the Stevens is favored at high temperatures and the Sommelet-Hauser at low temperatures.²⁴⁹ The mechanism is



²⁴³Ibne-Rasa; Koubek *J. Org. Chem.* **1963**, 28, 3240.

²⁴⁴Samuel *J. Chem. Soc.* **1960**, 1318. For other evidence, see Cullen; L'Ecuyer *Can. J. Chem.* **1961**, 39, 144, 155, 382; Ullman; Bartkus *Chem. Ind. (London)* **1962**, 93.

²⁴⁵For reviews, see Pine, *Org. React.* **1970**, 18, 403-464; Lepley; Giumanini *Mech. Mol. Migr.* **1971**, 3, 297-440; Wittig *Bull. Soc. Chim. Fr.* **1971**, 1921-1924; Stevens; Watts *Selected Molecular Rearrangements*; Van Nostrand-Reinhold: Princeton, 1973, pp. 81-88; Shine, Ref. 240, pp. 316-326.

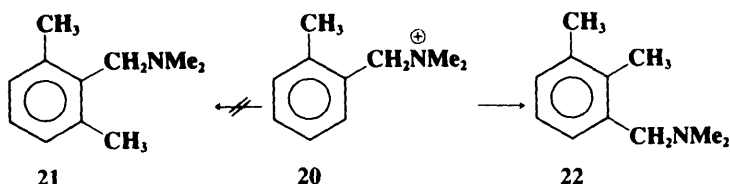
²⁴⁶Beard; Hauser *J. Org. Chem.* **1960**, 25, 334.

²⁴⁷Beard; Hauser *J. Org. Chem.* **1961**, 26, 371; Jones; Beard; Hauser *J. Org. Chem.* **1963**, 28, 199.

²⁴⁸For a method that uses nonbasic conditions, and gives high yields of the Sommelet-Hauser product, with little or no Stevens rearrangement, see Nakano; Sato *J. Org. Chem.* **1987**, 52, 1844; Shirai; Sato *J. Org. Chem.* **1988**, 53, 194.

²⁴⁹Wittig; Streib *Liebigs Ann. Chem.* **1953**, 584, 1.

The benzylic hydrogen is most acidic and is the one that first loses a proton to give the ylide **18**. However, **19**, which is present in smaller amount, is the species that undergoes the rearrangement, shifting the equilibrium in its favor. This mechanism is an example of a [2,3] sigmatropic rearrangement (see 8-37). Another mechanism that might be proposed is one in which a methyl group actually breaks away (in some form) from the nitrogen and then attaches itself to the ring. That this is not so was shown by a product study.²⁵⁰ If the second mechanism were true, **20** should give **21**, but the first mechanism predicts the formation of **22**, which is what was actually obtained.²⁵¹

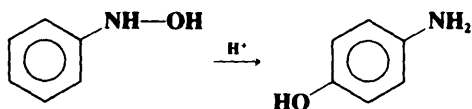


The mechanism as we have pictured it can lead only to an ortho product. However, a small amount of para product has been obtained in some cases.²⁵² A mechanism²⁵³ in which there is a dissociation of the ArC—N bond (similar to the ion-pair mechanism of the Stevens rearrangement, p. 1101) has been invoked to explain the obtention of the para products.

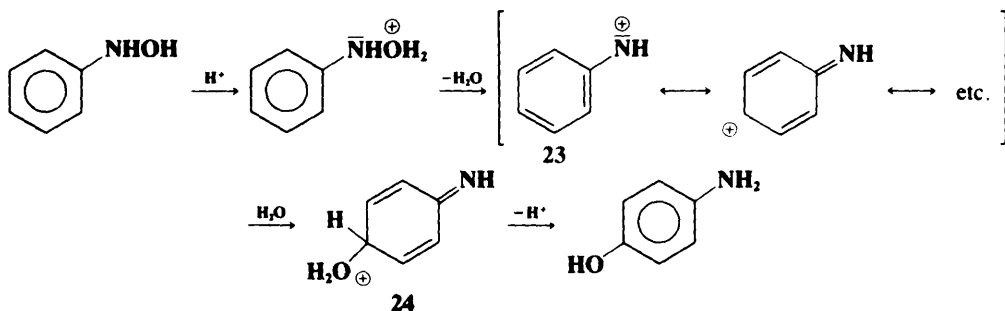
Sulfur ylides containing a benzylic group (analogous to **19**) undergo an analogous rearrangement.²⁵⁴

OS IV, 585.

3-27 Rearrangement of Aryl Hydroxylamines 1/C-Hydro-5/N-hydroxy-interchange



Aryl hydroxylamines treated with acids rearrange to aminophenols.²⁵⁵ Although this reaction (known as the *Bamberger rearrangement*) is similar in appearance to **1-32** to **1-36**, the attack on the ring is not electrophilic but nucleophilic. The rearrangement is intermolecular, with the following mechanism:



²⁵⁰For other evidence for the mechanism given, see Hauser; Van Ecnam *J. Am. Chem. Soc.* **1957**, 79, 5512; Jones; Hauser *J. Org. Chem.* **1961**, 26, 2979; Puterbaugh; Hauser *J. Am. Chem. Soc.* **1964**, 86, 1105; Pine; Sanchez *Tetrahedron Lett.* **1969**, 1319; Shirai; Watanabe; Sato *J. Org. Chem.* **1990**, 55, 2767.

²⁵¹Kantor; Hauser *J. Am. Chem. Soc.* **1951**, 73, 4122.

²⁵²Pine *Tetrahedron Lett.* **1967**, 3393; Pine, Ref. 245, p. 418.

²⁵³Bumgardner *J. Am. Chem. Soc.* **1963**, 85, 73.

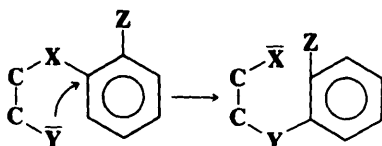
²⁵⁴See *Block Reactions of Organosulfur Compounds*; Academic Press: New York, 1978, pp. 118-124.

²⁵⁵For a review, see Ref. 240, pp. 182-190.

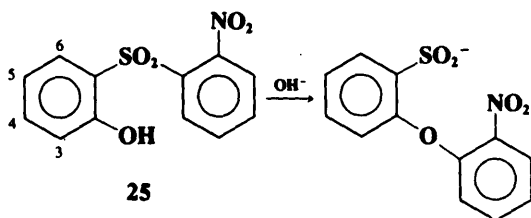
Among the evidence²⁵⁶ for this mechanism are the facts that other products are obtained when the reaction is run in the presence of competing nucleophiles, e.g., *p*-ethoxyaniline when ethanol is present, and that when the para position is blocked, compounds similar to **24** are isolated. In the case of 2,6-dimethylphenylhydroxylamine, the intermediate nitrenium ion **23** was trapped, and its lifetime in solution was measured.²⁵⁷ The reaction of **23** with water was found to be diffusion controlled.²⁵⁷

OS IV, 148.

3-28 The Smiles Rearrangement



The *Smiles rearrangement* actually comprises a group of rearrangements that follow the pattern given above.²⁵⁸ A specific example is



Smiles rearrangements are simply intramolecular nucleophilic substitutions. In the example given, SO_2Ar is the leaving group and ArO^- the nucleophile, and the nitro group serves to activate its ortho position. The ring at which the substitution takes place is nearly always activated, usually by ortho or para nitro groups. X is usually S, SO, SO_2 ,²⁵⁹ O, or COO. Y is usually the conjugate base of OH, NH_2 , NHR, or SH. The reaction has even been carried out with $\text{Y} = \text{CH}_2^-$ (phenyllithium was the base here).²⁶⁰

The reaction rate is greatly enhanced by substitution in the 6 position of the attacking ring, for steric reasons. For example, a methyl, chloro, or bromo group in the 6 position of **25** caused the rate to be about 10^5 times faster than when the same groups were in the 4 position,²⁶¹ though electrical effects should be similar at these positions. The enhanced rate comes about because the most favorable conformation the molecule can adopt to suit the bulk of the 6-substituent is also the conformation required for the rearrangement. Thus, less entropy of activation is required.

²⁵⁶For additional evidence, see Sone; Hamamoto; Seiji; Shinkai; Manabe *J. Chem. Soc., Perkin Trans. 2* **1981**, 1596; Kohnstam; Petch; Williams *J. Chem. Soc., Perkin Trans. 2* **1984**, 423; Sternson; Chandrasakar *J. Org. Chem.* **1984**, 49, 4295, and references cited in these papers.

²⁵⁷Fishbein; McClelland *J. Am. Chem. Soc.* **1987**, 109, 2824.

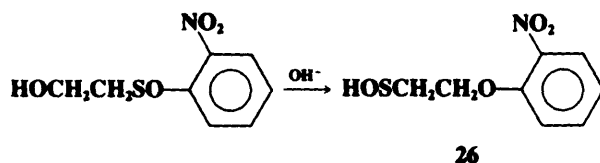
²⁵⁸For reviews, see Truce; Kreider; Brand *Org. React.* **1971**, 18, 99-215; Shine, Ref. 240, pp. 307-316; Stevens; Watts, Ref. 245, pp. 120-126.

²⁵⁹For a review for the case of $\text{X} = \text{SO}_2$, see Cerfontain *Mechanistic Aspects in Aromatic Sulfonation and Desulfonation*; Wiley: New York, 1968, pp. 262-274.

²⁶⁰Truce; Ray *J. Am. Chem. Soc.* **1959**, 81, 481; Truce; Robbins; Kreider **1966**, 88, 4027; Drozd; Nikonova *J. Org. Chem. USSR* **1969**, 5, 313.

²⁶¹Bunnett; Okamoto *J. Am. Chem. Soc.* **1956**, 78, 5363.

Although the Smiles rearrangement is usually carried out on compounds containing two rings, this need not be the case; e.g.,²⁶²



In this case the sulfenic acid (**26**) is unstable²⁶³ and the actual products isolated were the corresponding sulfinic acid (RSO₂H) and disulfide (R₂S₂).

²⁶²Kent; Smiles *J. Chem. Soc.* **1934**, 422.

²⁶³For a stable sulfenic acid, see Nakamura *J. Am. Chem. Soc.* **1983**, 105, 7172.

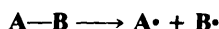
14

FREE-RADICAL SUBSTITUTION

MECHANISMS

Free-Radical Mechanisms in General¹

A free-radical process consists of at least two steps. The first step involves the *formation* of free radicals, usually by homolytic cleavage of bond, i.e., a cleavage in which each fragment retains one electron:



This is called an *initiation* step. It may happen spontaneously or may be induced by heat or light (see the discussion on p. 193), depending on the type of bond. Peroxides, including hydrogen peroxide, dialkyl, diacyl, and alkyl acyl peroxides, and peracids are the most common source of free radicals induced spontaneously or by heat, but other organic compounds with low-energy bonds, such as azo compounds, are also used. Molecules that are cleaved by light are most often chlorine, bromine, and various ketones (see Chapter 7). Radicals can also be formed in another way, by a one-electron transfer (loss or gain), e.g., $\text{A}^+ + \text{e}^- \rightarrow \text{A}\cdot$. One-electron transfers usually involve inorganic ions or electrochemical processes.

The second step involves the *destruction* of free radicals. This usually happens by a process opposite to the first, namely, a combination of two like or unlike radicals to form a new bond:²



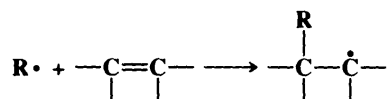
This type of step is called *termination*, and it ends the reaction as far as these particular radicals are concerned.³ However, it is not often that termination follows *directly* upon initiation. The reason is that most radicals are very reactive and will react with the first available species with which they come in contact. In the usual situation, in which the concentration of radicals is low, this is much more likely to be a molecule than another radical. When a radical (which has an odd number of electrons) reacts with a molecule

¹For books on free-radical mechanisms, see Nonhebel; Tedder; Walton *Radicals*; Cambridge University Press: Cambridge, 1979; Nonhebel; Walton *Free-Radical Chemistry*; Cambridge University Press: London, 1974; Huyser *Free-Radical Chain Reactions*; Wiley: New York, 1970; Pryor *Free Radicals*; McGraw-Hill: New York, 1966; For reviews, see Huyser, in McManus *Organic Reactive Intermediates*; Academic Press: New York, 1973, pp. 1-59; Lloyd, *CHEMTECH* **1971**, 176-180, 371-381, 687-696, **1972**, 182-188. For monographs on the use of free-radical reactions in synthesis, see Giese *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon: Elmsford, NY, 1986; Davies; Parrott *Free Radicals in Organic Synthesis*; Springer: New York, 1978. For reviews, see Curran *Synthesis* **1988**, 417-439, 489-513; Ramaiah *Tetrahedron* **1987**, 43, 3541-3676.

²For a review of the stereochemistry of this type of combination reaction, see Porter; Krebs *Top. Stereochem.* **1988**, 18, 97-127.

³Another type of termination is disproportionation (see p. 194).

(which has an even number), the total number of electrons in the products must be odd. The product in a particular step of this kind may be one particle, e.g.,



in which case it may be another free radical; or it may consist of two particles, e.g.,



in which case one must be a molecule and one a free radical, but in any case a *new radical is generated*. This type of step is called *propagation*, since the newly formed radical can now react with another molecule and produce another radical, and so on, until two radicals do meet each other and terminate the sequence. The process just described is called a *chain reaction*,⁴ and there may be hundreds or thousands of propagation steps between an initiation and a termination. Two other types of propagation reactions do not involve a molecule at all. These are (1) cleavage of a radical into, necessarily, a radical and a molecule and (2) rearrangement of one radical to another (see Chapter 18). When radicals are highly reactive, e.g., alkyl radicals, chains are long, since reactions occur with many molecules; but with radicals of low reactivity, e.g., aryl radicals, the radical may be unable to react with anything until it meets another radical, so that chains are short, or the reaction may be a nonchain process. In any particular chain process there is usually a wide variety of propagation and termination steps. Because of this, these reactions lead to many products and are often difficult to treat kinetically.⁵

The following are some general characteristics of free-radical reactions:

1. Reactions are fairly similar whether they are occurring in the vapor or liquid phase, though solvation of free radicals in solution does cause some differences.⁶
2. They are largely unaffected by the presence of acids or bases or by changes in the polarity of solvents, except that nonpolar solvents may suppress competing ionic reactions.
3. They are initiated or accelerated by typical free-radical sources, such as the peroxides referred to, or by light. In the latter case the concept of quantum yield applies (p. 247). Quantum yields can be quite high, e.g., 1000, if each quantum generates a long chain, or low, in the case of nonchain processes.
4. Their rates are decreased or the reactions are suppressed entirely by substances that scavenge free radicals, e.g., nitric oxide, molecular oxygen, or benzoquinone. These substances are called *inhibitors*.⁷

In this chapter are discussed free-radical substitution reactions. Free-radical additions to unsaturated compounds and rearrangements are discussed in Chapters 15 and 18, respectively. In addition, many of the oxidation-reduction reactions considered in Chapter 19 involve free-radical mechanisms. Several important types of free-radical reactions do not usually lead to reasonable yields of pure products and are not generally treated in this book. Among these are polymerizations and high-temperature pyrolyses.

⁴For a discussion of radical chain reactions from a synthetic point of view, see Walling *Tetrahedron* **1985**, *41*, 3887.

⁵For a discussion of the kinetic aspects of radical chain reactions, see Huyser *Free-Radical Chain Reactions*, Ref. 1, pp. 39-65.

⁶For a discussion, see Mayo *J. Am. Chem. Soc.* **1967**, *89*, 2654.

⁷For a review of the action of inhibitors, see Denisov; Khudyakov *Chem. Rev.* **1987**, *87*, 1313-1357.

Free-Radical Substitution Mechanisms⁸

In a free-radical substitution reaction



there must first be a cleavage of the substrate RX so that R• radicals are produced. This can happen by a spontaneous cleavage



or it can be caused by light or heat, or, more often, there is no actual cleavage, but R• is produced by an *abstraction*



W• is produced by adding a compound, such as a peroxide, that spontaneously forms free radicals. Such a compound is called an *initiator*. Once R• is formed, it can go to product in two ways, by abstraction



or by coupling with another radical



In a reaction with a moderately long chain, much more of the product will be produced by abstraction (4) than by coupling (5). Cleavage steps like (2) have been called SH1 (H for homolytic), and abstraction steps like (3) and (4) have been called SH2; reactions can be classified as SH1 or SH2 on the basis of whether RX is converted to R by (2) or (3).⁹ Most chain substitution mechanisms follow the pattern (3), (4), (3), (4) . . . Chains are long and reactions go well where both (3) and (4) are energetically favored (no worse than slightly endothermic, see pp. 683, 693). The IUPAC designation of a chain reaction that follows the pattern (3), (4) . . . is $A_rD_r + A_rD_r$ (R stands for radical).

With certain radicals the transition state in an abstraction reaction has some polar character. For example, consider the abstraction of hydrogen from the methyl group of toluene by a bromine atom. Since bromine is more electronegative than carbon, it is reasonable to assume that in the transition state there is a separation of charge, with a partial negative charge on the halogen and a partial positive charge on the carbon:



Evidence for the polar character of the transition state is that electron-withdrawing groups in the para position of toluene (which would destabilize a positive charge) decrease the rate of hydrogen abstraction by bromine while electron-donating groups increase it.¹⁰ However, as we might expect, substituents have a smaller effect here ($\rho \approx -1.4$) than they do in reactions where a completely ionic intermediate is involved, e.g., the SN1 mechanism (see p. 344). Other evidence for polar transition states in radical abstraction reactions is mentioned on p. 685. For abstraction by radicals such as methyl or phenyl, polar effects are

⁸For a review, see Poutsma, in *Kochi Free Radicals*, vol. 2; Wiley: New York, 1973, pp. 113-158.

⁹Eliel, in *Newman Steric Effects in Organic Chemistry*; Wiley: New York, 1956, pp. 142-143.

¹⁰For example, see Pearson; Martin *J. Am. Chem. Soc.* **1963**, *85*, 354, 3142; Kim; Choi; Kang *J. Am. Chem. Soc.* **1985**, *107*, 4234.

very small or completely absent. For example, rates of hydrogen abstraction from ring-substituted toluenes by the methyl radical were relatively unaffected by the presence of electron-donating or electron-withdrawing substituents.¹¹ Those radicals (e.g., Br•) that have a tendency to abstract electron-rich hydrogen atoms are called *electrophilic radicals*.

When the reaction step $R-X \rightarrow R\cdot$ takes place at a chiral carbon, racemization is almost always observed because free radicals do not retain configuration. Exceptions to this rule are found at cyclopropyl substrates, where both inversion¹² and retention¹³ of configuration have been reported, and in the reactions mentioned on p. 682.

Mechanisms at an Aromatic Substrate¹⁴

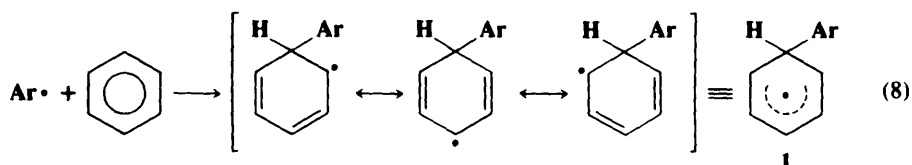
When R in reaction (1) is aromatic, the simple abstraction mechanism just discussed may be operating, especially in gas-phase reactions. However, mechanisms of this type cannot account for all reactions of aromatic substrates. In processes such as the following (see 4-18, 4-21, and 4-22):



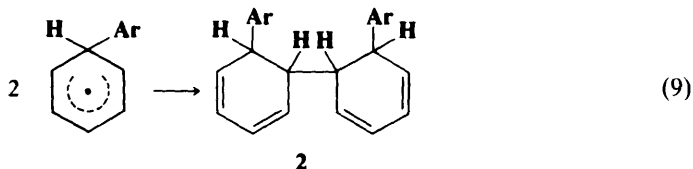
which occur in solution, the coupling of two rings cannot be explained on the basis of a simple abstraction



since, as discussed on p. 683, abstraction of an entire group such as phenyl by a free radical is very unlikely. The products can be explained by a mechanism similar to that of electrophilic and nucleophilic aromatic substitution. In the first step, the radical attacks the ring in much the same way as would an electrophile or a nucleophile:



The intermediate is relatively stable because of the resonance. The reaction can terminate in three ways: by simple coupling, or by disproportionation

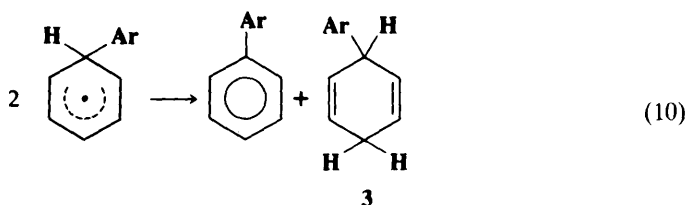


¹¹For example, see Kalatzis; Williams *J. Chem. Soc. B* **1966**, 1112; Pryor; Tonellato; Fuller; Jumonville *J. Org. Chem.* **1969**, 34, 2018.

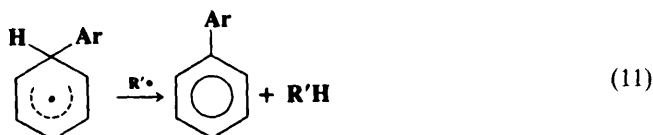
¹²Altman; Nelson *J. Am. Chem. Soc.* **1969**, 91, 5163.

¹³Jacobus; Pensak *Chem. Commun.* **1969**, 400.

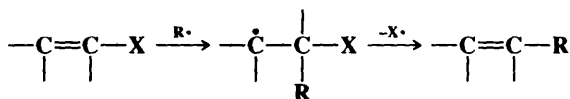
¹⁴For reviews, see Kobrina *Russ. Chem. Rev.* **1977**, 46, 348-360; Perkins, in Kochi, Ref. 8, vol. 2, 231-271; Bolton; Williams, *Adv. Free-Radical Chem.* **1975**, 5, 1-25; Nonhebel; Walton, Ref. 1, pp. 417-469; Minisci; Porta *Adv. Heterocycl. Chem.* **1974**, 16, 123-180; Bass; Nababsing *Adv. Free-Radical Chem.* **1972**, 4, 1-47; Hey *Bull. Soc. Chim. Fr.* **1968**, 1591.



or, if a species ($R'\bullet$) is present which abstracts hydrogen, by abstraction¹⁵



2 is a partially hydrogenated quaterphenyl. Of course, the coupling need not be ortho-ortho, and other isomers can also be formed. Among the evidence for steps (9) and (10) was isolation of compounds of types **2** and **3**,¹⁶ though normally under the reaction conditions dihydrobiphenyls like **3** are oxidized to the corresponding biphenyls. Other evidence for this mechanism is the detection of the intermediate **1** by CIDNP¹⁷ and the absence of isotope effects, which would be expected if the rate-determining step were (7), which involves cleavage of the Ar—H bond. In the mechanism just given, the rate-determining step (8) does not involve loss of hydrogen. The reaction between aromatic rings and the $\text{OH}\bullet$ radical takes place by the same mechanism. A similar mechanism has been shown for substitution at some vinylic and acetylenic substrates, e.g.:¹⁸



This is reminiscent of the nucleophilic tetrahedral mechanism at a vinylic carbon (p. 336)

Neighboring-Group Assistance in Free-Radical Reactions

In a few cases it has been shown that cleavage steps (2) and abstraction steps (3) have been accelerated by the presence of neighboring groups. Photolytic halogenation (**4-1**) is a process that normally leads to mixtures of many products. However, bromination of carbon chains containing a bromine atom occurs with high regioselectivity. Bromination of alkyl bromides gave 84 to 94% substitution at the carbon adjacent to the bromine already in the molecule.¹⁹ This result is especially surprising because, as we shall see (p. 685), positions close to a polar group such as bromine should actually be *deactivated* by the electron-withdrawing field effect

¹⁵**1** can also be oxidized to the arene ArPh by atmospheric O_2 . For a discussion of the mechanism of this oxidation, see Narita; Tezuka *J. Am. Chem. Soc.* **1982**, *104*, 7316.

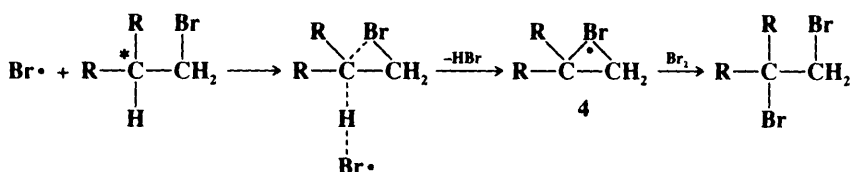
¹⁶De Tar; Long *J. Am. Chem. Soc.* **1958**, *80*, 4742. See also Ref. 334.

¹⁷Fahrenholtz; Trozzolo *J. Am. Chem. Soc.* **1972**, *94*, 282.

¹⁸Russell; Ngoviwatthai *Tetrahedron Lett.* **1986**, *27*, 3479, and references cited therein.

¹⁹Thaler *J. Am. Chem. Soc.* **1963**, *85*, 2607. See also Traynham; Hines *J. Am. Chem. Soc.* **1968**, *90*, 5208; Ucciani; Pierri; Naudet *Bull. Soc. Chim. Fr.* **1970**, 791; Hargis *J. Org. Chem.* **1973**, *38*, 346.

of the bromine. The unusual regioselectivity is explained by a mechanism in which abstraction (3) is assisted by a neighboring bromine atom:²⁰



In the normal mechanism, $\text{Br}\cdot$ abstracts a hydrogen from RH , leaving $\text{R}\cdot$. When a bromine is present in the proper position, it assists this process, giving a cyclic intermediate (a *bridged free radical*, 4).²¹ In the final step (very similar to $\text{R}\cdot + \text{Br}_2 \rightarrow \text{RBr} + \text{Br}\cdot$) the ring is broken. If this mechanism is correct, the configuration at the substituted carbon (marked *) should be retained. This has been shown to be the case: optically active 1-bromo-2-methylbutane gave 1,2-dibromo-2-methylbutane with retention of configuration.²⁰ Furthermore, when this reaction was carried out in the presence of DBr , the “recovered” 1-bromo-2-methylbutane was found to be deuterated in the 2 position, and its configuration was retained.²² This is just what would be predicted if some of the 4 present abstracted D from DBr . There is evidence that Cl can form bridged radicals,²³ though esr spectra show that the bridging is not necessarily symmetrical.²⁴ Still more evidence for bridging by Br has been found in isotope effect and other studies.²⁵ However, evidence from CIDNP shows that the methylene protons of the β -bromoethyl radical are not equivalent, at least while the radical is present in the radical pair $[\text{PhCOO}\cdot\text{CH}_2\text{CH}_2\text{Br}]$ within a solvent cage.²⁶ This evidence indicates that under these conditions $\text{BrCH}_2\text{CH}_2\cdot$ is not a symmetrically bridged radical, but it could be unsymmetrically bridged. A bridged intermediate has also been invoked, when a bromo group is in the proper position, in the Hunsdiecker reaction²⁷ (4-39), and in abstraction of iodine atoms by the phenyl radical.²⁸ Participation by other neighboring groups, e.g. SR, SiR_3 , SnR_3 , has also been reported.²⁹

²⁰Skell; Tuleen; Readio *J. Am. Chem. Soc.* **1963**, 85, 2849. For other stereochemical evidence, see Huyser; Feng *J. Org. Chem.* **1971**, 36, 731. For another explanation, see Lloyd; Wood *J. Am. Chem. Soc.* **1975**, 97, 5986.

²¹For a monograph, see Kaplan *Bridged Free Radicals*; Marcel Dekker: New York, 1972. For reviews, see Skell; Traynham *Acc. Chem. Res.* **1984**, 17, 160-166; Skell; Shea, in Kochi, Ref. 8, vol. 2, pp. 809-852.

²²Shea; Skell *J. Am. Chem. Soc.* **1973**, 95, 283.

²³Everly; Schweinsberg; Traynham *J. Am. Chem. Soc.* **1978**, 100, 1200; Wells; Franke *Tetrahedron Lett.* **1979**, 4681.

²⁴Bowles; Hudson; Jackson *Chem. Phys. Lett.* **1970**, 5, 552; Cooper; Hudson; Jackson *Tetrahedron Lett.* **1973**, 831; Chen; Elson; Kochi *J. Am. Chem. Soc.* **1973**, 95, 5341.

²⁵Skell; Readio *J. Am. Chem. Soc.* **1964**, 86, 3334; Skell; Pavlis; Lewis; Shea *J. Am. Chem. Soc.* **1973**, 95, 6735; Juneja; Hodnett *J. Am. Chem. Soc.* **1967**, 89, 5685; Lewis; Kozuka *J. Am. Chem. Soc.* **1973**, 95, 282; Cain; Solly *J. Chem. Soc., Chem. Commun.* **1974**, 148; Chenier; Tremblay; Howard *J. Am. Chem. Soc.* **1975**, 97, 1618; Howard; Chenier; Holden *Can. J. Chem.* **1977**, 55, 1463. See however Tanner; Blackburn; Kosugi; Ruo *J. Am. Chem. Soc.* **1977**, 99, 2714.

²⁶Hargis; Shevlin *J. Chem. Soc., Chem. Commun.* **1973**, 179.

²⁷Applequist; Werner *J. Org. Chem.* **1963**, 28, 48.

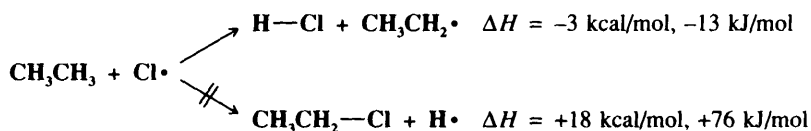
²⁸Danen; Winter *J. Am. Chem. Soc.* **1971**, 93, 716.

²⁹Tuleen; Bentruide; Martin *J. Am. Chem. Soc.* **1963**, 85, 1938; Fisher; Martin *J. Am. Chem. Soc.* **1966**, 88, 3382; Jackson; Ingold; Griller; Nazran *J. Am. Chem. Soc.* **1985**, 107, 208. For a review of neighboring-group participation in cleavage reactions, especially those involving SiR_3 as a neighboring group, see Reetz *Angew. Chem. Int. Ed. Engl.* **1979**, 18, 173-180 [*Angew. Chem.* **91**, 185-192].

REACTIVITY

Reactivity for Aliphatic Substrates³⁰

In a chain reaction, the step that determines what the product will be is most often an abstraction step. What is abstracted by a free radical is almost never a tetra-³¹ or trivalent atom³² (except in strained systems, see p. 757)³³ and seldom a divalent one.³⁴ Nearly always it is univalent, and so, for organic compounds, it is hydrogen or halogen. For example, a reaction between a chlorine atom and ethane gives an ethyl radical, not a hydrogen atom:



The principal reason for this is steric. A univalent atom is much more exposed to attack by the incoming radical than an atom with a higher valence. Another reason is that in many cases abstraction of a univalent atom is energetically more favored. For example, in the reaction given above, a $\text{C}_2\text{H}_5-\text{H}$ bond is broken ($D = 100 \text{ kcal/mol}$, 419 kJ/mol , from Table 5.3) whichever pathway is taken, but in the former case an $\text{H}-\text{Cl}$ bond is formed ($D = 103 \text{ kcal/mol}$, 432 kJ/mol) while in the latter case it is a $\text{C}_2\text{H}_5-\text{Cl}$ bond ($D = 82 \text{ kcal/mol}$, 343 kJ/mol). Thus the first reaction is favored because it is exothermic by 3 kcal/mol ($100 - 103$) [13 kJ/mol ($419 - 432$)], while the latter is endothermic by 18 kcal/mol ($100 - 82$) [76 kJ/mol ($419 - 343$)].³⁵ However, the steric reason is clearly more important, because even in cases where ΔH is not very different for the two possibilities, the univalent atom is chosen.

Most studies of aliphatic reactivity have been made with hydrogen as the leaving atom and chlorine atoms as the abstracting species.³⁶ In these reactions, every hydrogen in the substrate is potentially replaceable and mixtures are usually obtained. However, the abstracting radical is not totally unselective, and some positions on a molecule lose hydrogen more easily than others. We discuss the position of attack under several headings:³⁷

1. Alkanes. The tertiary hydrogens of an alkane are the ones preferentially abstracted by almost any radical, with secondary hydrogens being next preferred. This is in the same order as D values for these types of $\text{C}-\text{H}$ bonds (Table 5.3). The extent of the preference

³⁰For a review of the factors involved in reactivity and regioselectivity in free-radical substitutions and additions, see Tedder *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 401-410 [*Angew. Chem.* **94**, 433-442].

³¹Abstraction of a tetravalent carbon has been seen in the abstraction by $\text{F}\cdot$ of R from RCl : Firouzbakht; Ferrieri; Wolf; Rack *J. Am. Chem. Soc.* **1987**, *109*, 2213.

³²See, for example, Back *Can. J. Chem.* **1983**, *61*, 916.

³³For an example of an abstraction occurring to a small extent at an unstrained carbon atom, see Jackson; Townson *J. Chem. Soc., Perkin Trans. 2* **1980**, 1452. See also Johnson *Acc. Chem. Res.* **1983**, *16*, 343-349.

³⁴For a monograph on abstractions of divalent and higher-valent atoms, see Ingold; Roberts *Free-Radical Substitution Reactions*; Wiley: New York, 1971.

³⁵ ΔH for a free-radical abstraction reaction can be regarded simply as the difference in D values for the bond being broken and the one formed.

³⁶For a review that lists many rate constants for abstraction of hydrogen at various positions of many molecules, see Hendry; Mill; Piskiewicz; Howard; Eigenmann *J. Phys. Chem. Ref. Data* **1974**, *3*, 937-978.

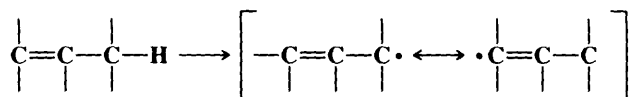
³⁷For reviews, see Tedder *Tetrahedron* **1982**, *38*, 313-329; Kerr, in Bamford; Tipper *Comprehensive Chemical Kinetics*, vol. 18; Elsevier: New York, 1976, pp. 39-109; Russell, in Kochi, Ref. 8, vol. 2, pp. 275-331; Rüchardt *Angew. Chem. Int. Ed. Engl.* **1970**, *9*, 830-843 [*Angew. Chem.* **82**, 845-858]; Poutsma *Methods Free-Radical Chem.* **1969**, *1*, 79-193; Davidson *Q. Rev., Chem. Soc.* **1967**, *21*, 249-258; Pryor; Fuller; Stanley *J. Am. Chem. Soc.* **1972**, *94*, 1632.

TABLE 14.1 Relative susceptibility to attack by $\text{Cl}\cdot$ of primary, secondary, and tertiary positions at 100 and 600°C in the gas phase³⁸

Temp., °C	Primary	Secondary	Tertiary
100	1	4.3	7.0
600	1	2.1	2.6

depends on the selectivity of the abstracting radical and on the temperature. Table 14.1 shows³⁸ that at high temperatures selectivity decreases, as might be expected.³⁹ An example of the effect of radical selectivity may be noted in a comparison of fluorine atoms with bromine atoms. For the former, the ratio of primary to tertiary abstraction (of hydrogen) is 1:1.4, while for the less reactive bromine atom this ratio is 1:1600. With certain large radicals there is a steric factor that may change the selectivity pattern. For example, in the photochemical chlorination of isopentane in H_2SO_4 with N-chloro-di-*t*-butylamine and N-chloro-*t*-butyl-*t*-pentylamine, the primary hydrogens are abstracted 1.7 times *faster* than the tertiary hydrogen.⁴⁰ In this case the attacking radicals (the radical ions $\text{R}_2\text{NH}\cdot^+$, see p. 692) are bulky enough for steric hindrance to become a major factor.

2. Olefins. When the substrate molecule contains a double bond, treatment with chlorine or bromine usually leads to addition rather than substitution. However, for other radicals (and even for chlorine or bromine atoms when they do abstract a hydrogen) the position of attack is perfectly clear. Vinylic hydrogens are practically never abstracted, and allylic hydrogens are greatly preferred to other positions of the molecule. This is generally attributed⁴¹ to resonance stabilization of the allylic radical:



As might be expected, allylic rearrangements (see p. 327) are common in these cases.⁴²

3. Alkyl side chains of aromatic rings. The preferential position of attack on a side chain is usually the one α to the ring. Both for active radicals such as chlorine and phenyl and for more selective ones such as bromine such attack is faster than that at a primary carbon, but for the active radicals benzylic attack is slower than for tertiary positions, while for the selective ones it is faster. Two or three aryl groups on a carbon activate its hydrogens even more, as would be expected from the resonance involved. These statements can be illustrated by the following abstraction ratios:⁴³

	Me-H	MeCH ₂ -H	Me ₂ CH-H	Me ₃ C-H	PhCH ₂ -H	Ph ₂ CH-H	Ph ₃ C-H
Br	0.0007	1	220	19,400	64,000	1.1×10^6	6.4×10^6
Cl	0.004	1	4.3	6.0	1.3	2.6	9.5

³⁸Hass; McBee; Weber *Ind. Eng. Chem.* **1936**, 28, 333.

³⁹For a similar result with phenyl radicals, see Kopinke; Zimmermann; Anders *J. Org. Chem.* **1989**, 54, 3571.

⁴⁰Deno; Fishbein; Wyckoff *J. Am. Chem. Soc.* **1971**, 93, 2065. Similar steric effects, though not a reversal of primary-tertiary reactivity, were found by Dneprovskii; Mil'tsov *J. Org. Chem. USSR* **1988**, 24, 1836.

⁴¹See however Kwart; Brechbiel; Miles; Kwart *J. Org. Chem.* **1982**, 47, 4524.

⁴²For reviews, see Wilt, in Kochi, Ref. 8, vol. 1, pp. 458-466.

⁴³Russell, Ref. 37, p. 289.

However, many anomalous results have been reported for these substrates. The benzylic position is not always the most favored. One thing certain is that *aromatic* hydrogens are seldom abstracted if there are aliphatic ones to compete (note from Table 5.3, that *D* for Ph—H is higher than that for any alkyl H bond). Several σ^* scales (similar to the σ , σ^+ and σ^- scales discussed in Chapter 9) have been developed for benzylic radicals.⁴⁴

4. *Compounds containing electron-withdrawing substituents.* In halogenations electron-withdrawing groups greatly deactivate adjacent positions. Compounds of the type Z—CH₂—CH₃ are attacked predominantly or exclusively at the β position when Z is COOH, COCl, COOR, SO₂Cl, or CX₃. Such compounds as acetic acid and acetyl chloride are not attacked at all. This is in sharp contrast to electrophilic halogenations (2-4 to 2-6), where *only* the α position is substituted. This deactivation of α positions is also at variance with the expected stability of the resulting radicals, since they would be expected to be stabilized by resonance similar to that for allylic and benzylic radicals. This behavior is a result of the polar transition states discussed on p. 679. Halogen atoms are electrophilic radicals and look for positions of high electron density. Hydrogens on carbon atoms next to electron-withdrawing groups have low electron densities (because of the field effect of Z) and are therefore shunned. Radicals that are not electrophilic do not display this behavior. For example, the methyl radical is essentially nonpolar and does not avoid positions next to electron-withdrawing groups; relative rates of abstraction at the α and β carbons of propionic acid are:⁴⁵

	CH ₃ —CH ₂ —COOH	
Me•	1	7.8
Cl•	1	0.03

Some radicals, e.g., *t*-butyl,⁴⁶ benzyl,⁴⁷ and cyclopropyl,⁴⁸ are *nucleophilic* (they tend to abstract electron-poor hydrogen atoms). The phenyl radical appears to have a very small degree of nucleophilic character.⁴⁹ For longer chains, the field effect continues, and the β position is also deactivated to attack by halogen, though much less so than the α position. We have already mentioned (p. 679) that abstraction of an α hydrogen atom from ring-substituted toluenes can be correlated by the Hammett equation.

5. *Stereoelectronic effects.* On p. 334 we saw an example of a stereoelectronic effect. It has been shown that such effects are important where a hydrogen is abstracted from a carbon adjacent to a C—O or C—N bond. In such cases hydrogen is abstracted from C—H bonds that have a relatively small dihedral angle ($\sim 30^\circ$) with the unshared orbitals of the O or N much more easily than from those with a large angle ($\sim 90^\circ$). For example, the starred hydrogen of 5 was abstracted about 8 times faster than the starred hydrogen of 6.⁵⁰

⁴⁴Sec. for example, Dinçtürk; Jackson *J. Chem. Soc., Perkin Trans. 2* **1981**, 1127; Dust; Arnold *J. Am. Chem. Soc.* **1983**, 105, 1221, 6531; Creary; Mehrsheikh-Mohammadi; McDonald *J. Org. Chem.* **1987**, 52, 3254, **1989**, 54, 2904; Fisher; Dershem; Prewitt *J. Org. Chem.* **1990**, 55, 1040.

⁴⁵Russell, Ref. 37, p. 311.

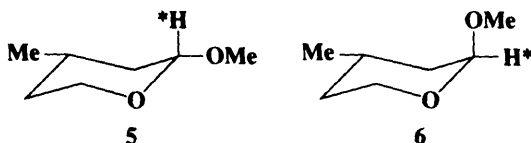
⁴⁶Pryor; Davis; Stanley *J. Am. Chem. Soc.* **1973**, 95, 4754; Pryor; Tang; Tang; Church *J. Am. Chem. Soc.* **1982**, 104, 2885; Dütsch; Fischer *Int. J. Chem. Kinet.* **1982**, 14, 195.

⁴⁷Clerici; Minisci; Porta *Tetrahedron* **1973**, 29, 2775.

⁴⁸Stefani; Chuang; Todd *J. Am. Chem. Soc.* **1970**, 92, 4168.

⁴⁹Suhiro; Suzuki; Tsuchida; Yamazaki *Bull. Chem. Soc. Jpn.* **1977**, 50, 3324.

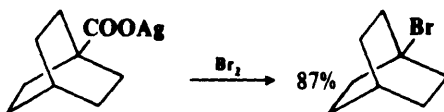
⁵⁰Hayday; McKelvey *J. Org. Chem.* **1976**, 41, 2222. For additional examples, see Malatesta; Ingold *J. Am. Chem. Soc.* **1981**, 103, 609; Beckwith; Easton *J. Am. Chem. Soc.* **1981**, 103, 615; Beckwith; Westwood *Aust. J. Chem.* **1983**, 36, 2123; Griller; Howard; Marriott; Scaiano *J. Am. Chem. Soc.* **1981**, 103, 619. For a stereoselective abstraction step, see Dneprovskii; Pertsikov; Temnikova *J. Org. Chem. USSR* **1982**, 18, 1951. See also Bunce; Cheung; Langshaw *J. Org. Chem.* **1986**, 51, 5421.



Abstraction of a halogen has been studied much less,⁵¹ but the order of reactivity is $\text{RI} > \text{RBr} > \text{RCl} \gg \text{RF}$.

Reactivity at a Bridgehead⁵²

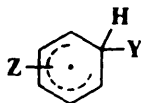
Many free-radical reactions have been observed at bridgehead carbons, e.g. (see 4-39),⁵³



demonstrating that the free radical need not be planar. However, treatment of norbornane with sulfuryl chloride and benzoyl peroxide gave mostly 2-chloronorbornane, though the bridgehead position is tertiary.⁵⁴ So, while bridgehead free-radical substitution is possible, it is not preferred, presumably because of the strain involved.⁵⁵

Reactivity in Aromatic Substrates

Free-radical substitution at an aromatic carbon seldom takes place by a mechanism in which a hydrogen is abstracted to give an aryl radical. Reactivity considerations here are similar to those in Chapters 11 and 13; i.e., we need to know which position on the ring will be attacked to give the intermediate



The obvious way to obtain this information is to carry out reactions with various Z groups and to analyze the products for percent ortho, meta, and para isomers, as has so often been done for electrophilic substitution. However, this procedure is much less accurate in the case of free-radical substitutions because of the many side reactions. It may be, for example, that in a given case the ortho position is more reactive than the para, but the intermediate from the para attack may go on to product while that from ortho attack gives a side reaction. In such a case, analysis of the three products does not give a true picture of which position

⁵¹For a review, see Danen *Methods Free-Radical Chem.* **1974**, 5, 1-99.

⁵²For reviews, see Bingham; Schleyer *Fortschr. Chem. Forsch.* **1971**, 18, 1-102, pp. 79-81; Fort; Schleyer *Adv. Alicyclic Chem.* **1966**, 1, 283-370, pp. 337-352.

⁵³Grob; Ohta; Renk; Weiss *Helv. Chim. Acta* **1958**, 41, 1191.

⁵⁴Roberts; Urbanek; Armstrong *J. Am. Chem. Soc.* **1949**, 71, 3049. See also Kooyman; Vegter *Tetrahedron* **1958**, 4, 382; Walling; Mayahi *J. Am. Chem. Soc.* **1959**, 81, 1485.

⁵⁵See, for example, Koch; Gleicher *J. Am. Chem. Soc.* **1971**, 93, 1657.

is most susceptible to attack. The following generalizations can nevertheless be drawn, though there has been much controversy over just how meaningful such conclusions are:⁵⁶

1. All substituents increase reactivity at ortho and para positions over that of benzene. There is no great difference between electron-donating and electron-withdrawing groups.
2. Reactivity at meta positions is usually similar to that of benzene, perhaps slightly higher or lower. This fact, coupled with the preceding one, means that all substituents are activating and ortho-para-directing; none are deactivating or (chiefly) meta-directing.
3. Reactivity at ortho positions is usually somewhat greater than at para positions, except where a large group decreases ortho reactivity for steric reasons.
4. In direct competition, electron-withdrawing groups exert a somewhat greater influence than electron-donating groups. Arylation of para-disubstituted compounds $\text{XC}_6\text{H}_4\text{Y}$ showed that substitution ortho to the group X became increasingly preferred as the electron-withdrawing character of X increases (with Y held constant).⁵⁷ The increase could be correlated with the Hammett σ_p values for X.
5. Substituents have a much smaller effect than in electrophilic or nucleophilic substitution; hence the partial rate factors (see p. 516) are not great.⁵⁸ Partial rate factors for a few groups are given in Table 14.2.⁵⁹
6. Although hydrogen is the leaving group in most free-radical aromatic substitutions, ipso attack (p. 512) and ipso substitution (e.g., with Br, NO_2 , or CH_3CO as the leaving group) have been found in certain cases.⁶⁰

Reactivity in the Attacking Radical⁶¹

We have already seen that some radicals are much more selective than others (p. 684). The bromine atom is so selective that when only primary hydrogens are available, as in neo-

TABLE 14.2 Partial rate factors for attack of substituted benzenes by phenyl radicals generated from Bz_2O_2 (reaction 4-21)⁵⁹

Z	Partial rate factor		
	<i>o</i>	<i>m</i>	<i>p</i>
H	1	1	1
NO₂	5.50	0.86	4.90
CH₃	4.70	1.24	3.55
CMe₃	0.70	1.64	1.81
Cl	3.90	1.65	2.12
Br	3.05	1.70	1.92
MeO	5.6	1.23	2.31

⁵⁶De Tar *J. Am. Chem. Soc.* **1961**, 83, 1014 (book review); Dickerman; Vermont *J. Am. Chem. Soc.* **1962**, 84, 4150; Morrison; Cazes; Samkoff; Howe *J. Am. Chem. Soc.* **1962**, 84, 4152; Ohta; Tokumaru *Bull. Chem. Soc. Jpn.* **1971**, 44, 3218; Vidal; Court; Bonnier *J. Chem. Soc. Perkin Trans. 2* **1973**, 2071; Tezuka; Ichikawa; Marusawa; Narita *Chem. Lett.* **1983**, 1013.

⁵⁷Davies; Hey; Summers *J. Chem. Soc. C* **1970**, 2653.

⁵⁸For a quantitative treatment, see Charton; Charton *Bull. Soc. Chim. Fr.* **1988**, 199.

⁵⁹Davies; Hey; Summers *J. Chem. Soc. C* **1971**, 2681.

⁶⁰For reviews, see Traynham *J. Chem. Educ.* **1983**, 60, 937-941; *Chem. Rev.* **1979**, 79, 323-330; Tiecco *Acc. Chem. Res.* **1980**, 13, 51-57; *Pure Appl. Chem.* **1981**, 53, 239-258.

⁶¹For reviews with respect to $\text{CH}_3\cdot$ and $\text{CF}_3\cdot$, see Trotman-Dickenson *Adv. Free-Radical Chem.* **1965**, 1, 1-38; Spirin *Russ. Chem. Rev.* **1969**, 38, 529-539; Gray; Herod; Jones *Chem. Rev.* **1971**, 71, 247-294.

pentane or *t*-butylbenzene, the reaction is slow or nonexistent; and isobutane can be selectively brominated to give *t*-butyl bromide in high yields. However, toluene reacts with bromine atoms instantly. Bromination of other alkylbenzenes, e.g., ethylbenzene and cumene, takes place exclusively at the α position,⁶² emphasizing the selectivity of Br \cdot . The dissociation energy *D* of the C—H bond is more important for radicals of low reactivity than for highly reactive radicals, since bond breaking in the transition state is greater. Thus, bromine shows a greater tendency than chlorine to attack α to an electron-withdrawing group because the energy of the C—H bond there is lower than in other places in the molecule.

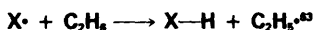
Some radicals, e.g., triphenylmethyl, are so unreactive that they abstract hydrogens very poorly if at all. Table 14.3 lists some common free radicals in approximate order of reactivity.⁶³

It has been mentioned that some free radicals, e.g., chloro, are electrophilic and some, e.g., *t*-butyl, are nucleophilic. It must be borne in mind that these tendencies are relatively slight compared with the electrophilicity of a positive ion or the nucleophilicity of a negative ion. The predominant character of a free radical is neutral, whether it has slight electrophilic or nucleophilic tendencies.

The Effect of Solvent on Reactivity⁶⁵

As has been noted earlier, the solvent usually has little effect on free-radical substitutions in contrast to ionic ones: indeed, reactions in solution are often quite similar in character to those in the gas phase, where there is no solvent at all. However, in certain cases the solvent *can* make an appreciable difference. Chlorination of 2,3-dimethylbutane in aliphatic solvents gave about 60% (CH₃)₂CHCH(CH₃)CH₂Cl and 40% (CH₃)₂CHCCl(CH₃)₂, while in aromatic solvents the ratio became about 10:90.⁶⁶ This result is attributed to complex

TABLE 14.3 Some common free radicals in decreasing order of activity
The *E* values represent activation energies for the reaction



iso-Pr \cdot is less active than Me \cdot and *t*-Bu \cdot still less so⁶⁴

Radical	<i>E</i>		Radical	<i>E</i>	
	kcal/mol	kJ/mol		kcal/mol	kJ/mol
F \cdot	0.3	1.3	H \cdot	9.0	38
Cl \cdot	1.0	4.2	Me \cdot	11.8	49.4
MeO \cdot	7.1	30	Br \cdot	13.2	55.2
CF ₃ \cdot	7.5	31			

⁶²Huyser *Free-Radical Chain Reactions*. Ref. 1, p. 97.

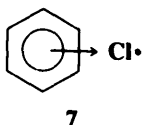
⁶³Trotman-Dickenson, Ref. 61.

⁶⁴Kharasch; Hambling; Rudy *J. Org. Chem.* **1959**, 24, 303.

⁶⁵For reviews, see Reichardt *Solvent Effects in Organic Chemistry*; Verlag Chemie: Deerfield Beach, FL, 1979, pp. 110-123; Martin, in Kochi, Ref. 8, vol. 2, pp. 493-524; Huyser *Adv. Free-Radical Chem.* **1965**, 1, 77-135.

⁶⁶Russell *J. Am. Chem. Soc.* **1958**, 80, 4987, 4997, 5002, *J. Org. Chem.* **1959**, 24, 300.

formation between the aromatic solvent and the chlorine atom which makes the chlorine more selective.⁶⁷ This type of effect is not found in cases where the differences in abstract-



ability are caused by field effects of electron-withdrawing groups (p. 685). In such cases aromatic solvents make little difference.⁶⁸ The complex **7** has been detected⁶⁹ as a very short-lived species by observation of its visible spectrum in the pulse radiolysis of a solution of benzene in CCl_4 .⁷⁰ Differences caused by solvents have also been reported in reactions of other radicals.⁷¹ Some of the anomalous results obtained in the chlorination of aromatic side chains (p. 685) can also be explained by this type of complexing, in this case not with the solvent but with the reacting species.⁷² Much smaller, though real, differences in selectivity have been found when the solvent in the chlorination of 2,3-dimethylbutane is changed from an alkane to CCl_4 .⁷³ However, these differences are not caused by formation of a complex between Cl^\bullet and the solvent.

REACTIONS

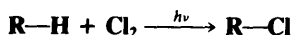
The reactions in this chapter are classified according to leaving group. The most common leaving groups are hydrogen and nitrogen (from the diazonium ion); these are considered first.

Hydrogen as Leaving Group

A. Substitution by Halogen

4-1 Halogenation at an Alkyl Carbon⁷⁴

Halogenation or Halo-de-hydrogenation



⁶⁷See also Soumilion; Bruylants *Bull. Soc. Chim. Belg.* **1969**, 78, 425; Potter; Tedder *J. Chem. Soc., Perkin Trans. 2* **1982**, 1689; Aver'yanov; Ruban; Shvets *J. Org. Chem. USSR* **1987**, 23, 782; Aver'yanov; Ruban *J. Org. Chem. USSR* **1987**, 23, 1119; Raner; Luszytk; Ingold *J. Am. Chem. Soc.* **1989**, 111, 3652; Ingold; Luszytk; Raner *Acc. Chem. Res.* **1990**, 23, 219-225.

⁶⁸Russell *Tetrahedron* **1960**, 8, 101; Nagai; Horikawa; Ryang; Tokura *Bull. Chem. Soc. Jpn.* **1971**, 44, 2771.

⁶⁹It has been contended that another species, a chlorocyclohexadienyl radical (the structure of which is the same as **1**, except that Cl replaces Ar), can also be attacking when the solvent is benzene: Skell; Baxter; Taylor *J. Am. Chem. Soc.* **1983**, 105, 120; Skell; Baxter; Tanko; Chebolu *J. Am. Chem. Soc.* **1986**, 108, 6300. For arguments against this proposal, see Bunce; Ingold; Landers; Luszytk; Scaiano *J. Am. Chem. Soc.* **1985**, 107, 5464; Walling *J. Org. Chem.* **1988**, 53, 305; Aver'yanov; Shvets; Semenov *J. Org. Chem. USSR* **1990**, 26, 1261.

⁷⁰Bühler *Helv. Chim. Acta* **1968**, 51, 1558. For other spectral observations, see Raner; Luszytk; Ingold *J. Phys. Chem.* **1989**, 93, 564.

⁷¹Walling; Azar *J. Org. Chem.* **1968**, 33, 3885; Walling; Wagner *J. Am. Chem. Soc.* **1963**, 85, 2333; Ito; Matsuda *J. Am. Chem. Soc.* **1982**, 104, 568; Minisci; Vismara; Fontana; Morini; Serravalle; Giordano *J. Org. Chem.* **1987**, 52, 730.

⁷²Russell; Ito; Hendry *J. Am. Chem. Soc.* **1963**, 85, 2976; Corbiau; Bruylants *Bull. Soc. Chim. Belg.* **1970**, 79, 203, 211; Newkirk; Gleicher *J. Am. Chem. Soc.* **1974**, 96, 3543.

⁷³See Raner; Luszytk; Ingold *J. Org. Chem.* **1988**, 53, 5220.

⁷⁴For lists of reagents, with references, see Larock *Comprehensive Organic Transformations*; VCH: New York, 1989, pp. 311-313.

Alkanes can be chlorinated or brominated by treatment with chlorine or bromine in the presence of visible or uv light.⁷⁵ The reaction can also be applied to alkyl chains containing many functional groups. The chlorination reaction is usually not useful for preparative purposes precisely because it is so general: not only does substitution take place at virtually every alkyl carbon in the molecule, but di- and polychloro substitution almost invariably occur even if there is a large molar ratio of substrate to halogen. When functional groups are present, the principles are those outlined on p. 684; favored positions are those α to aromatic rings, while positions α to electron-withdrawing groups are least likely to be substituted. Tertiary carbons are most likely to be attacked and primary least. Positions α to an OR group are very readily attacked. Nevertheless, mixtures are nearly always obtained. This can be contrasted to the regioselectivity of electrophilic halogenation (2-4 to 2-6), which always takes place α to a carbonyl group (except when the reaction is catalyzed by AgSbF_6 ; see following). Of course, if a mixture of chlorides is wanted, the reaction is usually quite satisfactory. For obtaining pure compounds, the chlorination reaction is essentially limited to substrates with only one type of replaceable hydrogen, e.g., ethane, cyclohexane, neopentane. The most common are methylbenzenes and other substrates with methyl groups on aromatic rings, since few cases are known where halogen atoms substitute at an aromatic position.⁷⁶ Of course, ring substitution *does* take place in the presence of a positive-ion-forming catalyst (1-11). In addition to mixtures of various alkyl halides, traces of other products are obtained. These include H_2 , olefins, higher alkanes, lower alkanes, and halogen derivatives of these compounds.

The bromine atom is much more selective than the chlorine atom. As indicated on p. 688, it is often possible to brominate tertiary and benzylic positions selectively. High regioselectivity can also be obtained where the neighboring-group mechanism (p. 681) can operate.

As already mentioned, halogenation can be performed with chlorine or bromine. Fluorine has also been used,⁷⁷ but seldom, because it is too reactive and hard to control.⁷⁸ It often breaks carbon chains down into smaller units, a side reaction that sometimes becomes troublesome in chlorinations too. Fluorination^{78a} has been achieved by the use of chlorine trifluoride ClF_3 at -75°C .⁷⁹ For example, cyclohexane gave 41% fluorocyclohexane and methylcyclohexane gave 47% 1-fluoro-1-methylcyclohexane. Fluoroxytrifluoromethane CF_3OF fluorinates tertiary positions of certain molecules in good yields with high regioselectivity.⁸⁰ For example, adamantane gave 75% 1-fluoroadamantane. F_2 at -70°C , diluted with N_2 ,⁸¹ and bromine trifluoride at $25\text{--}35^\circ\text{C}$ ⁸² are also highly regioselective for tertiary

⁷⁵For reviews, see Poutsma, in Kochi, Ref. 8, vol. 2, pp. 159-229; Huyser, in Patai *The Chemistry of the Carbon-Halogen Bond*, pt. 1; Wiley: New York, 1973, pp. 549-607; Poutsma, Ref. 37 (chlorination); Thaler *Methods Free-Radical Chem.* **1969**, 2, 121-227 (bromination).

⁷⁶Dermer; Edmison *Chem. Rev.* **1957**, 57, 77-122, pp. 110-112. An example of free-radical ring halogenation can be found in Engelsma; Kooyman *Revl. Trav. Chim. Pays-Bas* **1961**, 80, 526, 537. For a review of aromatic halogenation in the gas phase, see Kooyman *Adv. Free-Radical Chem.* **1965**, 1, 137-153.

⁷⁷Rozen *Acc. Chem. Res.* **1988**, 21, 307-312; Purrington; Kagen; Patrick *Chem. Rev.* **1986**, 86, 997-1018, pp. 1003-1005; Gerstenberger; Haas *Angew. Chem. Int. Ed. Engl.* **1981**, 20, 647-667 [*Angew. Chem.* 93, 659-680]; Hudlický *The Chemistry of Organic Fluorine Compounds*, 2nd ed.; Ellis Horwood: Chichester, 1976; pp. 67-91. For descriptions of the apparatus necessary for handling F_2 , see Vypel *Chimia* **1985**, 39, 305-311.

⁷⁸However, there are several methods by which all the C—H bonds in a molecule can be converted to C—F bonds. For reviews, see Rozhkov, in Baizer; Lund *Organic Electrochemistry*; Marcel Dekker: New York, 1983, pp. 805-825; Lagow; Margrave *Prog. Inorg. Chem.* **1979**, 26, 161-210. See also Adcock; Horita; Renk *J. Am. Chem. Soc.* **1981**, 103, 6937; Adcock; Evans *J. Org. Chem.* **1984**, 49, 2719; Huang; Lagow *Bull. Soc. Chim. Fr.* **1986**, 993.

^{78a}For a monograph on fluorinating agents, see German; Zemskov *New Fluorinating Agents in Organic Synthesis*; Springer: New York, 1989.

⁷⁹Brower *J. Org. Chem.* **1987**, 52, 798.

⁸⁰Alker; Barton; Hesse; Lister-James; Markwell; Pechet; Rozen; Takeshita; Toh *Nouv. J. Chem.* **1980**, 4, 239.

⁸¹Rozen; Gal; Faust *J. Am. Chem. Soc.* **1980**, 102, 6860; Gal; Rozen *Tetrahedron Lett.* **1984**, 25, 449; Rozen; Ben-Shushan *J. Org. Chem.* **1986**, 51, 3522; Rozen; Gal *J. Org. Chem.* **1987**, 52, 4928, **1988**, 53, 2803; Ref. 80.

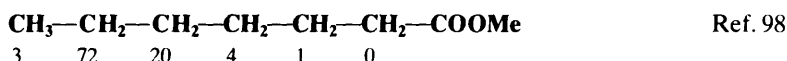
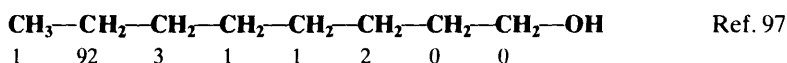
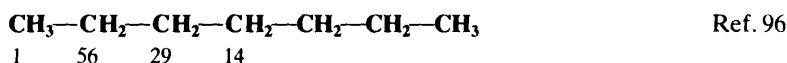
⁸²Boguslavskaya; Kartashov; Chuvatkina *J. Org. Chem. USSR* **1989**, 25, 1835.

positions. These reactions probably have electrophilic,⁸³ not free-radical mechanisms. In fact, the success of the F₂ reactions depends on the suppression of free radical pathways, by dilution with an inert gas, by working at low temperatures, and/or by the use of radical scavengers.

Iodine can be used if the activating light has a wavelength of 184.9 nm,⁸⁴ but iodinations are seldom attempted, largely because the HI formed reduces the alkyl iodide.

Many other halogenation agents have been employed, the most common of which is sulfonyl chloride SO₂Cl₂.⁸⁵ A mixture of Br₂ and HgO is a more active brominating agent than bromine alone.⁸⁶ The actual brominating agent in this case is believed to be bromine monoxide Br₂O. Among other agents used have been N-bromosuccinimide (see 4-2), CCl₄,⁸⁷ dichlorine monoxide Cl₂O,⁸⁸ BrCCl₃,⁸⁹ PCl₅,⁹⁰ phosgene, *t*-butyl hypobromite⁹¹ and hypochlorite,⁹² and N-haloamines and sulfuric acid.⁹³ In all these cases a chain-initiating catalyst is required, usually peroxides or uv light.

When chlorination is carried out with N-haloamines and sulfuric acid (catalyzed by either uv light or metal ions), selectivity is much greater than with other reagents.⁹³ In particular, alkyl chains are chlorinated with high regioselectivity at the position next to the end of the chain (the ω - 1 position).⁹⁴ Some typical selectivity values are⁹⁵



Furthermore, di- and polychlorination are much less prevalent. Dicarboxylic acids are predominantly chlorinated in the middle of the chain,⁹⁹ and adamantane and bicyclo[2.2.2]octane at the bridgeheads¹⁰⁰ by this procedure. The reasons for the high ω - 1 specificity are not clearly understood.¹⁰¹ Alkyl bromides can be regioselectively chlorinated

⁸³See, for example, Rozen; *Gal J. Org. Chem.* **1987**, 52, 2769.

⁸⁴Gover; Willard *J. Am. Chem. Soc.* **1960**, 82, 3816.

⁸⁵For a review of this reagent, see Tabushi; Kitaguchi, in *Pizey Synthetic Reagents*, vol. 4; Wiley: New York, 1981, pp. 336-396.

⁸⁶Bunce *Can. J. Chem.* **1972**, 50, 3109.

⁸⁷For a discussion of the mechanism with this reagent, see Hawari; Davis; Engel; Gilbert; Griller *J. Am. Chem. Soc.* **1985**, 107, 4721.

⁸⁸Marsh; Farnham; Sam; Smart *J. Am. Chem. Soc.* **1982**, 104, 4680.

⁸⁹Huyser *J. Am. Chem. Soc.* **1960**, 82, 391; Baldwin; O'Neill *Synth. Commun.* **1976**, 6, 109.

⁹⁰Wyman; Wang; Freeman *J. Org. Chem.* **1963**, 28, 3173.

⁹¹Walling; Padwa *J. Org. Chem.* **1962**, 27, 2976.

⁹²Walling; Mintz *J. Am. Chem. Soc.* **1967**, 89, 1515.

⁹³For reviews, see Minisci *Synthesis* **1973**, 1-24; Deno *Methods Free-Radical Chem.* **1972**, 3, 135-154; Sosnovsky; Rawlinson *Adv. Free-Radical Chem.* **1972**, 4, 203-284.

⁹⁴The ω - 1 regioselectivity diminishes when the chains are longer than 10 carbons; see Deno; Jedziniak *Tetrahedron Lett.* **1976**, 1259; Konen; Maxwell; Silbert *J. Org. Chem.* **1979**, 44, 3594.

⁹⁵The ω - 1 selectivity values shown here may actually be lower than the true values because of selective solvolysis of the ω - 1 chlorides in concentrated H₂SO₄; see Deno; Pohl *J. Org. Chem.* **1975**, 40, 380.

⁹⁶Bernardi; Galli; Minisci *J. Chem. Soc. B* **1968**, 324. See also Deno; Gladfelter; Pohl *J. Org. Chem.* **1979**, 44, 3728; Fuller; Lindsay Smith; Norman; Higgins *J. Chem. Soc., Perkin Trans. 2* **1981**, 545.

⁹⁷Deno; Billups; Fishbein; Pierson; Whalen; Wyckoff *J. Am. Chem. Soc.* **1971**, 93, 438.

⁹⁸Minisci; Galli; Galli; Bernardi *Tetrahedron Lett.* **1967**, 2207; Minisci; Gardini; Bertini *Can. J. Chem.* **1970**, 48, 544.

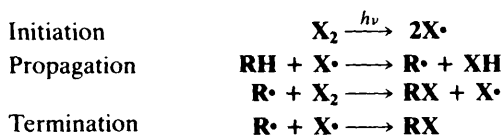
⁹⁹Kämper; Schäfer; Luftmann *Angew. Chem. Int. Ed. Engl.* **1976**, 15, 306 [*Angew. Chem.* **88**, 334].

¹⁰⁰Smith; Billups *J. Am. Chem. Soc.* **1974**, 96, 4307.

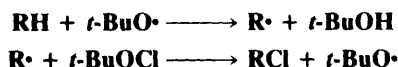
¹⁰¹It has been reported that the selectivity in one case is in accord with a pure electrostatic (field effect) explanation: Dneprovskii; Mil'tsov; Arbizov *J. Org. Chem. USSR* **1988**, 24, 1826. See also Tanner; Arhart; McIntzer *Tetrahedron* **1985**, 41, 4261; Ref. 95.

one carbon away from the bromine (to give *vic*-bromochlorides) by treatment with PCl_5 .¹⁰² Alkyl chlorides can be converted to *vic*-dichlorides by treatment with MoCl_5 .¹⁰³ Enhanced selectivity at a terminal position of *n*-alkanes has been achieved by absorbing the substrate onto a pentasil zeolite.¹⁰⁴ In another regioselective chlorination, alkanesulfonamides $\text{RCH}_2\text{CH}_2\text{CH}_2\text{SO}_2\text{NHR}'$ are converted primarily to $\text{RCHClCH}_2\text{CH}_2\text{CH}_2\text{SO}_2\text{NHR}'$ by sodium peroxydisulfate $\text{Na}_2\text{S}_2\text{O}_8$ and CuCl_2 .¹⁰⁵ For regioselective chlorination at certain positions of the steroid nucleus, see 9-2.

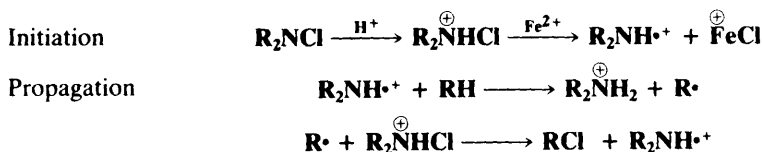
In almost all cases, the mechanism involves a free-radical chain:



When the reagent is halogen, initiation occurs as shown above.¹⁰⁶ When it is another reagent, a similar cleavage occurs (catalyzed by light or, more commonly, peroxides), followed by propagation steps that do not necessarily involve abstraction by halogen. For example, the propagation steps for chlorination by *t*-BuOCl have been formulated as¹⁰⁷



and the abstracting radicals in the case of N-haloamines are the aminium radical cations $\text{R}_2\text{NH}\cdot^+$ (p. 527), with the following mechanism (in the case of initiation by Fe^{2+}):⁹³



This mechanism is similar to that of the Hofmann-Löffler reaction (8-42).

The two propagation steps shown above for X_2 are those that lead directly to the principal products (RX and HX), but many other propagation steps are possible and many occur. Similarly, the only termination step shown is the one that leads to RX, but any two radicals may combine. Thus, products like H_2 , higher alkanes, and higher alkyl halides can be

¹⁰²Lucas; Bertin; Kagan *Tetrahedron Lett.* **1974**, 759.

¹⁰³San Filippo; Sowinski; Romano *J. Org. Chem.* **1975**, *40*, 3463.

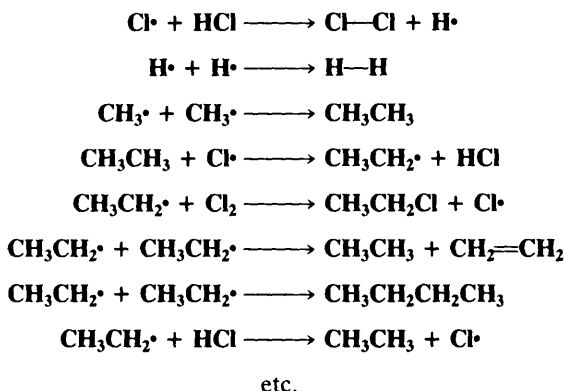
¹⁰⁴Turro; Fehlner; Hessler; Welsh; Ruderman; Firnberg; Braun *J. Org. Chem.* **1988**, *53*, 3731.

¹⁰⁵Nikishin; Troyansky; Lazareva *Tetrahedron Lett.* **1985**, *26*, 3743.

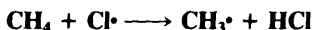
¹⁰⁶There is evidence (unusually high amounts of multiply chlorinated products) that under certain conditions in the reaction of RH with Cl_2 , the products of the second propagation step ($\text{RX} + \text{X}\cdot$) are enclosed within a solvent cage. See Skell; Baxter *J. Am. Chem. Soc.* **1985**, *107*, 2823; Raner; Luszyk; Ingold *J. Am. Chem. Soc.* **1988**, *110*, 3519; Tanko; Anderson *J. Am. Chem. Soc.* **1988**, *110*, 3525.

¹⁰⁷Carlsson; Ingold *J. Am. Chem. Soc.* **1967**, *89*, 4885, 4891; Walling; Kurkov *J. Am. Chem. Soc.* **1967**, *89*, 4895; Walling; McGuinness *J. Am. Chem. Soc.* **1969**, *91*, 2053. See also Zhulin; Rubinshtein *Bull. Acad. Sci. USSR. Div. Chem. Sci.* **1977**, *26*, 2082.

accounted for by steps like these (these are for chlorination of methane, but analogous steps can be written for other substrates):



At least when methane is the substrate, the rate-determining step is



since an isotope effect of 12.1 was observed at 0°C.¹⁰⁸ For chlorinations, chains are very long, typically 10⁴ to 10⁶ propagations before a termination step takes place.

The order of reactivity of the halogens can be explained by energy considerations. For the substrate methane, ΔH values for the two principal propagation steps are

	kcal/mol				kJ/mol			
	F ₂	Cl ₂	Br ₂	I ₂	F ₂	Cl ₂	Br ₂	I ₂
CH₄ + X· → CH₃· + HX	-31	+2	+17	+34	-132	+6	+72	+140
CH₃· + X₂ → CH₃X + X·	-70	-26	-24	-21	-293	-113	-100	-87

In each case D for CH₃—H is 105 kcal/mol (438 kJ/mol), while D values for the other bonds involved are given in Table 14.4.¹⁰⁹ F₂ is so reactive¹¹⁰ that neither uv light nor any other initiation is needed (total $\Delta H = -101$ kcal/mol; -425 kJ/mol);¹¹¹ while Br₂ and I₂ essentially do not react with methane. The second step is exothermic in all four cases, but it cannot take place before the first, and it is this step that is very unfavorable for Br₂ and I₂. It is apparent that the most important single factor causing the order of halogen reactivity

¹⁰⁸Wiberg; Motell *Tetrahedron* **1963**, 19, 2009.

¹⁰⁹Kerr, in *Weast Handbook of Chemistry and Physics*, 69th ed.; CRC Press: Boca Raton, FL, 1988, pp. F174-F189.

¹¹⁰It has been reported that the reaction of F atoms with CH₄ at 25 K takes place with practically zero activation energy: Johnson; Andrews *J. Am. Chem. Soc.* **1980**, 102, 5736.

¹¹¹For F₂ the following initiation step is possible: F₂ + RH → R· + F· + HF [first demonstrated by Miller; Koch; McLafferty *J. Am. Chem. Soc.* **1956**, 78, 4992]. ΔH for this reaction is equal to the small positive value of 5 kcal/mol (21 kJ/mol). The possibility of this reaction (which does not require an initiator) explains why fluorination can take place without uv light (which would otherwise be needed to furnish the 38 kcal/mol (159 kJ/mol) necessary to break the F—F bond). Once the reaction has been initiated, the large amount of energy given off by the propagation steps is ample to cleave additional F₂ molecules. Indeed, it is the magnitude of this energy that is responsible for the cleavage of carbon chains by F₂.

TABLE 14.4 Some D values¹⁰⁹

Bond	D	
	kcal/mol	kJ/mol
H-F	136	570
H-Cl	103	432
H-Br	88	366
H-I	71	298
F-F	38	159
Cl-Cl	59	243
Br-Br	46	193
I-I	36	151
CH ₃ -F	108	452
CH ₃ -Cl	85	356
CH ₃ -Br	70	293
CH ₃ -I	57	238

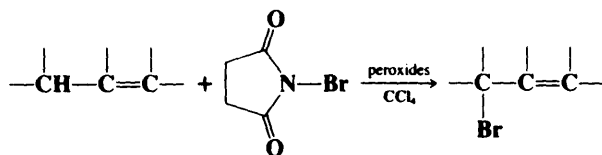
to be $F_2 > Cl_2 > Br_2 > I_2$ is the decreasing strength of the HX bond in the order $HF > HCl > HBr > HI$. The increased reactivity of secondary and tertiary positions is in accord with the decrease in D values for R—H in the order primary > secondary > tertiary (Table 5.3). (Note that for chlorination step 1 is exothermic for practically all substrates other than CH_4 , since most other aliphatic C—H bonds are weaker than those in CH_4 .)

Bromination and chlorination of alkanes and cycloalkanes can also take place by an electrophilic mechanism if the reaction is catalyzed by $AgSbF_6$.¹¹² Direct chlorination at a vinylic position by an electrophilic mechanism has been achieved with benzeneseleninyl chloride $PhSe(O)Cl$ and $AlCl_3$ or $AlBr_3$.¹¹³ However, while some substituted alkenes give high yields of chloro substitution products, others (such as styrene) undergo addition of Cl_2 to the double bond (5-26).¹¹³ Electrophilic fluorination has already been mentioned (p. 690).

OS II, 89, 133, 443, 549; III, 737, 788; IV, 807, 921, 984; V, 145, 221, 328, 504, 635, 825; VI, 271, 404, 715; VII, 491; 65, 68.

4-2 Allylic Halogenation

Halogenation or Halo-de-hydrogenation



This reaction is a special case of 4-1, but is important enough to be treated separately.¹¹⁴ Olefins can be halogenated in the allylic position by a number of reagents, of which N-bromosuccinimide (NBS)¹¹⁵ is by far the most common. When this reagent is used, the

¹¹²Olah; Renner; Schilling; Mo *J. Am. Chem. Soc.* **1973**, 95, 7686. See also Olah; Wu; Farooq *J. Org. Chem.* **1989**, 54, 1463.

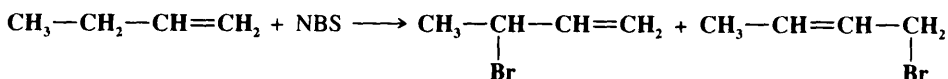
¹¹³Kamigata; Satoh; Yoshida *Bull. Chem. Soc. Jpn.* **1988**, 44, 449.

¹¹⁴For a review, see Nechvatal *Adv. Free-Radical Chem.* **1972**, 4, 175-201.

¹¹⁵For a review of this reagent, see Pizey, Ref. 85, vol. 2, pp. 1-63, 1974.

reaction is known as *Wohl-Ziegler bromination*. A nonpolar solvent is used, most often CCl_4 . Other N-bromo amides have also been used. To a much lesser extent, allylic chlorination has been carried out, with N-chlorosuccinimide, N-chloro-N-cyclohexylbenzenesulfonamide,¹¹⁶ or *t*-butyl hypochlorite.¹¹⁷ With any reagent an initiator is needed; this is usually a peroxide or, less often, uv light.

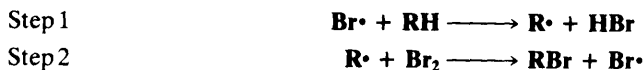
The reaction is usually quite specific at the allylic position and good yields are obtained. However, when the allylic radical intermediate is unsymmetrical, allylic rearrangements can take place, so that mixtures of both possible products are obtained, e.g.,



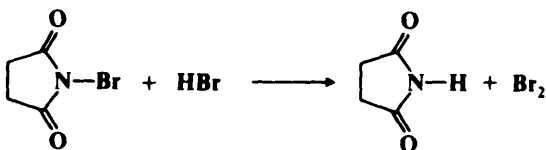
When a double bond has two different allylic positions, e.g., $\text{CH}_3\text{CH}=\text{CHCH}_2\text{CH}_3$, a secondary position is substituted more readily than a primary. The relative reactivity of tertiary hydrogen is not clear, though many substitutions at allylic tertiary positions have been performed.¹¹⁸ It is possible to brominate both sides of the double bond.¹¹⁹ Because of the electron-withdrawing nature of bromine, the second bromine substitutes on the other side of the double bond rather than α to the first bromine.

NBS is also a highly regioselective brominating agent at other positions, including positions α to a carbonyl group, to a $\text{C}\equiv\text{C}$ triple bond, and to an aromatic ring (benzylic position). When both a double and a triple bond are in the same molecule, the preferred position is α to the triple bond.¹²⁰

That the mechanism of allylic bromination is of the free-radical type was demonstrated by Dauben and McCoy,¹²¹ who showed that the reaction is very sensitive to free-radical initiators and inhibitors and indeed does not proceed at all unless at least a trace of initiator is present. Subsequent work indicated that the species that actually abstracts hydrogen from the substrate is the bromine atom. The reaction is initiated by small amounts of $\text{Br}\cdot$. Once it is formed, the main propagation steps are



The source of the Br_2 is a fast ionic reaction between NBS and the HBr liberated in step 1:



The function of the NBS is therefore to provide a source of Br_2 in a low, steady-state concentration and to use up the HBr liberated in step 1.¹²² The main evidence for this

¹¹⁶Theilacker; Wessel *Liebigs Ann. Chem.* **1967**, 703, 34.

¹¹⁷Walling; Thaler *J. Am. Chem. Soc.* **1961**, 83, 3877.

¹¹⁸Dauben; McCoy *J. Org. Chem.* **1959**, 24, 1577.

¹¹⁹Ucciani; Naudet *Bull. Soc. Chim. Fr.* **1962**, 871.

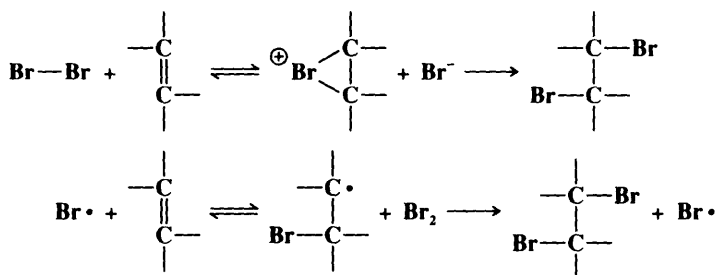
¹²⁰Peiffer *Bull. Soc. Chim. Fr.* **1963**, 537.

¹²¹Dauben; McCoy *J. Am. Chem. Soc.* **1959**, 81, 4863.

¹²²This mechanism was originally suggested by Adam; Gosselain; Goldfinger *Nature* **1953**, 171, 704, *Bull. Soc. Chim. Belg.* **1956**, 65, 533.

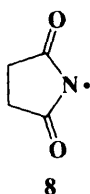
mechanism is that NBS and Br_2 show similar selectivity¹²³ and that the various N-bromo amides also show similar selectivity,¹²⁴ which is consistent with the hypothesis that the same species is abstracting in each case.¹²⁵

It may be asked why, if Br_2 is the reacting species, it does not add to the double bond, either by an ionic or by a free-radical mechanism (see 5-26). Apparently the concentration is too low. In bromination of a double bond, only one atom of an attacking bromine molecule becomes attached to the substrate, whether the addition is electrophilic or free-radical:



The other bromine atom comes from another bromine-containing molecule or ion. If the concentration is sufficiently low, there is a low probability that the proper species will be in the vicinity once the intermediate forms. The intermediate in either case reverts to the initial species and the allylic substitution competes successfully. If this is true, it should be possible to brominate an olefin in the allylic position without competition from addition, even in the absence of NBS or a similar compound, if a very low concentration of bromine is used and if the HBr is removed as it is formed so that it is not available to complete the addition step. This has indeed been demonstrated.¹²⁶

When NBS is used to brominate non-olefinic substrates such as alkanes, another mechanism, involving abstraction of the hydrogen of the substrate by the succinimidyl radical¹²⁷ **8** can operate.¹²⁸ This mechanism is facilitated by solvents (such as CH_2Cl_2 , CHCl_3 , or



¹²³Walling; Rieger *J. Am. Chem. Soc.* **1963**, *85*, 3129; Russell; Desmond *J. Am. Chem. Soc.* **1963**, *85*, 3139; Russell; DeBoer; Desmond *J. Am. Chem. Soc.* **1963**, *85*, 365; Pearson; Martin *J. Am. Chem. Soc.* **1963**, *85*, 3142; Skell; Tuleen; Readio *J. Am. Chem. Soc.* **1963**, *85*, 2850.

¹²⁴Walling; Rieger *J. Am. Chem. Soc.* **1963**, *85*, 3134; Pearson; Martin, Ref. 123; Incremona; Martin *J. Am. Chem. Soc.* **1970**, *92*, 627.

¹²⁵For other evidence, see Day; Lindstrom; Skell *J. Am. Chem. Soc.* **1974**, *96*, 5616.

¹²⁶McGrath; Tedder *Proc. Chem. Soc.* **1961**, 80.

¹²⁷For a review of this radical, see Chow; Naguib *Rev. Chem. Intermed.* **1984**, *5*, 325-345.

¹²⁸Skell; Day *Acc. Chem. Res.* **1978**, *11*, 381; Walling; El-Taliawi; Zhao *J. Am. Chem. Soc.* **1983**, *105*, 5119; Tanner; Reed; Tan; Meintzer; Walling; Sopchik *J. Am. Chem. Soc.* **1985**, *107*, 6576; Luning; Skell *Tetrahedron* **1985**, *41*, 4289; Skell; Luning; McBain; Tanko *J. Am. Chem. Soc.* **1986**, *108*, 121; Luning; Seshadri; Skell *J. Org. Chem.* **1986**, *51*, 2071; Chow; Zhao *J. Org. Chem.* **1987**, *52*, 1931, **1989**, *54*, 530; Zhang; Dong; Jiang; Chow *Can. J. Chem.* **1990**, *68*, 1668.

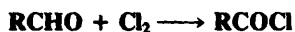
MeCN) in which NBS is more soluble, and by the presence of small amounts of an alkene that lacks an allylic hydrogen (e.g., ethene). The alkene serves to scavenge any $\text{Br}\cdot$ that forms from the reagent. Among the evidence for the mechanism involving **8** are abstraction selectivities similar to those of $\text{Cl}\cdot$ atoms and the isolation of β -bromopropionyl isocyanate $\text{BrCH}_2\text{CH}_2\text{CONCO}$, which is formed by ring-opening of **8**.

Allylic chlorination has also been carried out¹²⁹ with N-chlorosuccinimide and either arylselenenyl chlorides ArSeCl , aryl diselenides ArSeSeAr , or TsNSO as catalysts. Use of the selenium catalysts produces almost entirely the allylically rearranged chlorides in high yields. With TsNSO the products are the unrearranged chlorides in lower yields. Dichlorine monoxide Cl_2O , with no catalyst, also gives allylically rearranged chlorides in high yields.¹³⁰ A free-radical mechanism is unlikely in these reactions.

OS IV, 108; V, 825; VI, 462.

4-3 Halogenation of Aldehydes

Halogenation or Halo-de-hydrogenation



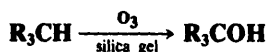
Aldehydes can be directly converted to acyl chlorides by treatment with chlorine; however, the reaction operates only when the aldehyde does not contain an α hydrogen and even then it is not very useful. When there is an α hydrogen, α halogenation (**2-4**) occurs instead. Other sources of chlorine have also been used, among them SO_2Cl_2 ¹³¹ and $t\text{-BOCl}$.¹³² The mechanisms are probably of the free-radical type. NBS, with AIBN (p. 664) as a catalyst, has been used to convert aldehydes to acyl bromides.¹³³

OS I, 155.

B. Substitution by Oxygen

4-4 Hydroxylation at an Aliphatic Carbon

Hydroxylation or Hydroxy-de-hydrogenation



Compounds containing susceptible C—H bonds can be oxidized to alcohols.¹³⁴ Nearly always, the C—H bond involved is tertiary, so the product is a tertiary alcohol. This is partly because tertiary C—H bonds are more susceptible to free-radical attack than primary and secondary bonds and partly because the reagents involved would oxidize primary and secondary alcohols further. In the best method the reagent is ozone and the substrate is absorbed on silica gel.¹³⁵ Yields as high as 99% have been obtained by this method. Other reagents, which often give much lower yields, are chromic acid,¹³⁶ alkaline permanganate,¹³⁷ potassium

¹²⁹Hori; Sharpless *J. Org. Chem.* **1979**, *44*, 4204.

¹³⁰Torii; Tanaka; Tada; Nagao; Sasaoka *Chem. Lett.* **1984**, 877.

¹³¹Arai *Bull. Chem. Soc. Jpn.* **1964**, *37*, 1280, **1965**, *38*, 252.

¹³²Walling; Mintz, Ref. 92.

¹³³Markó; Mekhafia *Tetrahedron Lett.* **1990**, *31*, 7237. For a related procedure, see Cheung *Tetrahedron Lett.* **1979**, 3809.

¹³⁴For reviews, see Chinn *Selection of Oxidants in Synthesis*; Marcel Dekker: New York, 1971, pp. 7-11; Lee, in *Augustine Oxidation*, vol. 1; Marcel Dekker: New York, 1969, pp. 2-6. For a monograph on all types of alkane activation, see Hill *Activation and Functionalization of Alkanes*; Wiley: New York, 1989.

¹³⁵Cohen; Keinan; Mazur; Varkony *J. Org. Chem.* **1975**, *40*, 2141, *Org. Synth.* *VI*, 43; Keinan; Mazur *Synthesis* **1976**, 523; McKillop; Young *Synthesis* **1979**, 401-422, pp. 418-419.

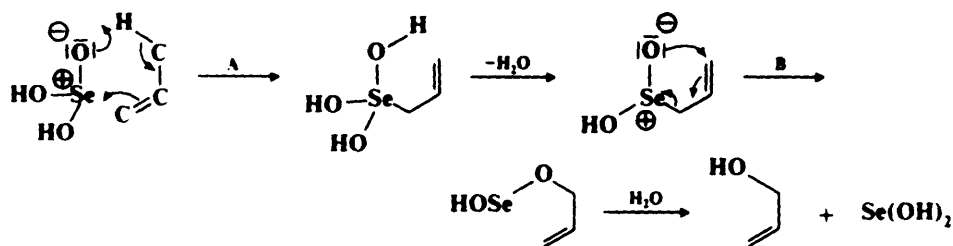
¹³⁶For a review, see Cainelli; Cardillo *Chromium Oxidations in Organic Chemistry*; Springer: New York, 1984, pp. 8-23.

¹³⁷Eastman; Quinn *J. Am. Chem. Soc.* **1969**, *82*, 4249.

hydrogen persulfate KHSO_5 ,¹³⁸ methyl(trifluoromethyl)dioxirane,¹³⁹ ruthenium tetroxide RuO_4 ,¹⁴⁰ F_2 in $\text{MeCN-H}_2\text{O}$,¹⁴¹ sodium chlorite NaClO_2 with a metalloporphyrin catalyst,¹⁴² and certain perbenzoic acids.¹⁴³ Alkanes and cycloalkanes have been oxidized at secondary positions, to a mixture of alcohols and trifluoroacetates, by 30% aqueous H_2O_2 in trifluoroacetic acid.¹⁴⁴ This reagent does not oxidize the alcohols further and ketones are not found. As in the case of chlorination with N-haloamines and sulfuric acid (see 4-1), the $\omega - 1$ position is the most favored. Another reagent¹⁴⁵ that oxidizes secondary positions is iodosylbenzene, catalyzed by Fe(III)-porphyrin catalysts.¹⁴⁶ Use of an optically active Fe(III)-porphyrin gave enantioselective hydroxylation, with moderate enantiomeric excesses.¹⁴⁷

When chromic acid is the reagent, the mechanism is probably as follows: a Cr^{6+} species abstracts a hydrogen to give $\text{R}_3\text{C}^\bullet$, which is held in a solvent cage near the resulting Cr^{5+} species. The two species then combine to give $\text{R}_3\text{COCr}^{4+}$, which is hydrolyzed to the alcohol. This mechanism predicts retention of configuration; this is largely observed.¹⁴⁸ The oxidation by permanganate also involves predominant retention of configuration, and a similar mechanism has been proposed.¹⁴⁹

Treatment of double-bond compounds with selenium dioxide introduces an OH group into the allylic position (see also 9-16).¹⁵⁰ Allylic rearrangements are common. There is evidence that the mechanism does not involve free radicals but includes two pericyclic steps (A and B):¹⁵¹



The step marked A is similar to the ene synthesis (5-16). The step marked B is a [2,3] sigmatropic rearrangement (see 8-37). The reaction can also be accomplished with

¹³⁸De Poorter; Ricci; Meunier *Tetrahedron Lett.* **1985**, 26, 4459.

¹³⁹Mello; Fiorentino; Fusco; Curci *J. Am. Chem. Soc.* **1989**, 111, 6749. For a review of dioxiranes as oxidizing agents, see Adam; Curci; Edwards *Acc. Chem. Res.* **1989**, 22, 205-211. See also Murray; Jeyaraman; Mohan *J. Am. Chem. Soc.* **1986**, 108, 2470.

¹⁴⁰Bakke; Lundquist *Acta Chem. Scand., Ser. B* **1986**, 40, 430; Tenaglia; Terranova; Waegell *Tetrahedron Lett.* **1989**, 30, 5271; Bakke; Braenden *Acta Chem. Scand.* **1991**, 45, 418.

¹⁴¹Rozen; Brand; Kol *J. Am. Chem. Soc.* **1989**, 111, 8325.

¹⁴²Collman; Tanaka; Hembre; Brauman *J. Am. Chem. Soc.* **1990**, 112, 3689.

¹⁴³Schneider; Müller *Angew. Chem. Int. Ed. Engl.* **1982**, 21, 146 [*Angew. Chem.* 94, 153]; *J. Org. Chem.* **1985**, 50, 4609; Takaishi; Fujikura; Inamoto *Synthesis* **1983**, 293; Tori; Sono; Asakawa *Bull. Chem. Soc. Jpn.* **1985**, 58, 2669. See also Querci; Ricci *Tetrahedron Lett.* **1990**, 31, 1779.

¹⁴⁴Deno; Jedziniak; Messer; Meyer; Stroud; Tomesko *Tetrahedron* **1977**, 33, 2503.

¹⁴⁵For other procedures, see Sharma; Sonawane; Dev *Tetrahedron* **1985**, 41, 2483; Nam; Valentine *New J. Chem.* **1989**, 13, 677.

¹⁴⁶See Groves; Nemo *J. Am. Chem. Soc.* **1983**, 105, 6243.

¹⁴⁷Groves; Viski *J. Org. Chem.* **1990**, 55, 3628.

¹⁴⁸Wiberg; Foster *J. Am. Chem. Soc.* **1961**, 83, 423; *Chem. Ind. (London)* **1961**, 108; Wiberg; Eisenthal *Tetrahedron* **1964**, 20, 1151.

¹⁴⁹Wiberg; Fox *J. Am. Chem. Soc.* **1963**, 85, 3487; Brauman; Pandell *J. Am. Chem. Soc.* **1970**, 92, 329; Stewart; Spitzer *Can. J. Chem.* **1978**, 56, 1273.

¹⁵⁰For reviews, see Rabjohn, *Org. React.* **1976**, 24, 261-415; Jerussi *Sel. Org. Transform.* **1970**, 1, 301-326; Trachtenberg, in Augustine, Ref. 134, pp. 123-153.

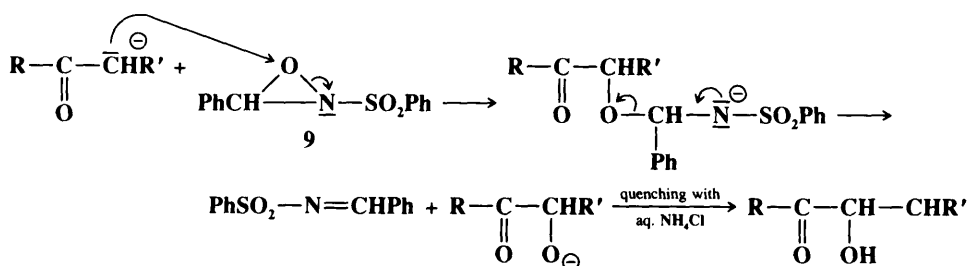
¹⁵¹Sharpless; Lauer *J. Am. Chem. Soc.* **1972**, 94, 7154; Arigoni; Vasella; Sharpless; Jensen *J. Am. Chem. Soc.* **1973**, 95, 7917; Woggon; Ruther; Egli *J. Chem. Soc., Chem. Commun.* **1980**, 706. For other mechanistic proposals, see Schaefer; Horvath; Klein *J. Org. Chem.* **1968**, 33, 2647; Trachtenberg; Nelson; Carver *J. Org. Chem.* **1970**, 35, 1653; Bhalarao; Rapoport *J. Am. Chem. Soc.* **1971**, 93, 4835; Stephenson; Speth *J. Org. Chem.* **1979**, 44, 4683.

t-butyl hydroperoxide, if SeO_2 is present in catalytic amounts (the *Sharpless method*).¹⁵² The SeO_2 is the actual reagent; the peroxide reoxidizes the $\text{Se}(\text{OH})_2$.¹⁵³ This method makes work-up easier, but gives significant amounts of side products when the double bond is in a ring.¹⁵⁴ Alkynes generally give α, α' dihydroxylation.¹⁵⁵

Ketones and carboxylic esters can be α hydroxylated by treatment of their enolate forms (prepared by adding the ketone or ester to lithium diisopropylamide) with a molybdenum peroxide reagent (MoO_5 -pyridine-HMPA) in THF-hexane at -70°C .¹⁵⁶ The enolate forms of amides and esters¹⁵⁷ and the enamine derivatives of ketones¹⁵⁸ can similarly be converted to their α hydroxy derivatives by reaction with molecular oxygen. The MoO_5 method can also be applied to certain nitriles.¹⁵⁶ Ketones have also been α hydroxylated by treating the corresponding silyl enol ethers with *m*-chloroperbenzoic acid,¹⁵⁹ or with certain other oxidizing agents.¹⁶⁰ When the silyl enol ethers are treated with iodosobenzene in the presence of trimethylsilyl trifluoromethyl sulfonate, the product is the α -keto triflate.¹⁶¹

Ketones can be α hydroxylated in good yields, without conversion to the enolates, by treatment with the hypervalent iodine reagents¹⁶² *o*-iodosobenzoic acid¹⁶³ or phenyliodosoacetate $\text{PhI}(\text{OAc})_2$ in methanolic NaOH .¹⁶⁴ The latter reagent has also been used on carboxylic esters.¹⁶⁵ O_2 and a chiral phase transfer catalyst gave enantioselective α hydroxylation of ketones, if the α position was tertiary.¹⁶⁶

A different method for the conversion of ketones to α -hydroxy ketones consists of treating the enolate with a 2-sulfonyloxaziridine (such as **9**).¹⁶⁷ This is not a free-radical process; the following mechanism is likely:



¹⁵²Umbreit; Sharpless *J. Am. Chem. Soc.* **1977**, 99, 5526. See also Uemura; Fukuzawa; Toshimitsu; Okano *Tetrahedron Lett.* **1982**, 23, 87; Singh; Sabharwal; Sayal; Chhabra *Chem. Ind. (London)* **1989**, 533.

¹⁵³For the use of the peroxide with O_2 instead of SeO_2 , see Sabol; Wiglesworth; Watt *Synth. Commun.* **1988**, 18, 1.

¹⁵⁴Warphoski; Chabaud; Sharpless *J. Org. Chem.* **1982**, 47, 2897.

¹⁵⁵Chabaud; Sharpless *J. Org. Chem.* **1979**, 44, 4202.

¹⁵⁶Vedejs *J. Am. Chem. Soc.* **1974**, 96, 5944; Vedejs; Telschow *J. Org. Chem.* **1976**, 41, 740; Vedejs; Larsen *Org. Synth.* **VII**, 277; Gamboni; Tamm *Tetrahedron Lett.* **1986**, 27, 3999; *Helv. Chim. Acta* **1986**, 69, 615. See also Anderson; Smith *Synlett* **1990**, 107.

¹⁵⁷Wasserman; Lipshutz *Tetrahedron Lett.* **1975**, 1731. For another method, see Pohmakotr; Winotai *Synth. Commun.* **1988**, 18, 2141.

¹⁵⁸Cuvigny; Valette; Larcheveque; Normant *J. Organomet. Chem.* **1978**, 155, 147.

¹⁵⁹Rubottom; Vazquez; Pelegrina *Tetrahedron Lett.* **1974**, 4319; Rubottom; Gruber *J. Org. Chem.* **1978**, 43, 1599; Hassner; Reuss; Pinnick *J. Org. Chem.* **1975**, 40, 3427; Andriamialisoa; Langlois; Langlois *Tetrahedron Lett.* **1985**, 26, 3563; Rubottom; Gruber; Juve; Charleson *Org. Synth.* **VII**, 282. See also Horiguchi; Nakamura; Kuwajima *Tetrahedron Lett.* **1989**, 30, 3323.

¹⁶⁰McCormick; Tomasik; Johnson *Tetrahedron Lett.* **1981**, 22, 607; Moriarty; Prakash; Duncan *Synthesis* **1985**, 943; Iwata; Takemoto; Nakamura; Imanishi *Tetrahedron Lett.* **1985**, 26, 3227; Davis; Sheppard *J. Org. Chem.* **1987**, 52, 954; Takai; Yamada; Rhode; Mukaiyama *Chem. Lett.* **1991**, 281.

¹⁶¹Moriarty; Epa; Penmasta; Awasthi *Tetrahedron Lett.* **1989**, 30, 667.

¹⁶²For a review, see Moriarty; Prakash *Acc. Chem. Res.* **1986**, 19, 244-250.

¹⁶³Moriarty; Hou *Tetrahedron Lett.* **1984**, 25, 691; Moriarty; Hou; Prakash; Arora *Org. Synth.* **VII**, 263.

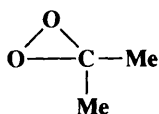
¹⁶⁴Moriarty; Hu; Gupta *Tetrahedron Lett.* **1981**, 22, 1283.

¹⁶⁵Moriarty; Hu *Tetrahedron Lett.* **1981**, 22, 2747.

¹⁶⁶Masui; Ando; Shioiri *Tetrahedron Lett.* **1988**, 29, 2835.

¹⁶⁷Davis; Vishwakarma; Billmers; Finn *J. Org. Chem.* **1984**, 49, 3241.

The method is also successful for carboxylic esters¹⁶⁷ and N,N-disubstituted amides,¹⁶⁸ and can be made enantioselective by the use of a chiral oxaziridine.¹⁶⁹ Dimethyldioxirane also oxidizes ketones (through their enolate forms) to α -hydroxy ketones.^{169a}



Dimethyldioxirane

Tetrahydrofuran was converted to the hemiacetal 2-hydroxytetrahydrofuran (which was relatively stable under the conditions used) by electrolysis in water¹⁷⁰ (see also 4-7).

OS IV, 23; VI, 43, 946; VII, 263, 277, 282.

4-5 Hydroxylation at an Aromatic Carbon¹⁷¹

Hydroxylation or Hydroxy-de-hydrogenation



A mixture of hydrogen peroxide and ferrous sulfate,¹⁷² called *Fenton's reagent*,¹⁷³ can be used to hydroxylate aromatic rings, though yields are usually not high.¹⁷⁴ Biaryls are usually side products.¹⁷⁵ Among other reagents used have been H_2O_2 and titanous ion; O_2 and Cu(I) ¹⁷⁶ or Fe(III) ,¹⁷⁷ a mixture of ferrous ion, oxygen, ascorbic acid, and ethylenetetra-aminetetraacetic acid (*Udenfriend's reagent*);¹⁷⁸ α -azo hydroperoxides $\text{ArN}=\text{NCHPhOOH}$;¹⁷⁹ O_2 and KOH in liquid NH_3 ;¹⁸⁰ and peracids such as pernitrous and trifluoroperacetic acids.

Much work has been done on the mechanism of the reaction with Fenton's reagent, and it is known that free aryl radicals (formed by a process such as $\text{HO}\cdot + \text{ArH} \rightarrow \text{Ar}\cdot + \text{H}_2\text{O}$) are not intermediates. The mechanism is essentially that outlined on p. 680, with $\text{HO}\cdot$ as the attacking species,¹⁸¹ formed by



¹⁶⁸Davis; Vishwakarma *Tetrahedron Lett.* **1985**, 26, 3539.

¹⁶⁹Evans; Morrissey; Dorow *J. Am. Chem. Soc.* **1985**, 107, 4346; Davis; Ulatowski; Haque *J. Org. Chem.* **1987**, 52, 5288; Enders; Bhushan *Tetrahedron Lett.* **1988**, 29, 2437; Davis; Sheppard; Chen; Haque *J. Am. Chem. Soc.* **1990**, 112, 6679; Davis; Weismiller *J. Org. Chem.* **1990**, 55, 3715.

^{169a}Guertin; Chan *Tetrahedron Lett.* **1991**, 32, 715.

¹⁷⁰Wermeckes; Beck; Schulz *Tetrahedron* **1987**, 43, 577.

¹⁷¹For reviews, see Vysotskaya *Russ. Chem. Rev.* **1973**, 42, 851-856; Sangster, in Patai *The Chemistry of the Hydroxyl Group*, pt. 1; Wiley: New York, 1971, pp. 133-191; Metelitsa *Russ. Chem. Rev.* **1971**, 40, 563-580; Enisov; Metelitsa *Russ. Chem. Rev.* **1968**, 37, 656-665; Loudon *Prog. Org. Chem.* **1961**, 5, 47-72.

¹⁷²For a review of reactions of H_2O_2 and metal ions with all kinds of organic compounds, including aromatic rings, see Sosnovsky; Rawlinson, in Swern *Organic Peroxides*, vol. 2; Wiley: New York, 1970, pp. 269-336. See also Sheldon; Kochi *Metal-Catalyzed Oxidations of Organic Compounds*; Academic Press: New York, 1981.

¹⁷³For a discussion of Fenton's reagent, see Walling *Acc. Chem. Res.* **1975**, 8, 125-131.

¹⁷⁴Yields can be improved with phase transfer catalysis: Karakhanov; Narin; Filippova; Dedov *Doklad. Chem.* **1987**, 292, 81.

¹⁷⁵See the discussion of the aromatic free-radical substitution mechanism on pp. 680-681.

¹⁷⁶See Karlin; Hayes; Gultneh; Cruse; McKown; Hutchinson; Zubieta *J. Am. Chem. Soc.* **1984**, 106, 2121; Cruse; Kaderli; Meyer; Zuberbühler; Karlin *J. Am. Chem. Soc.* **1988**, 110, 5020; Ito; Kunai; Okada; Sasaki *J. Org. Chem.* **1988**, 53, 296.

¹⁷⁷Funabiki; Tsujimoto; Ozawa; Yoshida *Chem. Lett.* **1989**, 1267.

¹⁷⁸Udenfriend; Clark; Axelrod; Brodie *J. Biol. Chem.* **1954**, 208, 731; Brodie; Shore; Udenfriend *J. Biol. Chem.* **1954**, 208, 741. See also Tamagaki; Suzuki; Tagaki *Bull. Chem. Soc. Jpn.* **1989**, 62, 148, 153, 159.

¹⁷⁹Tezuka; Narita; Ando; Oae *J. Am. Chem. Soc.* **1981**, 103, 3045.

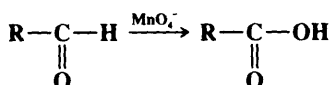
¹⁸⁰Malykhin; Kolesnichenko; Shteingarts *J. Org. Chem. USSR* **1986**, 22, 720.

¹⁸¹Jefcoate; Lindsay Smith; Norman; *J. Chem. Soc. B* **1969**, 1013; Brook; Castle; Lindsay Smith; Higgins; Morris *J. Chem. Soc., Perkin Trans. 2* **1982**, 687; Lai; Piette *Tetrahedron Lett.* **1979**, 775; Kunai; Hata; Ito; Sasaki *J. Am. Chem. Soc.* **1986**, 108, 6012.

The rate-determining step is formation of HO• and not its reaction with the aromatic substrate.

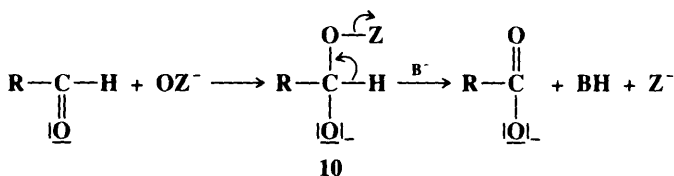
See also 1-29.

4-6 Oxidation of Aldehydes to Carboxylic Acids Hydroxylation or Hydroxy-de-hydrogenation



Oxidation of aldehydes to carboxylic acids is one of the most common oxidation reactions in organic chemistry¹⁸² and has been carried out with many oxidizing agents, the most popular of which is permanganate in acid, basic, or neutral solution.¹⁸³ Chromic acid¹⁸⁴ and bromine are other reagents frequently employed. Silver oxide is a fairly specific oxidizing agent for aldehydes and does not readily attack other groups. Benedict's and Fehling's solutions oxidize aldehydes,¹⁸⁵ and a test for aldehydes depends on this reaction, but the method is seldom used for preparative purposes and in any case gives very poor results with aromatic aldehydes. α,β -Unsaturated aldehydes can be oxidized by sodium chlorite without disturbing the double bond.¹⁸⁶ Aldehydes are also oxidized to carboxylic acids by atmospheric oxygen, but the actual direct oxidation product in this case is the peroxy acid RCO_3H ,¹⁸⁷ which with another molecule of aldehyde disproportionates to give two molecules of acid (see 4-9).¹⁸⁸

Mechanisms of aldehyde oxidation¹⁸⁹ are not firmly established, but there seem to be at least two main types—a free-radical mechanism and an ionic one. In the free-radical process, the aldehydic hydrogen is abstracted to leave an acyl radical, which obtains OH from the oxidizing agent. In the ionic process, the first step is addition of a species OZ^- to the carbonyl bond to give **10** in alkaline solution and **11** in acid or neutral solution. The aldehydic hydrogen of **10** or **11** is then lost as a proton to a base, while Z leaves with its electron pair.



¹⁸²For reviews, see Haines *Methods for the Oxidation of Organic Compounds*; Academic Press: New York, 1988, pp. 241-263, 423-428; Chinn, Ref. 134, pp. 63-70; Lee, Ref. 134, pp. 81-86.

¹⁸³For lists of some of the oxidizing agents used, with references, see Hudlicky *Oxidations in Organic Chemistry*; American Chemical Society: Washington, 1990, pp. 174-180; Ref. 74, pp. 838-840; Srivastava; Venkataramani *Synth. Commun.* **1988**, 18, 2193. See also Haines, Ref. 182.

¹⁸⁴For a review, see Cainelli; Cardillo, Ref. 136, pp. 217-225.

¹⁸⁵For a review, see Nigh, in Trahanovsky *Oxidation in Organic Chemistry*, pt. B; Academic Press: New York, 1973, pp. 31-34.

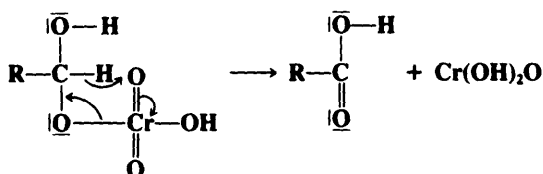
¹⁸⁶Bal; Childers; Pinnick *Tetrahedron* **1981**, 37, 2091; Dalcanale; Montanari *J. Org. Chem.* **1986**, 51, 567. See also Bayle; Perez; Courtieu *Bull. Soc. Chim. Fr.* **1990**, 565.

¹⁸⁷For a review of the preparation of peroxy acids by this and other methods, see Swern, in Swern, Ref. 172, vol. 1, pp. 313-516.

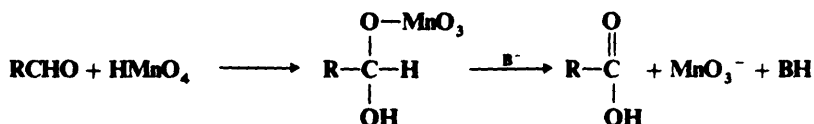
¹⁸⁸For reviews of the autooxidation of aldehydes, see Vardanyan; Nalbandyan *Russ. Chem. Rev.* **1985**, 54, 532-543 (gas phase); Sajus; Séré de Roch, in Bamford; Tipper, Ref. 37, vol. 16, 1980, pp. 89-124 (liquid phase); Maslov; Blyumberg *Russ. Chem. Rev.* **1976**, 45, 155-167 (liquid phase). For a review of photochemical oxidation of aldehydes by O_2 , see Niclauss; Lemaire; Letort *Adv. Photochem.* **1966**, 4, 25-48. For a discussion of the mechanism of catalyzed atmospheric oxidation of aldehydes, see Larkin *J. Org. Chem.* **1990**, 55, 1563.

¹⁸⁹For a review, see Roček, in Patai *The Chemistry of the Carbonyl Group*, vol. 1; Wiley: New York, 1966, pp. 461-505.

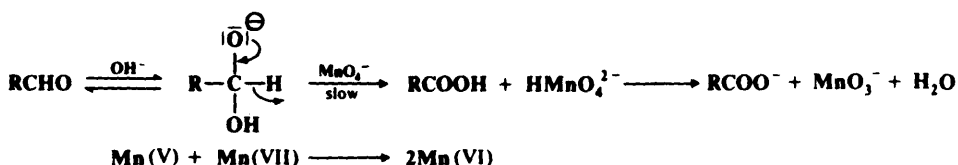
been proposed in which the chromic acid ester decomposes as follows:¹⁹¹



The mechanism with permanganate is less well-known, but an ionic mechanism has been proposed¹⁹² for neutral and acid permanganate, similar to steps 1 and 2 for dichromate:



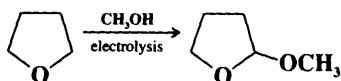
For alkaline permanganate, the following mechanism has been proposed:¹⁹³



OS I, 166; II, 302, 315, 538; III, 745; IV, 302, 493, 499, 919, 972, 974.

4-7 Electrochemical Alkoxylation

Alkoxylation or Alkoxy-de-hydrogenation



Ethers can be converted to acetals, and acetals to ortho esters, by anodic oxidation in an alcohol as solvent.¹⁹⁴ Yields are moderate. In a similar reaction, certain amides, carbamates, and sulfonamides can be alkoxyated α to the nitrogen, e.g., $\text{MeSO}_2\text{NMe}_2 \rightarrow \text{MeSO}_2\text{N}(\text{Me})\text{CH}_2\text{OCH}_3$.¹⁹⁵

OS VII, 307.

¹⁹¹See Roček; Ng *J. Org. Chem.* **1973**, 38, 3348.

¹⁹²See, for example, Freeman; Lin; Moore *J. Org. Chem.* **1982**, 47, 56; Jain; Banerji *J. Chem. Res. (S)* **1983**, 60.

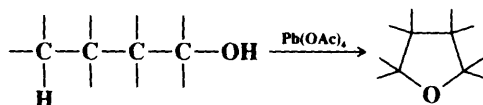
¹⁹³Freeman; Brant; Hester; Kamego; Kasner; McLaughlin; Paull *J. Org. Chem.* **1970**, 35, 982.

¹⁹⁴Shono; Matsumura; Onomura; Yamada *Synthesis* **1987**, 1099; Ginzle; Steckhan *Tetrahedron* **1987**, 43, 5797.

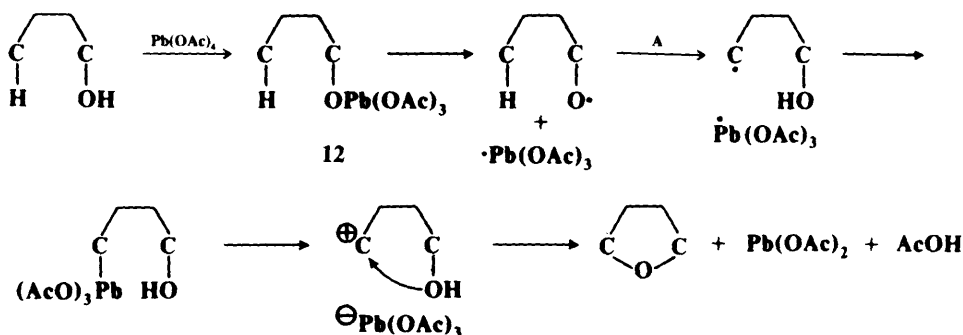
¹⁹⁵Ross; Finkelstein; Rudd *J. Org. Chem.* **1972**, 37, 2387. See also Moeller; Tarazi; Marzabadi *Tetrahedron Lett.* **1989**, 30, 1213; Shono; Matsumura; Tsubata *Org. Synth. VII*, 307. For a table of compounds subjected to this reaction, see Shono *Electroorganic Chemistry as a New Tool in Organic Synthesis*; Springer: New York, 1984, pp. 63-66.

4-8 Formation of Cyclic Ethers

(5) OC-cyclo-Alkoxy-de-hydro-substitution



Alcohols with a hydrogen in the δ position can be cyclized with lead tetraacetate.¹⁹⁶ The reaction is usually carried out at about 80°C (most often in refluxing benzene) but can also be done at room temperature if the reaction mixture is irradiated with uv light. Tetrahydrofurans are formed in high yields. Little or no four- and six-membered cyclic ethers (oxetanes and tetrahydropyrans, respectively) are obtained even when γ and ϵ hydrogens are present. The reaction has also been carried out with a mixture of halogen (Br_2 or I_2) and a salt or oxide of silver or mercury (especially HgO or AgOAc),¹⁹⁷ with iodo-sobenzene diacetate and I_2 ,¹⁹⁸ and with ceric ammonium nitrate (CAN).¹⁹⁹ The following mechanism is likely for the lead tetraacetate reaction:²⁰⁰



though **12** has never been isolated. The step marked **A** is a 1,5 internal hydrogen abstraction. Such abstractions are well-known (see p. 1153) and are greatly favored over 1,4 or 1,6 abstractions (the small amounts of tetrahydropyran formed result from 1,6 abstractions).²⁰¹

Reactions that sometimes compete are oxidation to the aldehyde or acid (**9-3** and **9-22**) and fragmentation of the substrate. When the OH group is on a ring of at least seven

¹⁹⁶For reviews, see Mihailović; Partch *Sel. Org. Transform.* **1972**, 2, 97-182; Milhailović; Čeković *Synthesis* **1970**, 209-224. For a review of the chemistry of lead tetraacetate, see Butler, in Pizey, Ref. 85, vol. 3, 1977, pp. 277-419.

¹⁹⁷Akhtar; Barton *J. Am. Chem. Soc.* **1964**, 86, 1528; Sneen; Matheny *J. Am. Chem. Soc.* **1964**, 86, 3905, 5503; Roscher; Shaffer *Tetrahedron* **1984**, 40, 2643. For a review, see Kalvoda; Heusler *Synthesis* **1971**, 501-526. For a list of references, see Ref. 74, p. 445.

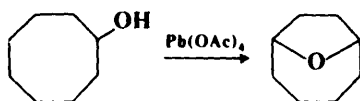
¹⁹⁸Concepción; Francisco; Hernández; Salazar; Suárez *Tetrahedron Lett.* **1984**, 25, 1953; Furuta; Nagata; Yamamoto *Tetrahedron Lett.* **1988**, 29, 2215.

¹⁹⁹See, for example, Trahanovsky; Young; Nave *Tetrahedron Lett.* **1969**, 2501; Doyle; Zuidema; Bade *J. Org. Chem.* **1975**, 40, 1454.

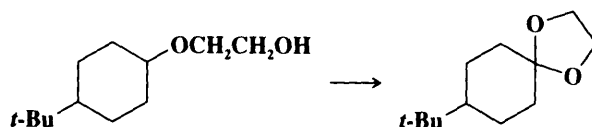
²⁰⁰Milhailović; Čeković; Maksimović; Jeremić; Lorenc; Mamuzić *Tetrahedron* **1965**, 21, 2799.

²⁰¹Milhailović; Čeković; Jeremić *Tetrahedron* **1965**, 21, 2813.

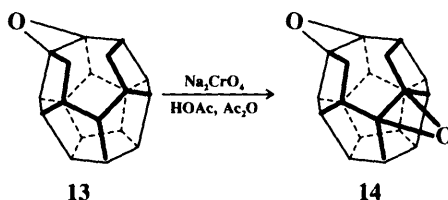
members, a transannular product can be formed, e.g.,²⁰²



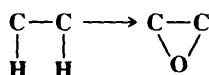
β -Hydroxy ethers can give cyclic acetals, e.g.,²⁰³



A different kind of formation of a cyclic ether was reported by Paquette and Kobayashi,²⁰⁴ who found that when the epoxide **13** of secododecahedrane was treated with sodium chromate and $\text{HOAc}-\text{Ac}_2\text{O}$, the diepoxide **14** was obtained. Thus, the unusual transformation



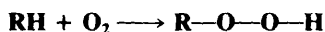
mate and $\text{HOAc}-\text{Ac}_2\text{O}$, the diepoxide **14** was obtained. Thus, the unusual transformation



was achieved in this case. It is likely that the large degree of strain in this system was at least partially responsible for the formation of this product.

There are no references in *Organic Syntheses*, but see OS V, 692; VI, 958, for related reactions.

4-9 Formation of Hydroperoxides Hydroperoxy-de-hydrogenation



The slow atmospheric oxidation (*slow* meaning without combustion) of $\text{C}-\text{H}$ to $\text{C}-\text{O}-\text{O}-\text{H}$ is called *autoxidation*.²⁰⁵ The reaction occurs when compounds are allowed to stand in air and is catalyzed by light, so unwanted autoxidations can be greatly slowed by keeping the compounds in dark places. The hydroperoxides produced often react further

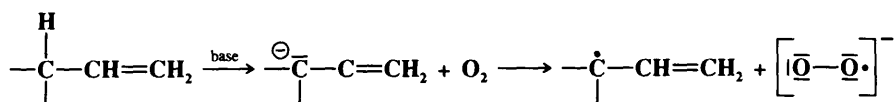
²⁰²Cope; Gordon; Moon; Park *J. Am. Chem. Soc.* **1965**, 87, 3119; Moriarty; Walsh *Tetrahedron Lett.* **1965**, 465; Milhailović; Čeković; Andrejević; Matić; Jeremić *Tetrahedron* **1968**, 24, 4947.

²⁰³Furuta et al., Ref. 198.

²⁰⁴Paquette; Kobayashi *Tetrahedron Lett.* **1987**, 28, 3531.

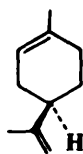
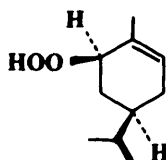
²⁰⁵The term autoxidation actually applies to any slow oxidation with atmospheric oxygen. For reviews, see Sheldon; Kochi *Adv. Catal.* **1976**, 25, 272-413; Howard, in Kochi, Ref. 8, vol. 2, pp. 3-62; Lloyd *Methods Free-Radical Chem.* **1973**, 4, 1-131; Betts *Q. Rev., Chem. Soc.* **1971**, 25, 265-288; Huyser *Free-Radical Chain Reactions*, Ref. 1, pp. 306-312; Chinn, Ref. 134, pp. 29-39; Ingold *Acc. Chem. Res.* **1969**, 2, 1-9; Mayo *Acc. Chem. Res.* **1968**, 1, 193-201. For monographs on these and similar reactions, see Bamford; Tipper, Ref. 37, Vol. 16, 1980; Sheldon; Kochi, Ref. 172.

In at least some cases (in alkaline media)²¹² the radical $R\cdot$ can be produced by formation of a carbanion and its oxidation (by O_2) to a radical, e.g.,²¹³



Autooxidations in alkaline media can also proceed by a different mechanism: $R-H + \text{base} \rightarrow R^- + O_2 \rightarrow ROO^-$.²¹⁴

When alkenes are treated with oxygen that has been photosensitized (p. 241), they are substituted by OOH in the allylic position in a synthetically useful reaction.²¹⁵ Although superficially similar to autooxidation, this reaction is clearly different because 100% allylic rearrangement always takes place. The reagent here is not the ground-state oxygen (a triplet) but an excited singlet state²¹⁶ (in which all electrons are paired), and the function of the photosensitization is to promote the oxygen to this singlet state. Singlet oxygen can also be produced by nonphotochemical means,²¹⁷ e.g., by the reaction between H_2O_2 and $NaOCl$ ²¹⁸ or sodium molybdate,²¹⁹ or between ozone and triphenyl phosphite.²²⁰ The oxygen generated by either photochemical or nonphotochemical methods reacts with olefins in the same way;²²¹ this is evidence that singlet oxygen is the reacting species in the photochemical reaction and not some hypothetical complex between triplet oxygen and the photosensitizer, as had previously been suggested. The fact that 100% allylic rearrangement always takes place is incompatible with a free-radical mechanism, and further evidence that free radicals are not involved comes from the treatment of optically active limonene (**15**) with singlet oxygen. Among other products is the optically active hydroperoxide **16**, though if **17** were an inter-

**15****16****17**

²¹²For a review of base-catalyzed autooxidations in general, see Sosnovsky; Zaret, in Swern, Ref. 172, vol. 1, pp. 517-560.

²¹³Barton; Jones *J. Chem. Soc.* **1965**, 3563; Russell; Bemis *J. Am. Chem. Soc.* **1966**, 88, 5491.

²¹⁴Gersmann; Bickel *J. Chem. Soc. B* **1971**, 2230.

²¹⁵For reviews, see Frimer; Stephenson, in Frimer, Ref. 216, vol. 2, pp. 67-91; Wasserman; Ives *Tetrahedron* **1981**, 37, 1825-1852; Gollnick; Kuhn, in Wasserman; Murray, Ref. 216, pp. 287-427; Denny; Nickon *Org. React.* **1973**, 20, 133-336; Adams, in Augustine, Ref. 134, vol. 2, pp. 65-112.

²¹⁶For books on singlet oxygen, see Frimer *Singlet O₂*, 4 vols.; CRC Press: Boca Raton, FL, 1985; Wasserman; Murray *Singlet Oxygen*; Academic Press: New York, 1979. For reviews, see Frimer, in Patai, Ref. 206, pp. 201-234; Gorman; Rodgers, *Chem. Soc. Rev.* **1981**, 10, 205-231; Shinkarenko; Aleskovskii *Russ. Chem. Rev.* **1981**, 50, 220-231; Shlyapintokh; Ivanov *Russ. Chem. Rev.* **1976**, 45, 99-110; Ohloff *Pure Appl. Chem.* **1975**, 43, 481-502; Kearns *Chem. Rev.* **1971**, 71, 395-427; Wayne *Adv. Photochem.* **1969**, 7, 311-371.

²¹⁷For reviews, see Turro; Ramamurthy, in *de Mayo Rearrangements in Ground and Excited States*, vol. 3; Academic Press: New York, 1980, pp. 1-23; Murray, in Wasserman; Murray, Ref. 216, pp. 59-114. For a general monograph, see Adam; Cilento, *Chemical and Biological Generation of Excited States*; Academic Press: New York, 1982.

²¹⁸Footo; Wexler *J. Am. Chem. Soc.* **1964**, 86, 3879.

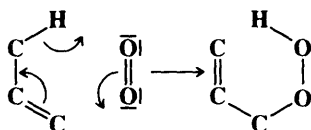
²¹⁹Aubry; Cazin; Duprat *J. Org. Chem.* **1989**, 54, 726.

²²⁰Murray; Kaplan *J. Am. Chem. Soc.* **1969**, 91, 5358; Bartlett; Mendenhall; Durham *J. Org. Chem.* **1980**, 45, 4269.

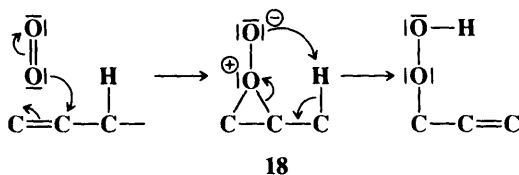
²²¹Footo; Wexler; Ando; Higgins *J. Am. Chem. Soc.* **1968**, 90, 975. See also McKown; Waters *J. Chem. Soc. B* **1966**, 1040.

mediate, it could not give an optically active product since it possesses a plane of symmetry.²²² In contrast, autoxidation of **15** gave optically inactive **16** (a mixture of four diastereomers in which the two pairs of enantiomers are present as racemic mixtures). As this example shows, singlet oxygen reacts faster with more-highly substituted than with less-highly substituted alkenes. The order of alkene reactivity is tetrasubstituted > trisubstituted > disubstituted. Electron-withdrawing substituents deactivate the olefin.²²³ In simple trisubstituted olefins, there is a general preference for the hydrogen to be removed from the more highly congested side of the double bond.²²⁴ With *cis*-alkenes of the form $\text{RCH=CHR}'$, the hydrogen is removed from the larger R group.²²⁵ Many functional groups in an allylic position cause the hydrogen to be removed from that side rather than the other (geminal selectivity).²²⁶ Also, in alkyl-substituted alkenes, the hydrogen that is preferentially removed is the one geminal to the larger substituent on the double bond.²²⁷

Several mechanisms have been proposed for the reaction with singlet oxygen.²²⁸ One of these is a pericyclic mechanism, similar to that of the ene synthesis (**5-16**) and to the first



step of the reaction between alkenes and SeO_2 (**4-4**). However, there is strong evidence against this mechanism,²²⁹ and a more likely mechanism involves addition of singlet oxygen to the double bond to give a perepoxide (**18**),²³⁰ followed by internal proton transfer.²³¹



Still other proposed mechanisms involve diradicals or dipolar intermediates.²³² OS IV, 895.

²²²Schenck; Gollnick; Buchwald; Schroeter; Ohloff *Liebigs Ann. Chem.* **1964**, 674, 93; Schenck; Neumüller; Ohloff; Schroeter *Liebigs Ann. Chem.* **1965**, 687, 26.

²²³For example, see Foote; Denny *J. Am. Chem. Soc.* **1971**, 93, 5162.

²²⁴Schulte-Elte; Muller; Rautenstrauch *Helv. Chim. Acta* **1978**, 61, 2777; Orfanopoulos; Grdina; Stephenson *J. Am. Chem. Soc.* **1979**, 101, 275; Rautenstrauch; Thommen; Schulte-Elte *Helv. Chim. Acta* **1986**, 69, 1638.

²²⁵Orfanopoulos; Stratakis; Elemen *Tetrahedron Lett.* **1989**, 30, 4875.

²²⁶Clennan; Chen; Koola *J. Am. Chem. Soc.* **1990**, 112, 5193, and references cited therein.

²²⁷Orfanopoulos; Stratakis; Elemen *J. Am. Chem. Soc.* **1990**, 112, 6417.

²²⁸For reviews of the mechanism, see Frimer; Stephenson, Ref. 215, pp. 80-87; Stephenson; Grdina; Orfanopoulos *Acc. Chem. Res.* **1980**, 13, 419-425; Gollnick; Kuhn, Ref. 215, pp. 288-341; Frimer *Chem. Rev.* **1979**, 79, 359-387; Foote *Acc. Chem. Res.* **1968**, 1, 104-110; *Pure Appl. Chem.* **1971**, 27, 635-645; Gollnick *Adv. Photochem.* **1968**, 6, 1-122; Kearns, Ref. 216.

²²⁹Asveld; Kellogg *J. Org. Chem.* **1982**, 47, 1250.

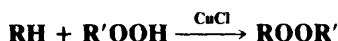
²³⁰For a review of perepoxides as intermediates in organic reactions, see Mitchell *Chem. Soc. Rev.* **1985**, 14, 399-419, pp. 401-406.

²³¹For evidence in favor of this mechanism, at least with some kinds of substrates, see Jefford; Rimbault *J. Am. Chem. Soc.* **1978**, 100, 6437; Okada; Mukai *J. Am. Chem. Soc.* **1979**, 100, 6509; Paquette; Hertel; Gleiter; Böhm *J. Am. Chem. Soc.* **1978**, 100, 6510; Hurst; Wilson; Schuster *Tetrahedron* **1985**, 41, 2191; Wilson; Schuster *J. Org. Chem.* **1986**, 51, 2056; Davies; Schiesser *Tetrahedron Lett.* **1989**, 30, 7099; Orfanopoulos; Smonou; Foote *J. Am. Chem. Soc.* **1990**, 112, 3607.

²³²See, for example, Jefford *Helv. Chim. Acta* **1981**, 64, 2534.

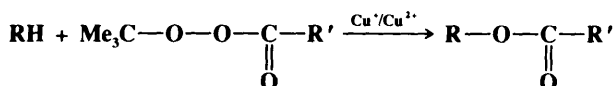
4-10 Formation of Peroxides

Alkyldioxy-de-hydrogenation

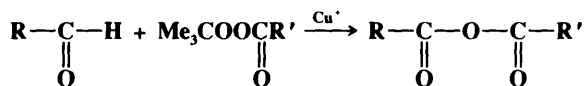


Peroxy groups (ROO) can be introduced into susceptible organic molecules by treatment with a hydroperoxide in the presence of cuprous chloride or other catalysts, e.g., cobalt and manganese salts.²³³ Very high yields can be obtained. The type of hydrogen replaced is similar to that with N-bromosuccinimide (4-2), i.e., mainly benzylic, allylic, and tertiary. The mechanism is therefore of the free-radical type, involving ROO• formed from ROOH and the metal ion. The reaction can be used to demethylate tertiary amines of the form R₂NCH₃, since the product R₂NHCH₂OOR' can easily be hydrolyzed by acid (0-6) to give R₂NH.²³⁴

4-11 Acyloxylation or Acyloxy-de-hydrogenation



Susceptible positions of organic compounds can be directly acyloxylated²³⁵ by *t*-butyl peresters, the most frequently used being acetic and benzoic (R' = Me or Ph).²³⁶ The reaction requires a catalyst (cuprous ion is the actual catalyst, but a trace is all that is necessary, and such traces are usually present in cupric compounds, so that these are often used) and without it is not selective. Susceptible positions are similar to those in 4-9: benzylic, allylic, and the α position of ethers and sulfides. Terminal olefins are substituted almost entirely in the 3 position, i.e., with only a small amount of allylic rearrangement, but internal olefins generally give mixtures containing a large amount of allylic-shift product. If the reaction with olefins is carried out in an excess of another acid R''COOH, the ester produced is of that acid ROCOR''. Aldehydes give anhydrides:



Acyloxylation has also been achieved with metallic acetates such as lead tetraacetate,²³⁷ mercuric acetate,²³⁸ and palladium(II) acetate.²³⁹ In the case of the lead and mercuric acetates, not only does the reaction take place at allylic and benzylic positions and at those α to an OR or SR group but also at positions α to the carbonyl groups of aldehydes, ketones, or esters and at those α to two carbonyl groups (ZCH₂Z'). It is likely that in the latter cases

²³³For a review, see Sosnovsky; Rawlinson, Ref. 172, pp. 153-268. See also Murahashi; Naota; Kuwabara; Saito; Kumobayashi; Akutagawa *J. Am. Chem. Soc.* **1990**, *112*, 7820; Ref. 206.

²³⁴See Murahashi; Naota; Yonemura *J. Am. Chem. Soc.* **1988**, *110*, 8256.

²³⁵For a list of reagents, with references, see Ref. 74, pp. 823-827ff, 841-842.

²³⁶For reviews, see Rawlinson; Sosnovsky *Synthesis* **1972**, 1-28; Sosnovsky; Rawlinson, in Swern, Ref. 172, vol. 1, pp. 585-608; Doumaux, in Augustine, Ref. 134, vol. 2, 1971, pp. 141-185.

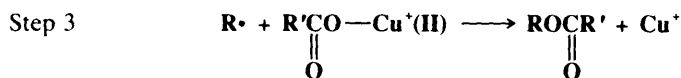
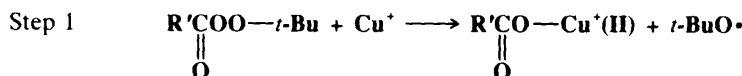
²³⁷For a review of lead tetraacetate, see Butler, Ref. 196.

²³⁸For reviews, see Larock *Organomercury Compounds in Organic Synthesis*; Springer: New York, 1985, pp. 190-208; Rawlinson; Sosnovsky *Synthesis* **1973**, 567-602.

²³⁹Hansson; Heumann; Rein; Åkermark *J. Org. Chem.* **1990**, *55*, 975; Byström; Larsson; Åkermark *J. Org. Chem.* **1990**, *55*, 5674.

it is the enol forms that react. Ketones can be α -acyloxylation indirectly by treatment of various enol derivatives with metallic acetates, for example, silyl enol ethers with silver carboxylates-iodine,²⁴⁰ enol thioethers with lead tetraacetate,²⁴¹ and enamines²⁴² with lead tetraacetate²⁴³ or thallium triacetate.²⁴⁴ α,β -Unsaturated ketones can be acyloxylation in good yields in the α' position with manganese triacetate.²⁴⁵ Palladium acetate converts alkenes to vinylic and/or allylic acetates.²⁴⁶ Lead tetraacetate even acyloxylation alkanes, in a slow reaction (10 days to 2 weeks), with tertiary and secondary positions greatly favored over primary ones.²⁴⁷ Yields are as high as 50%. Acyloxylation of certain alkanes has also been reported with palladium(II) acetate.²⁴⁸

Studies of the mechanism of the cuprous-catalyzed reaction show that the most common mechanism is the following:²⁴⁹



19

This mechanism, involving a free radical $\text{R}\cdot$, is compatible with the allylic rearrangements found.²⁵⁰ The finding that *t*-butyl peresters labeled with ^{18}O in the carbonyl oxygen gave ester with 50% of the label in each oxygen²⁵¹ is in accord with a combination of $\text{R}\cdot$ with the intermediate **19**, in which the copper is ionically bound, so that the oxygens are essentially equivalent. Other evidence is that *t*-butoxy radicals have been trapped with dienes.²⁵² Much less is known about the mechanisms of the reactions with metal acetates.²⁵³

Free-radical acyloxylation of aromatic substrates²⁵⁴ has been accomplished with a number of reagents including copper(II) acetate,²⁵⁵ benzoyl peroxide-iodine,²⁵⁶ silver(II) complexes,²⁵⁷ and cobalt(III) trifluoroacetate.²⁵⁸

OS **III**, 3; **V**, 70, 151; **68**, 109.

²⁴⁰Rubottom; Mott; Juve *J. Org. Chem.* **1981**, 46, 2717.

²⁴¹Trost; Tanigawa *J. Am. Chem. Soc.* **1979**, 101, 4413.

²⁴²For a review, see Cook, in *Cook Enamines*, 2nd ed.; Marcel Dekker: New York, 1988, pp. 251-258.

²⁴³See Butler, *Chem. Ind. (London)* **1976**, 499-500.

²⁴⁴Kuchne; Giacobbe *J. Org. Chem.* **1968**, 33, 3359.

²⁴⁵Dunlap; Sabol; Watt *Tetrahedron Lett.* **1984**, 25, 5839; Demir; Sayrac; Watt *Synthesis* **1990**, 1119.

²⁴⁶For reviews, see Rylander *Organic Synthesis with Noble Metal Catalysts*; Academic Press: New York, 1973, pp. 80-87; Jira; Freiesleben *Organomet. React.* **1972**, 3, 1-190, pp. 44-84; Heck *Fortschr. Chem. Forsch.* **1971**, 16, 221-242, pp. 231-237; Tsuji *Adv. Org. Chem.* **1969**, 6, 109-255, pp. 132-143.

²⁴⁷Bestre; Cole; Crank *Tetrahedron Lett.* **1983**, 24, 3891; Mosher; Cox *Tetrahedron Lett.* **1985**, 26, 3753.

²⁴⁸This was done in trifluoroacetic acid, and the products were trifluoroacetates: Sen; Gretz; Oliver; Jiang *New J. Chem.* **1989**, 13, 755.

²⁴⁹Kharasch; Sosnovsky; Yang *J. Am. Chem. Soc.* **1959**, 81, 5819; Kochi; Mains *J. Org. Chem.* **1965**, 30, 1862. See also Beckwith; Zavitsas *J. Am. Chem. Soc.* **1986**, 108, 8230.

²⁵⁰Goering; Mayer *J. Am. Chem. Soc.* **1964**, 86, 3753; Denney; Appelbaum; Denney *J. Am. Chem. Soc.* **1962**, 84, 4969.

²⁵¹Denney; Denney; Feig *Tetrahedron Lett.* **1959**, no. 15, p. 19.

²⁵²Kochi *J. Am. Chem. Soc.* **1962**, 84, 2785, 3271; Story *Tetrahedron Lett.* **1962**, 401.

²⁵³See, for example, Jones; Mellor *J. Chem. Soc., Perkin Trans. 2* **1977**, 511.

²⁵⁴For a review, see Haines *Methods for the Oxidation of Organic Compounds*; Academic Press: New York, 1985, pp. 177-180, 351-355.

²⁵⁵Takizawa; Tateishi; Sugiyama; Yoshida; Yoshihara *J. Chem. Soc., Chem. Commun.* **1991**, 104. See also Kaeding; Kerlinger; Collins *J. Org. Chem.* **1965**, 30, 3754.

²⁵⁶For example, see Kovacic; Reid; Brittain *J. Org. Chem.* **1970**, 35, 2152.

²⁵⁷Nyberg; Wistrand *J. Org. Chem.* **1978**, 43, 2613.

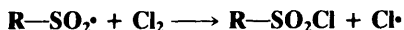
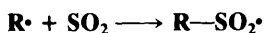
²⁵⁸Kochi; Tank; Bernath *J. Am. Chem. Soc.* **1973**, 95, 7114; DiCosimo; Szabo *J. Org. Chem.* **1986**, 51, 1365.

C. Substitution by Sulfur

4-12 Chlorosulfonation or Chlorosulfo-de-hydrogenation



The chlorosulfonation of organic molecules with chlorine and sulfur dioxide is called the *Reed reaction*.²⁵⁹ In scope and range of products obtained, the reaction is similar to 4-1. The mechanism is also similar, except that there are two additional main propagation steps:

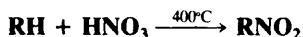


*Chlorosulfenation*²⁶⁰ can be accomplished by treatment with SCl_2 and uv light: $\text{RH} + \text{SCl}_2 \xrightarrow{h\nu} \text{RSCl}$.

D. Substitution by Nitrogen

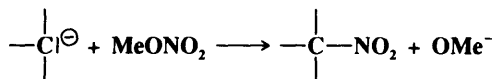
4-13 Nitration of Alkanes

Nitration or Nitro-de-hydrogenation



Nitration of alkanes²⁶¹ can be carried out in the gas phase at about 400°C or in the liquid phase. The reaction is not practical for the production of pure products for any alkane except methane. For other alkanes, not only does the reaction produce mixtures of the mono-, di-, and polynitrated alkanes at every combination of positions, but extensive chain cleavage occurs.²⁶² A free-radical mechanism is involved.²⁶³

Activated positions (e.g., $\text{ZCH}_2\text{Z}'$ compounds) can be nitrated by fuming nitric acid in acetic acid, by acetyl nitrate and an acid catalyst,²⁶⁴ or by alkyl nitrates under alkaline conditions.²⁶⁵ In the latter case it is the carbanionic form of the substrate that is actually nitrated. What is isolated under these alkaline conditions is the conjugate base of the nitro



compound. Yields are not high. Of course, the mechanism in this case is not of the free-radical type, but is electrophilic substitution with respect to the carbon (similar to the mechanisms of 2-7 and 2-8). Positions activated by only one electron-withdrawing group, e.g., α positions of simple ketones, nitriles, sulfones, or N,N-dialkyl amides, can be nitrated with alkyl nitrates if a very strong base, e.g., *t*-BuOK or NaNH_2 , is present to convert the substrate to the carbanionic form.²⁶⁶ Electrophilic nitration of alkanes has been performed

²⁵⁹For a review, see Gilbert *Sulfonation and Related Reactions*; Wiley: New York, 1965, pp. 126-131.

²⁶⁰Müller; Schmidt *Chem. Ber.* **1963**, 96, 3050, **1964**, 97, 2614. For a review of the formation and reactions of sulfonyl halides, see Kühle *Synthesis* **1970**, 561-580, **1971**, 563-586, 617-638.

²⁶¹For reviews, see Olah; Malhotra; Narang *Nitration*; VCH: New York, 1989, pp. 219-295; Ogata, in Trahanovsky, Ref. 185, part C, 1978, pp. 295-342; Ballod; Shtern *Russ. Chem. Rev.* **1976**, 45, 721-737.

²⁶²For a discussion of the mechanism of this cleavage, see Matasa; Hass *Can. J. Chem.* **1971**, 49, 1284.

²⁶³Titov *Tetrahedron* **1963**, 19, 557-580.

²⁶⁴Sifniades *J. Org. Chem.* **1975**, 40, 3562.

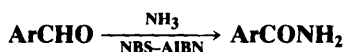
²⁶⁵For a review, see Larson, in Feuer *The Chemistry of the Nitro and Nitroso Groups*, vol. 1; Wiley: New York, 1969, pp. 310-316.

²⁶⁶For examples, see Feuer; Shepherd; Savides *J. Am. Chem. Soc.* **1956**, 78, 4364; Feuer; Lawrence *J. Org. Chem.* **1972**, 37, 2662; Truce; Christensen *Tetrahedron* **1969**, 25, 181; Pfeffer; Silbert *Tetrahedron Lett.* **1970**, 699; Feuer; Spinicelli *J. Org. Chem.* **1976**, 41, 2981; Feuer; Van Buren; Grutzner *J. Org. Chem.* **1978**, 43, 4676.

with nitronium salts, e.g., $\text{NO}_2^+ \text{PF}_6^-$ and with $\text{HNO}_3\text{--H}_2\text{SO}_4$ mixtures, but mixtures of nitration and cleavage products are obtained and yields are generally low.²⁶⁷

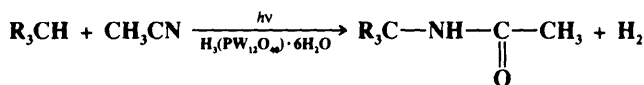
Aliphatic nitro compounds can be α nitrated [$\text{R}_2\text{CHNO}_2 \rightarrow \text{R}_2\text{C}(\text{NO}_2)_2$] by treatment of their conjugate bases RCNO_2^- with NO_2^- and $\text{K}_3\text{Fe}(\text{CN})_6$.²⁶⁸
OS I, 390; II, 440, 512.

4-14 The Direct Conversion of Aldehydes to Amides Amination or Amino-de-hydrogenation



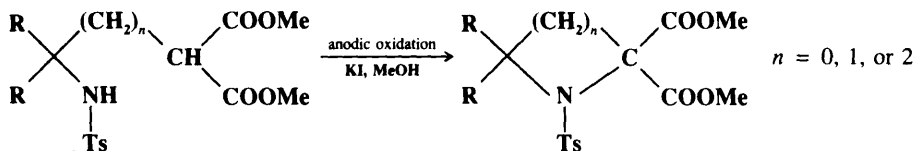
Aliphatic and aromatic aldehydes have been converted to the corresponding amides with ammonia or a primary or secondary amine, N-bromosuccinimide, and a catalytic amount of AIBN (p. 664).²⁶⁹ In a reaction of more limited scope, amides are obtained from aromatic and α,β -unsaturated aldehydes by treatment with dry ammonia gas and nickel peroxide.²⁷⁰ Best yields (80 to 90%) are obtained at -25 to -20°C . The reaction has also been performed with MnO_2 and NaCN along with ammonia or an amine at 0°C in isopropyl alcohol,²⁷¹ and with a secondary amine and a palladium acetate catalyst.²⁷² In the nickel peroxide reaction the corresponding alcohols (ArCH_2OH) have also been used as substrates. For an indirect way of converting aldehydes to amides, see 2-31. Thioamides RCSNR'_2 have been prepared in good yield from thioaldehydes (produced in situ from phosphoranes and sulfur) and secondary amines.²⁷³

4-15 Amidation and Amination at an Alkyl Carbon Acylamino-de-hydrogenation



When alkanes bearing a tertiary hydrogen are exposed to uv light in acetonitrile containing a heteropolytungstic acid, they are amidated.²⁷⁴ The oxygen in the product comes from the tungstic acid. When the substrate bears two adjacent tertiary hydrogens, alkenes are formed (by loss of two hydrogens), rather than amides (9-2).

An electrochemical method for amination has been reported by Shono and co-workers.²⁷⁵ Derivatives of malonic esters containing an N-tosyl group were cyclized in high yields by anodic oxidation:



Three-, four-, and five-membered rings were synthesized by this procedure.

²⁶⁷Olah; Lin *J. Am. Chem. Soc.* **1973**, 93, 1259. See also Bach; Holubka; Badger; Rajan *J. Am. Chem. Soc.* **1979**, 101, 4416.

²⁶⁸Matacz; Piotrowska; Urbanski *Pol. J. Chem.* **1979**, 53, 187; Kornblum; Singh; Kelly *J. Org. Chem.* **1983**, 48, 332; Garver; Grakauskas; Baum *J. Org. Chem.* **1985**, 50, 1699.

²⁶⁹Markó; Mekhafia, Ref. 133.

²⁷⁰Nakagawa; Onoue; Minami *Chem. Commun.* **1966**, 17.

²⁷¹Gilman *Chem. Commun.* **1971**, 733.

²⁷²Tamaru; Yamada; Yoshida *Synthesis* **1983**, 474.

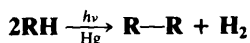
²⁷³Okuma; Komiya; Ohta *Chem. Lett.* **1988**, 1145.

²⁷⁴Renneke; Hill *J. Am. Chem. Soc.* **1986**, 108, 3528.

²⁷⁵Shono; Matsumura; Katoh; Ohshita *Chem. Lett.* **1988**, 1065.

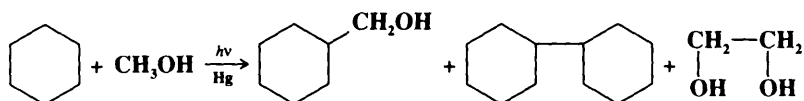
E. Substitution by Carbon In these reactions a new carbon-carbon bond is formed, and they may be given the collective title *coupling reactions*. In each case an alkyl or aryl radical is generated and then combines with another radical (a termination process) or attacks an aromatic ring or olefin to give the coupling product.²⁷⁶

4-16 Simple Coupling at a Susceptible Position De-hydrogen-coupling

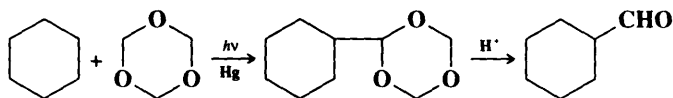


Alkanes can be dimerized by vapor-phase mercury photosensitization²⁷⁷ in a synthetically useful process. Best results are obtained for coupling at tertiary positions, but compounds lacking tertiary hydrogens (e.g., cyclohexane) also give good yields. Dimerization of *n*-alkanes gives secondary-secondary coupling in a nearly statistical distribution, with primary positions essentially unaffected. Alcohols and ethers dimerize at the position α to the oxygen [e.g., $2\text{EtOH} \rightarrow \text{MeCH(OH)CH(OH)Me}$].

When a mixture of compounds is treated, cross-dimerization and homodimerization take place statistically, e.g.:



Even with the limitation on yield implied by the statistical process, cross-dimerization is still useful when one of the reactants is an alkane, because the products are easy to separate, and because of the few other ways to functionalize an alkane. The cross-coupling of an alkane with trioxane is especially valuable, because hydrolysis of the product (0-6) gives an



aldehyde, thus achieving the conversion $RH \rightarrow RCHO$. The mechanism probably involves abstraction of H by the excited Hg atom, and coupling of the resulting radicals.

The reaction has been extended to ketones, carboxylic acids and esters (all of which couple α to the $C=O$ group), and amides (which couple α to the nitrogen) by running it in the presence of H_2 .²⁷⁸ Under these conditions it is likely that the excited Hg abstracts $H\cdot$ from H_2 , and that the remaining $H\cdot$ abstracts H from the substrate.

In an older reaction, substrates RH are treated with peroxides, which decompose to give a radical that abstracts a hydrogen from RH to give $R\cdot$, which dimerizes. Dialkyl and diacyl peroxides have been used, as well as Fenton's reagent (p. 700). This reaction is far from general, though in certain cases respectable yields have been obtained. Among susceptible positions are those at a tertiary carbon,²⁷⁹ as well as those α to a phenyl group (especially if there is also an α -alkyl or α -chloro group),²⁸⁰ an ether group,²⁸¹ a carbonyl group,²⁸² a

²⁷⁶For a monograph on the formation of C—C bonds by radical reactions, see Giese, Ref. 1. For a review of arylation at carbon, see Abramovitch; Barton; Finet *Tetrahedron* **1988**, *44*, 3039-3071. For a review of aryl-aryl coupling, see Sainsbury *Tetrahedron* **1980**, *36*, 3327-3359.

²⁷⁷Brown; Crabtree *J. Am. Chem. Soc.* **1989**, *111*, 2935, 2946, *J. Chem. Educ.* **1988**, *65*, 290.

²⁷⁸Boojamra; Crabtree; Ferguson; Muedas *Tetrahedron Lett.* **1989**, *30*, 5583.

²⁷⁹Meshcheryakov; Erzyutova *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1966**, 94.

²⁸⁰McBay; Tucker; Groves *J. Org. Chem.* **1959**, *24*, 536; Johnston; Williams *J. Chem. Soc.* **1960**, 1168.

²⁸¹Pfordte; Leuschner *Liebigs. Ann. Chem.* **1961**, 643, 1.

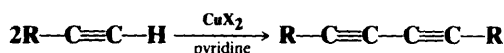
²⁸²Kharasch; McBay; Urry *J. Am. Chem. Soc.* **1948**, *70*, 1269; Leffingwell *Chem. Commun.* **1970**, 357; Hawkins; Large *J. Chem. Soc., Perkin Trans. I* **1974**, 280.

cyano group,²⁸³ a dialkylamino group,²⁸⁴ or a carboxylic ester group, either the acid or alcohol side.²⁸⁵

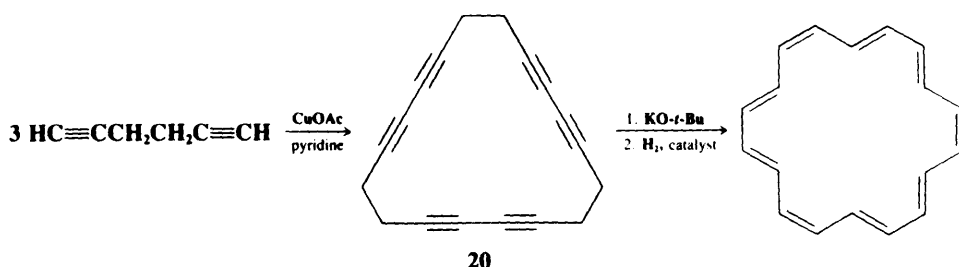
OS IV, 367; V, 1026; VII, 482.

4-17 Coupling of Alkynes

De-hydrogen-coupling

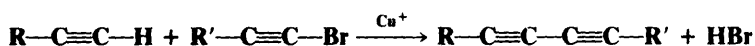


Terminal alkynes can be coupled by heating with stoichiometric amounts of cupric salts in pyridine or a similar base. This reaction, which produces symmetrical diynes in high yields, is called the *Eglinton reaction*.²⁸⁶ The large-ring annulenes of Sondheimer et al. (see p. 62) were prepared by rearrangement and hydrogenation of cyclic polyynes,²⁸⁷ prepared by Eglinton coupling of terminal diynes, e.g.,²⁸⁸



20 is a cyclic trimer of 1,5-hexadiyne. The corresponding tetramers (C_{24}), pentamers (C_{30}), and hexamers (C_{36}) were also formed.

The Eglinton reaction is of wide scope. Many functional groups can be present on the alkyne. The oxidation is usually quite specific for triple-bond hydrogen. Another common procedure is the use of catalytic amounts of cuprous salts in the presence of ammonia or ammonium chloride (this method is called the *Glaser reaction*). Atmospheric oxygen or some other oxidizing agent such as permanganate or hydrogen peroxide is required in the latter procedure. This method is not satisfactory for cyclic coupling. Unsymmetrical diynes can be prepared by *Cadiot-Chodkiewicz* coupling:²⁸⁹



This may be regarded as a variation of **0-100** but it must have a different mechanism since acetylenic halides give the reaction but ordinary alkyl halides do not, which is hardly compatible with a nucleophilic mechanism. However, the mechanism is not fully understood. Propargyl halides also give the reaction.²⁹⁰ A variation of the Cadiot-Chodkiewicz method

²⁸³Kharasch; Sosnovsky *Tetrahedron* **1958**, 3, 97.

²⁸⁴Schwetlick; Jentsch; Karl; Wolter *J. Prakt. Chem.* **1964**, [4] 25, 95.

²⁸⁵Boguslavskaya; Razuvaev *J. Gen. Chem. USSR* **1963**, 33, 1967.

²⁸⁶For reviews, see Simándi, in Patai; Rappoport *The Chemistry of Functional Groups, Supplement C*, pt. 1; Wiley: New York, 1983, pp. 529-534; Nigh, Ref. 185, pp. 11-31; Cadiot; Chodkiewicz, in *Viehe Acetylenes*; Marcel Dekker: New York, 1969, pp. 597-647.

²⁸⁷For a review of cyclic alkynes, see Nakagawa, in Patai *The Chemistry of the Carbon-Carbon Triple Bond*, pt. 2; Wiley: New York, 1978, pp. 635-712.

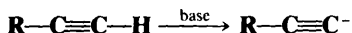
²⁸⁸Sondheimer; Wolovsky *J. Am. Chem. Soc.* **1962**, 84, 260; Sondheimer; Wolovsky; Amiel *J. Am. Chem. Soc.* **1962**, 84, 274.

²⁸⁹Chodkiewicz *Ann. Chim. (Paris)* **1957**, [13] 2, 819.

²⁹⁰Sevin; Chodkiewicz; Cadiot *Bull. Soc. Chim. Fr.* **1974**, 913.

consists of treating a haloalkyne ($R'C\equiv CX$) with a copper acetylide ($RC\equiv CCu$).²⁹¹ The Cadiot–Chodkiewicz procedure can be adapted to the preparation of diynes in which $R' = H$ by the use of $BrC\equiv CSiEt_3$ and subsequent cleavage of the $SiEt_3$ group.²⁹² This protecting group can also be used in the Eglinton or Glaser methods.²⁹³

The mechanism of the Eglinton and Glaser reactions probably begins with loss of a proton



since there is a base present and acetylenic protons are acidic. The last step is probably the coupling of two radicals:

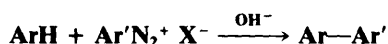


but just how the carbanion becomes oxidized to the radical and what part the cuprous ion plays (other than forming the acetylide salt) are matters of considerable speculation,²⁹⁴ and depend on the oxidizing agent. It is known, of course, that cuprous ion can form complexes with triple bonds.

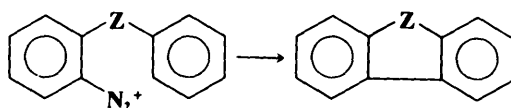
OS V, 517; VI, 68, 925; 65, 52.

4-18 Arylation of Aromatic Compounds by Diazonium Salts

Arylation or Aryl-de-hydrogenation



When the normally acidic solution of a diazonium salt is made alkaline, the aryl portion of the diazonium salt can couple with another aromatic ring. Known as the *Gomberg* or *Gomberg–Bachmann reaction*,²⁹⁵ it has been performed on several types of aromatic rings and on quinones. Yields are not high (usually under 40%) because of the many side reactions undergone by diazonium salts, though higher yields have been obtained under phase transfer conditions.²⁹⁶ The conditions of the Meerwein reaction (4-19), treatment of the solution with a copper–ion catalyst, have also been used, as has the addition of sodium nitrite in Me_2SO (to benzene diazonium fluoroborate in Me_2SO).²⁹⁷ When the Gomberg–Bachmann reaction is performed intramolecularly, either by the alkaline solution or by the copper–ion procedure,



it is called the *Pschorr ring closure*²⁹⁸ and yields are usually somewhat higher. Still higher yields have been obtained by carrying out the Pschorr reaction electrochemically.²⁹⁹ The Pschorr reaction has been carried out for $Z = CH=CH$, CH_2CH_2 , NH , $C=O$, CH_2 , and quite a few others. A rapid and convenient way to carry out the Pschorr synthesis is to

²⁹¹Curtis; Taylor *J. Chem. Soc. C* **1971**, 186.

²⁹²Eastmond; Walton *Tetrahedron* **1972**, 28, 4591; Ghose; Walton *Synthesis* **1974**, 890.

²⁹³Johnson; Walton *Tetrahedron* **1972**, 28, 5221.

²⁹⁴See the discussions in Nigh, Ref. 185, pp. 27-31; Fedenok; Berdnikov; Shvartsberg *J. Org. Chem. USSR* **1973**, 9, 1806; Clifford; Waters *J. Chem. Soc.* **1963**, 3056.

²⁹⁵For reviews, see Bolton; Williams *Chem. Soc. Rev.* **1986**, 15, 261-289; Hey *Adv. Free-Radical Chem.* **1966**, 2, 47-86. For a review applied to heterocyclic substrates, see Vernin; Dou; Metzger *Bull. Soc. Chim. Fr.* **1972**, 1173-1203.

²⁹⁶Beadle; Korzeniowski; Rosenberg; Garcia-Slanga; Gokel *J. Org. Chem.* **1984**, 49, 1594.

²⁹⁷Kamigata; Kurihara; Minato; Kobayashi *Bull. Chem. Soc. Jpn.* **1971**, 44, 3152.

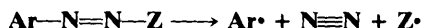
²⁹⁸For a review, see Abramovitch *Adv. Free-Radical Chem.* **1966**, 2, 87-138.

²⁹⁹Elofson; Gadallah *J. Org. Chem.* **1971**, 36, 1769.

diazotize the amine substrate with isopropyl nitrite in the presence of sodium iodide, in which case the ring-closed product is formed in one step.³⁰⁰

Other compounds with nitrogen–nitrogen bonds have been used instead of diazonium salts. Among these are N-nitroso amides [ArN(NO)COR], triazenes,³⁰¹ and azo compounds. Still another method involves treatment of an aromatic primary amine directly with an alkyl nitrite in an aromatic substrate as solvent.³⁰²

In each case the mechanism involves generation of an aryl radical from a covalent azo compound. In acid solution diazonium salts are ionic and their reactions are polar. When they cleave, the product is an aryl cation (see p. 644). However, in neutral or basic solution, diazonium ions are converted to covalent compounds, and these cleave to give free radicals:

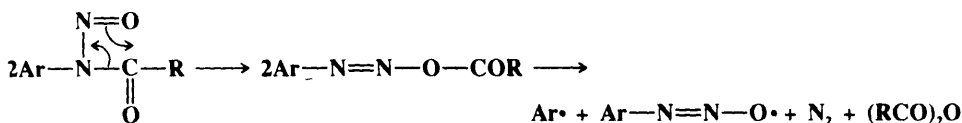


Under Gomberg–Bachmann conditions, the species that cleaves is the anhydride:³⁰³



21

The aryl radical thus formed attacks the substrate to give the intermediate **1** (p. 680), from which the radical **21** abstracts hydrogen to give the product. N-Nitroso amides probably rearrange to N-acyloxy compounds, which cleave to give aryl radicals:³⁰⁴

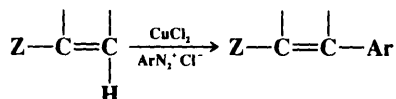


There is evidence that the reaction with alkyl nitrites also involves attack by aryl radicals.³⁰⁵

The Pschorr reaction can take place by two different mechanisms, depending on conditions: (1) attack by an aryl radical (as in the Gomberg–Bachmann reaction) or (2) attack by an aryl cation (similar to the S_N1 mechanism discussed on p. 644).³⁰⁶ Under certain conditions the ordinary Gomberg–Bachmann reaction can also involve attack by aryl cations.³⁰⁷

OS I, 113; IV, 718.

4-19 Arylation of Activated Olefins by Diazonium Salts. Meerwein Arylation Arylation or Aryl-de-hydrogenation



³⁰⁰Chauncy; Gellert *Aust. J. Chem.* **1969**, 22, 993. See also Duclos; Tung; Rapoport *J. Org. Chem.* **1984**, 49, 5243.

³⁰¹See, for example, Patrick; Willaredt; DeGonia *J. Org. Chem.* **1985**, 50, 2232; Butler; O'Shea; Shelly *J. Chem. Soc., Perkin Trans. 1* **1987**, 1039.

³⁰²Cadogan *J. Chem. Soc.* **1962**, 4257; Fillipi; Vernin; Dou; Metzger; Perkins *Bull. Soc. Chim. Fr.* **1974**, 1075.

³⁰³Rüchardt; Merz *Tetrahedron Lett.* **1964**, 2431; Eliel; Saha; Meyerson *J. Org. Chem.* **1965**, 30, 2451.

³⁰⁴Cadogan; Murray; Sharp *J. Chem. Soc., Perkin Trans. 2* **1976**, 583, and references cited therein.

³⁰⁵Gragerov; Levit *J. Org. Chem. USSR* **1968**, 4, 7.

³⁰⁶For an alternative to the second mechanism, see Gadallah; Cantu; Elofson *J. Org. Chem.* **1973**, 38, 2386.

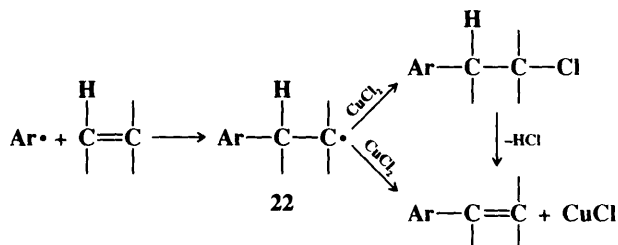
³⁰⁷For examples: see Kobori; Kobayashi; Minato *Bull. Chem. Soc., Jpn.* **1970**, 43, 223; Cooper; Perkins *Tetrahedron Lett.* **1969**, 2477; Burri; Zollinger *Helv. Chim. Acta* **1973**, 56, 2204; Eustathopoulos; Rinaudo; Bonnier *Bull. Soc. Chim. Fr.* **1974**, 2911. For a discussion, see Zollinger *Acc. Chem. Res.* **1973**, 6, 335-341, pp. 338-339.

Olefins activated by an electron-withdrawing group (Z may be C=C, halogen, C=O, Ar, CN, etc.) can be arylated by treatment with a diazonium salt and a cupric chloride³⁰⁸ catalyst. This is called the *Meerwein arylation reaction*.³⁰⁹ Addition of ArCl to the double bond (to

give $\text{Z}-\underset{\text{Cl}}{\underset{|}{\text{C}}}-\underset{\text{H}}{\underset{|}{\text{C}}}-\text{Ar}$) is a side reaction (5-33). In an improved procedure, an arylamine is

treated with an alkyl nitrite (generating ArN_2^+ in situ) and a copper(II) halide in the presence of the olefin.³¹⁰

The mechanism is probably of the free-radical type, with $\text{Ar}\cdot$ forming as in 4-25 and then³¹¹



The radical **22** can react with cupric chloride by two pathways, one of which leads to addition and the other to substitution. Even when the addition pathway is taken, however, the substitution product may still be formed by subsequent elimination of HCl.

OS IV, 15.

4-20 Arylation and Alkylation of Olefins by Organopalladium Compounds.

The Heck Reaction

Alkylation or **Alkyl-de-hydrogenation**, etc.



Arylation of olefins can also be achieved³¹² by treatment with an "arylpalladium" reagent that can be generated in situ by several³¹³ methods: (1) by treatment of an aryl bromide with a palladium-triarylphosphine complex ($\text{ArBr} \rightarrow \text{"ArPdBr"}$);³¹⁴ (2) by treatment of an aryl iodide³¹⁵ with palladium acetate³¹⁶ in the presence of a base such as tributylamine or

³⁰⁸ FeCl_2 is also effective: Ganushchak; Obushak; Luka *J. Org. Chem. USSR* **1981**, 17, 765.

³⁰⁹For reviews, see Dombrovskii *Russ. Chem. Rev.* **1984**, 53, 943-955; Rondestvedt *Org. React.* **1976**, 24, 225-259.

³¹⁰Doyle; Siegfried; Elliott; Dellaria *J. Org. Chem.* **1977**, 42, 2431.

³¹¹Dickerman; Vermont *J. Am. Chem. Soc.* **1962**, 84, 4150; Morrison; Cazes; Samkoff; Howe *J. Am. Chem. Soc.* **1962**, 84, 4152.

³¹²For reviews of this and related reactions, see Heck *Palladium Reagents in Organic Syntheses*; Academic Press: New York, 1985, pp. 179-321; Ryabov *Synthesis* **1985**, 233-252; Heck *Org. React.* **1982**, 27, 345-390; *Adv. Catal.* **1977**, 26, 323-349; Volkova; Levitin; Vol'pin *Russ. Chem. Rev.* **1975**, 44, 552-560; Moritani; Fujiwara *Synthesis* **1973**, 524-533; Jira; Freiesleben *Organomet. React.* **1972**, 3, 1-190, pp. 84-105.

³¹³For other methods, see Murahashi; Yamamura; Mita *J. Org. Chem.* **1977**, 42, 2870; Luong-Thi; Riviere *J. Chem. Soc., Chem. Commun.* **1978**, 918; Akiyama; Miyazaki; Kaneda; Teranishi; Fujiwara; Abe; Taniguchi *J. Org. Chem.* **1980**, 45, 2359; Tsuji; Nagashima *Tetrahedron* **1984**, 40, 2699; Kikukawa; Naritomi; He; Wada; Matsuda *J. Org. Chem.* **1985**, 50, 299; Chen; Yang *Tetrahedron Lett.* **1986**, 27, 1171; Kasahara; Izumi; Miyamoto; Sakai *Chem. Ind. (London)* **1989**, 192; Miura; Hashimoto; Itoh; Nomura *Tetrahedron Lett.* **1989**, 30, 975.

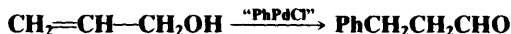
³¹⁴For reviews, see Heck *Acc. Chem. Res.* **1979**, 12, 146-151; *Pure Appl. Chem.* **1978**, 50, 691-701. See also Bender; Stakem; Heck *J. Org. Chem.* **1982**, 47, 1278; Spencer *J. Organomet. Chem.* **1983**, 258, 101.

³¹⁵For a method that uses an aryl chloride, but converts it to an aryl iodide in situ, see Bozell; Vogt *J. Am. Chem. Soc.* **1988**, 110, 2655.

³¹⁶For a more efficient palladium reagent, see Andersson; Karabelas; Hallberg; Andersson *J. Org. Chem.* **1985**, 50, 3891. See also Merlic; Semmelhack *J. Organomet. Chem.* **1990**, 391, C23.

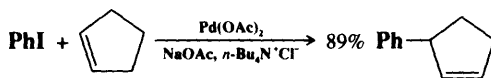
potassium acetate ($\text{ArI} \rightarrow \text{"ArPdI"}^{\text{317}}$); (3) by treatment of an arylmercury compound (either Ar_2Hg or $\text{ArHgX} \rightarrow \text{"ArPdX"}^{\text{318}}$ (in some cases other noble metal salts have been used); or (4) by the reaction of an aromatic compound with palladium acetate or palladium metal and silver acetate in acetic acid [in this case an aryl *hydrogen* is replaced ($\text{ArH} \rightarrow \text{"ArPdOAc"}^{\text{319}}$)].³¹⁹ Whichever of these methods is used, the reaction is known as the *Heck reaction*.

Unlike **4-19**, the Heck reaction is not limited to activated substrates. The substrate can be a simple olefin, or it can contain a variety of functional groups, such as ester, ether,^{319a} carboxyl, phenolic, or cyano groups.³²⁰ Primary and secondary allylic alcohols (and even nonallylic unsaturated alcohols³²¹) give aldehydes or ketones that are products of double-bond migration,³²² e.g.,



Ethylene is the most reactive olefin. Increasing substitution lowers the reactivity. Substitution therefore takes place at the less highly substituted side of the double bond.³²³ Alkylation can also be accomplished, but only if the alkyl group lacks a β hydrogen, e.g., the reaction is successful for the introduction of methyl, benzyl, and neopentyl groups.³²⁴ However, vinylic groups, even those possessing β hydrogens, have been successfully introduced (to give 1,3-dienes) by the reaction of the olefin with a vinylic halide in the presence of a trialkylamine and a catalyst composed of palladium acetate and a triarylphosphine at 100 to 150°C.³²⁵ The reaction has also been done with terminal alkynes as substrates.³²⁶

The evidence is in accord with an addition-elimination mechanism (addition of ArPdX followed by elimination of HPdX) in most cases.³²⁷ The reactions are stereospecific, yielding products expected from syn addition followed by syn elimination.³²⁸ Because the product is formed by an elimination step, with suitable substrates the double bond can go the other way, resulting in allylic rearrangement, e.g.,³²⁹



The Heck reaction has also been performed intramolecularly.³³⁰

OS VI, 815; VII, 361.

³¹⁷Mizoroki; Mori; Ozaki *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581; Mori; Mizoroki; Ozaki *Bull. Chem. Soc. Jpn.* **1973**, *46*, 1505; Heck; Nolley *J. Org. Chem.* **1972**, *37*, 2320; Ziegler; Heck *J. Org. Chem.* **1978**, *43*, 2941; Hirao; Enda; Ohshiro; Agawa *Chem. Lett.* **1981**, 403; Jeffery *J. Chem. Soc., Chem. Commun.* **1984**, 1287; Bumagin; More; Beletskaya *J. Organomet. Chem.* **1989**, *371*, 397; Larock; Johnson *J. Chem. Soc., Chem. Commun.* **1989**, 1368.

³¹⁸Heck *J. Am. Chem. Soc.* **1968**, *90*, 5518, 5526, 5535. For a review, see Larock, Ref. 238, pp. 273-292.

³¹⁹See, for example, Fujiwara; Moritani; Matsuda *Tetrahedron* **1968**, *24*, 4819; Fujiwara; Maruyama; Yoshidomi; Taniguchi *J. Org. Chem.* **1981**, *46*, 851. For a review, see Kozhevnikov *Russ. Chem. Rev.* **1983**, *52*, 138-151.

^{319a}For a review pertaining to enol ethers, see Daves *Adv. Met.-Org. Chem.* **1991**, *2*, 59-99.

³²⁰For a review of cases where the olefin contains an α hetero atom, see Daves; Hallberg *Chem. Rev.* **1989**, *89*, 1433-1445.

³²¹Larock; Leung; Stolz-Dunn *Tetrahedron Lett.* **1989**, *30*, 6629.

³²²See, for example, Melpolder; Heck *J. Org. Chem.* **1976**, *41*, 265; Chalk; Magennis *J. Org. Chem.* **1976**, *41*, 273, 1206.

³²³Heck *J. Am. Chem. Soc.* **1969**, *91*, 6707, **1971**, *93*, 6896.

³²⁴Heck *J. Organomet. Chem.* **1972**, *37*, 389; Heck; Nolley, Ref. 317.

³²⁵Dieck; Heck *J. Org. Chem.* **1975**, *40*, 1083; Kim; Patel; Heck *J. Org. Chem.* **1981**, *46*, 1067; Heck *Pure Appl. Chem.* **1981**, *53*, 2323-2332. See also Luong-Thi; Riviere *Tetrahedron Lett.* **1979**, 4657; Jeffery *Tetrahedron Lett.* **1985**, *26*, 2667. *J. Chem. Soc., Chem. Commun.* **1991**, 324; Scott; Peña; Swärd; Stoessel; Stille *J. Org. Chem.* **1985**, *50*, 2302; Larock; Gong *J. Org. Chem.* **1989**, *54*, 2047.

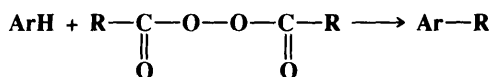
³²⁶Cassar *J. Organomet. Chem.* **1975**, *93*, 253; Dieck; Heck *J. Organomet. Chem.* **1975**, *93*, 259; Sonogashira; Tohda; Hagihara *Tetrahedron Lett.* **1975**, 4467; Singh; Just *J. Org. Chem.* **1989**, *54*, 4453. See also Heck *Palladium Reagents in Organic Syntheses*, Ref. 312, pp. 299-306.

³²⁷Heck *J. Am. Chem. Soc.* **1969**, *91*, 6707; Shue *J. Am. Chem. Soc.* **1971**, *93*, 7116; Heck; Nolley, Ref. 317.

³²⁸Heck, Ref. 327; Moritani; Danno; Fujiwara; Teranishi *Bull. Chem. Soc. Jpn.* **1971**, *44*, 578.

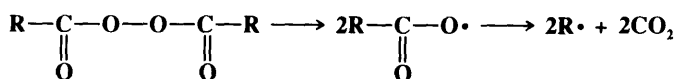
³²⁹Larock; Baker *Tetrahedron Lett.* **1988**, *29*, 905. Also see Larock; Gong; Baker *Tetrahedron Lett.* **1989**, *30*, 2603.

³³⁰See, for example, Abelman; Oh; Overman *J. Org. Chem.* **1987**, *52*, 4130; Negishi; Zhang; O'Connor *Tetrahedron Lett.* **1988**, *29*, 2915; Larock; Song; Baker; Gong *Tetrahedron Lett.* **1988**, *29*, 2919.

4-21 Alkylation and Arylation of Aromatic Compounds by Peroxides**Alkylation or Alkyl-de-hydrogenation**

This reaction is most often carried out with $\text{R} = \text{aryl}$, so the net result is the same as in **4-18**, though the reagent is different.³³¹ It is used less often than **4-18**, but the scope is similar. When $\text{R} = \text{alkyl}$, the scope is more limited.³³² Only certain aromatic compounds, particularly benzene rings with two or more nitro groups, and fused ring systems, can be alkylated by this procedure. 1,4-Quinones can be alkylated with diacyl peroxides or with lead tetraacetate (methylation occurs with this reagent).

The mechanism is as shown on p. 680 (CIDNP has been observed³³³); the radicals are produced by



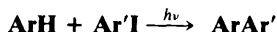
Since no relatively stable free radical is present (such as **21** in **4-18**), most of the product arises from dimerization and disproportionation.³³⁴ The addition of a small amount of nitrobenzene increases the yield of arylation product because the nitrobenzene is converted to diphenyl nitroxide, which abstracts the hydrogen from **1** and reduces the extent of side reactions.³³⁵

Aromatic compounds can also be arylated by aryllead tricarboxylates.³³⁶ Best yields (~70 to 85%) are obtained when the substrate contains alkyl groups; an electrophilic mechanism



is likely. Phenols are phenylated ortho to the OH group (and enols are α phenylated) by triphenylbismuth dichloride or by certain other Bi(V) reagents.³³⁷ O-Phenylation is a possible side reaction. As with the aryllead tricarboxylate reactions, a free-radical mechanism is unlikely.³³⁸

OS V, 51. See also OS V, 952; VI, 890.

4-22 Photochemical Arylation of Aromatic Compounds**Arylation or Aryl-de-hydrogenation**

Another free-radical arylation method consists of the photolysis of aryl iodides in an aromatic solvent.³³⁹ Yields are generally higher than in **4-18** or **4-21**. The aryl iodide may contain OH

³³¹For reviews, see Ref. 295.

³³²For reviews of the free-radical alkylation of aromatic compounds, see Tiecco; Testaferri *React. Intermed. (Plenum)* **1983**, 3, 61-11; Dou; Vernin; Metzger *Bull. Soc. Chim. Fr.* **1971**, 4593.

³³³Kaptein; Freeman; Hill; Bargon *J. Chem. Soc., Chem. Commun.* **1973**, 953.

³³⁴We have given the main steps that lead to biphenyls. The mechanism is actually more complicated than this and includes more than 100 elementary steps resulting in many side products, including those mentioned on p. 681: DeTar; Long; Rendleman; Bradley; Duncan *J. Am. Chem. Soc.* **1967**, 89, 4051; DeTar *J. Am. Chem. Soc.* **1967**, 89, 4058. See also Jandú; Nicolopoulou; Perkins *J. Chem. Res. (S)* **1985**, 88.

³³⁵Chalfont; Hey; Liang; Perkins *J. Chem. Soc. B* **1971**, 233.

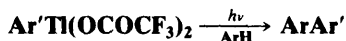
³³⁶Bell; Kalman; May; Pinhey; Sternhell *Aust. J. Chem.* **1979**, 32, 1531.

³³⁷For a review, see Abramovitch; Barton; Finet, Ref. 276, pp. 3040-3047.

³³⁸Barton; Finet; Giannotti; Halley *J. Chem. Soc., Perkin Trans. I* **1987**, 241.

³³⁹Wolf; Kharasch *J. Org. Chem.* **1965**, 30, 2493. For a review, see Sharma; Kharasch *Angew. Chem. Int. Ed. Engl.* **1968**, 7, 36-44 [*Angew. Chem.* 80, 69-77].

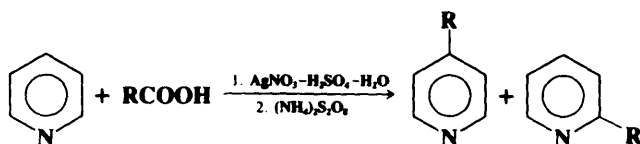
or COOH groups. The mechanism is similar to that of **4-18**. The aryl radicals are generated by the photolytic cleavage $\text{ArI} \rightarrow \text{Ar}\cdot + \text{I}\cdot$. The reaction has been applied to intramolecular arylation (analogous to the Pschorr reaction).³⁴⁰ A similar reaction is photolysis of an arylthallium bis(trifluoroacetate) (**2-22**) in an aromatic solvent. Here too, an unsymmetrical biaryl is produced in good yields.³⁴¹



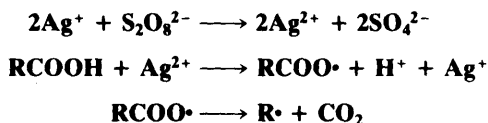
In this case it is the C—Tl bond that is cleaved to give aryl radicals.

4-23 Alkylation, Acylation, and Carbalkoxylation of Nitrogen Heterocycles³⁴²

Alkylation or Alkyl-de-hydrogenation, etc.



Alkylation of protonated nitrogen heterocycles (e.g., pyridines, quinolines) can be accomplished by treatment with a carboxylic acid, silver nitrate, sulfuric acid, and ammonium peroxydisulfate.³⁴³ R can be primary, secondary, or tertiary. The attacking species is $\text{R}\cdot$, formed by³⁴⁴



A hydroxymethyl group can be introduced ($\text{ArH} \rightarrow \text{ArCH}_2\text{OH}$) by several variations of this method.³⁴⁵ Alkylation of these substrates can also be accomplished by generating the alkyl radicals in other ways: from hydroperoxides and FeSO_4 ,³⁴⁶ from alkyl iodides and $\text{H}_2\text{O}_2\text{-Fe(II)}$,³⁴⁷ from carboxylic acids and lead tetraacetate, or from the photochemically induced decarboxylation of carboxylic acids by iodosobenzene diacetate.³⁴⁸ The reaction has also been applied to acetophenone and ferrocene.³⁴⁹

³⁴⁰See, for example, Kupchan; Wormser *J. Org. Chem.* **1965**, *30*, 3792; Jeffs; Hansen *J. Am. Chem. Soc.* **1967**, *89*, 2798; Thyagarajan; Kharasch; Lewis; Wolf *Chem. Commun.* **1967**, 614.

³⁴¹Taylor; Kienzie; McKillop *J. Am. Chem. Soc.* **1970**, *92*, 6088.

³⁴²For reviews; see Heinisch *Heterocycles* **1987**, *26*, 481-496; Minisci; Vismara; Fontana *Heterocycles* **1989**, *28*, 489-519; Minisci *Top. Curr. Chem.* **1976**, *62*, 1-48, pp. 17-46, *Synthesis* **1973**, 1-24, pp. 12-19. For a review of substitution of carbon groups on nitrogen heterocycles, see Vorbrüggen; Maas *Heterocycles* **1988**, *27*, 2659-2776.

³⁴³Minisci; Mondelli; Gardini; Porta *Tetrahedron* **1972**, *28*, 2403; Citterio; Minisci; Franchi *J. Org. Chem.* **1980**, *45*, 4752; Fontana; Minisci; Barbosa; Vismara *Tetrahedron* **1990**, *46*, 2525.

³⁴⁴Anderson; Kochi *J. Am. Chem. Soc.* **1970**, *92*, 1651.

³⁴⁵See Citterio; Gentile; Minisci; Serravalle; Ventura *Tetrahedron* **1985**, *41*, 617; Katz; Mistry; Mitchell *Synth. Commun.* **1989**, *19*, 317.

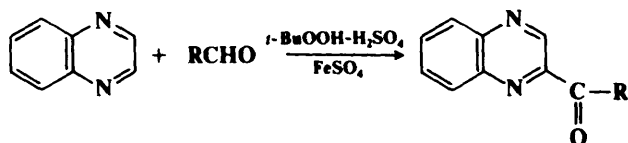
³⁴⁶Minisci; Selva; Porta; Barilli; Gardini *Tetrahedron* **1972**, *28*, 2415.

³⁴⁷Fontana; Minisci; Barbosa; Vismara *Acta Chem. Scand.* **1989**, *43*, 995.

³⁴⁸Minisci; Vismara; Fontana; Barbosa *Tetrahedron Lett.* **1989**, *30*, 4569.

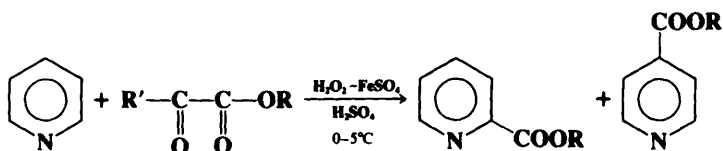
³⁴⁹Din; Meth-Cohn; Walshe *Tetrahedron Lett.* **1979**, 4783.

Protonated nitrogen heterocycles can be acylated by treatment with an aldehyde, *t*-butyl hydroperoxide, sulfuric acid, and ferrous sulfate, e.g.,³⁵⁰

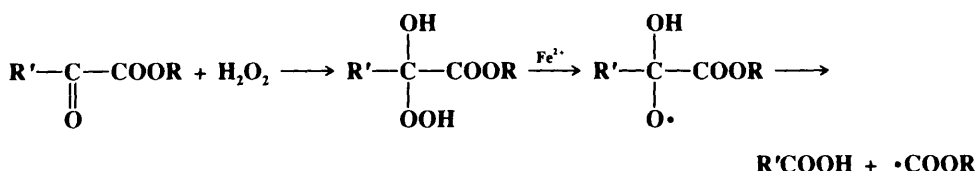


These alkylation and acylation reactions are important because Friedel-Crafts alkylation and acylation (1-12, 1-14) cannot be applied to most nitrogen heterocycles. See also 3-17.

Protonated nitrogen heterocycles can be carbalkoxylated³⁵¹ by treatment with esters of α -keto acids and Fenton's reagent:



The attack is by $\cdot\text{COOR}$ radicals generated from the esters:



Similarly, a carbamoyl group can be introduced³⁵² by the use of the radicals $\text{H}_2\text{NC}\cdot$ or $\text{Me}_2\text{NC}\cdot$ generated from formamide or dimethylformamide and H_2SO_4 , H_2O_2 , and FeSO_4 or other oxidants.

N_2 as Leaving Group³⁵³

In these reactions diazonium salts are cleaved to aryl radicals,³⁵⁴ in most cases with the assistance of copper salts. Reactions 4-18 and 4-19 may also be regarded as belonging to this category with respect to the attacking compound. For nucleophilic substitutions of diazonium salts, see 3-20 to 3-24.

4-24 Replacement of the Diazonium Group by Hydrogen

Dediazoniation or Hydro-de-diazoniation



³⁵⁰Caronna; Gardini; Minisci *Chem. Commun.* **1969**, 201; Arnoldi; Bellatti; Caronna; Citterio; Minisci; Porta; Sesana *Gazz. Chim. Ital.* **1977**, 107, 491.

³⁵¹Bernardi; Caronna; Galli; Minisci; Perchinunno *Tetrahedron Lett.* **1973**, 645; Heinisch; Lötsch *Angew. Chem. Int. Ed. Engl.* **1985**, 24, 692 [*Angew. Chem.* 97, 694].

³⁵²Minisci; Gardini; Galli; Bertini *Tetrahedron Lett.* **1970**, 15; Minisci; Citterio; Vismara; Giordano *Tetrahedron* **1985**, 41, 4157.

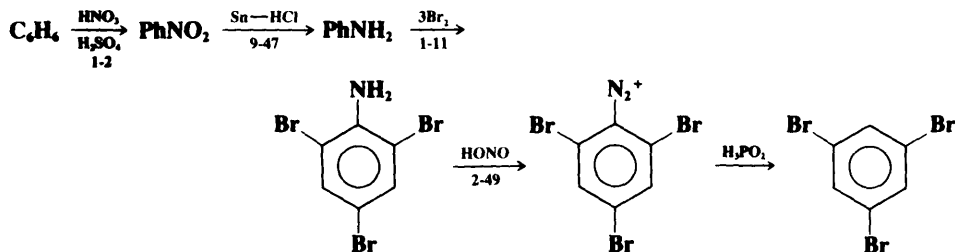
³⁵³For a review, see Wulfman, in Patai *The Chemistry of Diazonium and Diazo Groups*, pt. 1; Wiley: New York, 1978, pp. 286-297.

³⁵⁴For reviews, see Galli *Chem. Rev.* **1988**, 88, 765-792; Zollinger *Acc. Chem. Res.* **1973**, 6, 355-341, pp. 339-341.

Reduction of the diazonium group (*dediazonation*) provides an indirect method for the removal of an amino group from an aromatic ring.³⁵⁵ The best and most common way of accomplishing this is by use of hypophosphorous acid H_3PO_2 , though many other reducing agents³⁵⁶ have been used, among them ethanol, HMPA,³⁵⁶ thiophenol,³⁵⁷ and sodium stannite. Ethanol was the earliest reagent used, and it frequently gives good yields, but often ethers (ArOEt) are side products. When H_3PO_2 is used, 5 to 15 moles of this reagent are required per mole of substrate. Diazonium salts can be reduced in nonaqueous media by several methods,³⁵⁸ including treatment with Bu_3SnH or Et_3SiH in ethers or MeCN ³⁵⁹ and by isolation as the BF_4^- salt and reduction of this with NaBH_4 in DMF.³⁶⁰ Aromatic amines can be deaminated ($\text{ArNH}_2 \rightarrow \text{ArH}$) in one laboratory step by treatment with an alkyl nitrite in DMF³⁶¹ or boiling THF.³⁶² The corresponding diazonium salt is an intermediate.

Not many investigations of the mechanism have been carried out. It is generally assumed that the reaction of diazonium salts with ethanol to produce ethers takes place by an ionic ($\text{S}_{\text{N}}1$) mechanism while the reduction to ArH proceeds by a free-radical process.³⁶³ The reduction with H_3PO_2 is also believed to have a free-radical mechanism.³⁶⁴ In the reduction with NaBH_4 , an aryldiazene intermediate ($\text{ArN}=\text{NH}$) has been demonstrated,³⁶⁵ arising from nucleophilic attack by BH_4^- on the β nitrogen. Such diazenes can be obtained as moderately stable (half-life of several hours) species in solution.³⁶⁶ It is not entirely clear how the aryldiazene decomposes, but there are indications that either the aryl radical Ar^\cdot or the corresponding anion Ar^- may be involved.³⁶⁷

An important use of the dediazonation reaction is to remove an amino group after it has been used to direct one or more other groups to ortho and para positions. For example, the compound 1,3,5-tribromobenzene cannot be prepared by direct bromination of benzene because the bromo group is ortho-para-directing; however, this compound is easily prepared by the following sequence:



³⁵⁵For a review, see Zollinger in Patai; Rappoport, Ref. 286, pp. 603-669.

³⁵⁶For lists of some of these, with references, see Ref. 74, p. 25; Tröndlin; Rüchardt *Chem. Ber.* **1977**, *110*, 2494.

³⁵⁷Shono; Matsumura; Tsubata *Chem. Lett.* **1979**, 1051.

³⁵⁸For a list of some of these, with references, see Korzeniowski; Blum; Gokel *J. Org. Chem.* **1977**, *42*, 1469.

³⁵⁹Nakayama; Yoshida; Simamura *Tetrahedron* **1970**, *26*, 4609.

³⁶⁰Hendrickson *J. Am. Chem. Soc.* **1961**, *83*, 1251. See also Threadgill; Gledhill *J. Chem. Soc., Perkin Trans. 1* **1986**, 873.

³⁶¹Doyle; Dellaria; Siegfried; Bishop *J. Org. Chem.* **1977**, *42*, 3494.

³⁶²Cadogan; Molina *J. Chem. Soc., Perkin Trans. 1* **1973**, 541.

³⁶³For examples, see DeTar; Turetzky *J. Am. Chem. Soc.* **1955**, *77*, 1745, **1956**, *78*, 3925, 3928; DeTar; Kosuge *J. Am. Chem. Soc.* **1958**, *80*, 6072; Lewis; Chambers *J. Am. Chem. Soc.* **1971**, *93*, 3267; Broxton; Bunnett; Paik *J. Org. Chem.* **1977**, *42*, 643.

³⁶⁴See, for example, Kornblum; Cooper; Taylor *J. Am. Chem. Soc.* **1950**, *72*, 3013; Beckwith *Aust. J. Chem.* **1972**, *25*, 1887; Levit; Kiprianova; Gragerov *J. Org. Chem. USSR* **1975**, *11*, 2395.

³⁶⁵Bloch; Musso; Záhorsky *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 370 [*Angew. Chem.* *81*, 392]; König; Musso; Záhorsky *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 45 [*Angew. Chem.* *84*, 33]; McKenna; Traylor *J. Am. Chem. Soc.* **1971**, *93*, 2313.

³⁶⁶Huang; Kosower *J. Am. Chem. Soc.* **1968**, *90*, 2354, 2362, 2367; Smith; Hillhouse *J. Am. Chem. Soc.* **1988**, *110*, 4066.

³⁶⁷Rieker; Niederer; Leibfritz *Tetrahedron Lett.* **1969**, 4287; Kosower; Huang; Tsuji *J. Am. Chem. Soc.* **1969**, *91*, 2325; König; Musso; Záhorsky, Ref. 365; Broxton; McLeish *Aust. J. Chem.* **1983**, *36*, 1031.

Many other compounds that would otherwise be difficult to prepare are easily synthesized with the aid of the dediazonation reaction.

Unwanted dediazonation can be suppressed by using hexasulfonated calix[6]arenes (see p. 84).³⁶⁸

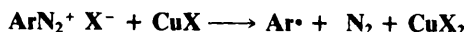
OS I, 133, 415; II, 353, 592; III, 295; IV, 947; VI, 334.

4-25 Replacement of the Diazonium Group by Chlorine or Bromine Chloro-de-diazonation, etc.



Treatment of diazonium salts with cuprous chloride or bromide leads to aryl chlorides or bromides, respectively. In either case the reaction is called the *Sandmeyer reaction*. The reaction can also be carried out with copper and HBr or HCl, in which case it is called the *Gatterman reaction* (not to be confused with 1-16). The Sandmeyer reaction is not useful for the preparation of fluorides or iodides, but for bromides and chlorides it is of wide scope and is probably the best way of introducing bromine or chlorine into an aromatic ring. The yields are usually high.

The mechanism is not known with certainty but is believed to take the following course:³⁶⁹



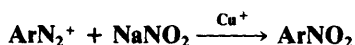
The first step involves a reduction of the diazonium ion by the cuprous ion, which results in the formation of an aryl radical. In the second step, the aryl radical abstracts halogen from cupric chloride, reducing it. CuX is regenerated and is thus a true catalyst.

Aryl bromides and chlorides can be prepared from primary aromatic amines in one step by several procedures,³⁷⁰ including treatment of the amine (1) with *t*-butyl nitrite and anhydrous CuCl₂ or CuBr₂ at 65°C,³⁷¹ and (2) with *t*-butyl thionitrite or *t*-butyl thionitrate and CuCl₂ or CuBr₂ at room temperature.³⁷² These procedures are, in effect, a combination of 2-49 and the Sandmeyer reaction. A further advantage is that cooling to 0°C is not needed.

For the preparation of fluorides and iodides from diazonium salts, see 3-24 and 3-23.

OS I, 135, 136, 162, 170; II, 130; III, 185; IV, 160. Also see OS III, 136; IV, 182.

4-26 Nitro-de-diazonation



Nitro compounds can be formed in good yields by treatment of diazonium salts with sodium nitrite in the presence of cuprous ion. The reaction occurs only in neutral or alkaline solution. This is not usually called the Sandmeyer reaction, although, like 4-25 and 4-28, it was discovered by Sandmeyer. BF₄⁻ is often used as the negative ion to avoid competition from the chloride ion. The mechanism is probably like that of 4-25.³⁷³ If electron-withdrawing

³⁶⁸Shinkai; Mori; Araki; Manabe *Bull. Chem. Soc. Jpn.* **1987**, 60, 3679.

³⁶⁹Dickerman; Weiss; Ingberman *J. Org. Chem.* **1956**, 21, 380, *J. Am. Chem. Soc.* **1958**, 80, 1904; Kochi *J. Am. Chem. Soc.* **1957**, 79, 2942; Dickerman; DeSouza; Jacobson *J. Org. Chem.* **1969**, 34, 710; Galli *J. Chem. Soc., Perkin Trans. 2* **1981**, 1459, **1982**, 1139, **1984**, 897. See also Hanson; Jones; Gilbert; Timms *J. Chem. Soc., Perkin Trans. 2* **1991**, 1009.

³⁷⁰For other procedures, see Brackman; Smit *Recl. Trav. Chim. Pays-Bas* **1966**, 85, 857; Cadogan; Roy; Smith *J. Chem. Soc. C* **1966**, 1249.

³⁷¹Doyle; Siegfried; Dellaria *J. Org. Chem.* **1977**, 42, 2426.

³⁷²Oae; Shinham; Kim *Chem. Lett.* **1979**, 939, *Bull. Chem. Soc. Jpn.* **1980**, 53, 1065.

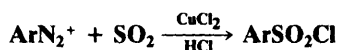
³⁷³For discussions, see Oppenorth; Rüchardt *Liebigs Ann. Chem.* **1974**, 1333; Singh; Kumar; Khanna *Tetrahedron Lett.* **1982**, 23, 5191.

groups are present, the catalyst is not needed; NaNO_2 alone gives nitro compounds in high yields.³⁷⁴

OS II, 225; III, 341.

4-27 Replacement of the Diazonium Group by Sulfur-containing Groups

Chlorosulfo-de-diazonation



Diazonium salts can be converted to sulfonyl chlorides by treatment with sulfur dioxide in the presence of cupric chloride.³⁷⁵ The use of FeSO_4 and copper metal instead of CuCl_2 gives sulfinic acids ArSO_2H .³⁷⁶ See also 3-21.

OS V, 60; VII, 508.

4-28 Cyano-de-diazonation

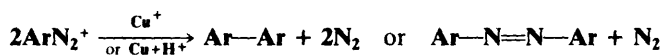


This reaction, also called the *Sandmeyer reaction*, is similar to 4-25 in scope and mechanism. It is usually conducted in neutral solution to avoid liberation of HCN .

OS I, 514.

4-29 Aryl Dimerization with Diazonium Salts

De-diazonio-coupling; Arylazo-de-diazonio-substitution

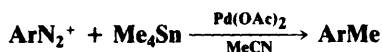


When diazonium salts are treated with cuprous ion (or with copper and acid, in which case it is called the *Gatterman method*), two products are possible. If the ring contains electron-withdrawing groups, the main product is the biaryl, but the presence of electron-donating groups leads mainly to the azo compound. This reaction is different from 4-18 (and from 1-4) in that *both* aryl groups in the product originate from ArN_2^+ , i.e., hydrogen is not a leaving group in this reaction. The mechanism probably involves free radicals.³⁷⁷

OS I, 222; IV, 872. Also see OS IV, 273.

4-30 Methylation and Vinylation of Diazonium Salts

Methyl-de-diazonation, etc.



A methyl group can be introduced into an aromatic ring by treatment of diazonium salts with tetramethyltin and a palladium acetate catalyst.³⁷⁸ The reaction has been performed with Me, Cl, Br, and NO_2 groups on the ring. A vinylic group can be introduced with $\text{CH}_2=\text{CHSnBu}_3$.

³⁷⁴Bagal; Pevzner; Frolov *J. Org. Chem. USSR* **1969**, 5, 1767.

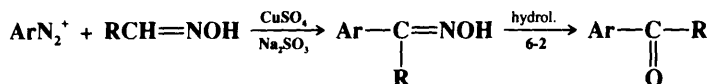
³⁷⁵Gilbert *Synthesis* **1969**, 1-10, p. 6.

³⁷⁶Wittig; Hoffmann *Org. Synth. V*, 60.

³⁷⁷See Cohen; Lewarchik; Tarino *J. Am. Chem. Soc.* **1974**, 96, 7753.

³⁷⁸Kikukawa; Kono; Wada; Matsuda *J. Org. Chem.* **1983**, 48, 1333.

4-31 Conversion of Diazonium Salts to Aldehydes, Ketones, or Carboxylic Acids **Acyl-de-diazonium**, etc.



Diazonium salts react with oximes to give aryl oximes, which are easily hydrolyzed to aldehydes (R = H) or ketones.³⁷⁹ A copper sulfate–sodium sulfite catalyst is essential. In most cases higher yields (40 to 60%) are obtained when the reaction is used for aldehydes than for ketones. In another method³⁸⁰ for achieving the conversion $\text{ArN}_2^+ \rightarrow \text{ArCOR}$, diazonium salts are treated with R_4Sn and CO with palladium acetate as catalyst.³⁸¹ In a different kind of reaction, silyl enol ethers of aryl ketones $\text{Ar}'\text{C}(\text{OSiMe}_3)=\text{CHR}$ react with solid diazonium fluoroborates $\text{ArN}_2^+ \text{BF}_4^-$ to give ketones $\text{ArCHRCOAr}'$.³⁸² This is, in effect, an α arylation of the aryl ketone.

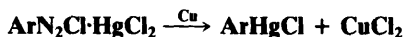
Carboxylic acids can be prepared in moderate-to-high yields by treatment of diazonium fluoroborates with carbon monoxide and palladium acetate³⁸³ or copper(II) chloride.³⁸⁴ The mixed anhydride ArCOOCOMe is an intermediate that can be isolated. Other mixed anhydrides can be prepared by the use of other salts instead of sodium acetate.³⁸⁵ An aryl-palladium compound is probably an intermediate.³⁸⁵

OS V, 139.

4-32 Replacement of the Diazonium Group by a Metal **Metallo-de-diazonium**



Aromatic organometallic compounds can be prepared by the treatment of diazonium salts (most often fluoroborates) with metals.³⁸⁶ Among the metals used have been Hg, Tl, Sn, Pb, Sb, and Bi. Another method consists of treating the double salt of the diazonium salt and a metal chloride with a metallic powder, e.g.,

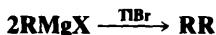


Organometallic compounds of Hg,³⁸⁷ Ge, Sn, and As have been among those prepared by this method. The mechanisms are not clear and may be either homolytic or heterolytic.

OS II, 381, 432, 494; III, 665.

Metals as Leaving Groups

4-33 Coupling of Grignard Reagents **De-metallo-coupling**



³⁷⁹Beech *J. Chem. Soc.* **1954**, 1297.

³⁸⁰For still another method, see Citterio; Serravalle; Vismara *Tetrahedron Lett.* **1982**, 23, 1831.

³⁸¹Kikukawa; Idemoto; Katayama; Kono; Wada; Matsuda *J. Chem. Soc., Perkin Trans. I* **1987**, 1511.

³⁸²Sakakura; Hara; Tanaka *J. Chem. Soc., Chem. Commun.* **1985**, 1545.

³⁸³Nagira; Kikukawa; Wada; Matsuda *J. Org. Chem.* **1980**, 45, 2365.

³⁸⁴Olah; Wu; Bagno; Prakash *Synlett* **1990**, 596.

³⁸⁵Kikukawa; Kono; Nagira; Wada; Matsuda *Tetrahedron Lett.* **1980**, 21, 2877; *J. Org. Chem.* **1981**, 46, 4413.

³⁸⁶For a review, see Reutov; Ptitsyna *Organomet. React.* **1972**, 4, 73-162.

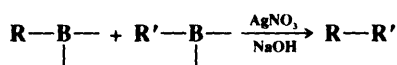
³⁸⁷For reviews with respect to Hg, see Wardell, in Zuckerman *Inorganic Reactions and Methods*, vol. 11; VCH: New York, 1988, pp. 320-323; Larock, *Ref.* 238, pp. 97-101.

Grignard reagents can be coupled to give symmetrical dimers³⁸⁸ by treatment with either thallium(I) bromide³⁸⁹ or with a transition-metal halide such as CrCl_2 , CrCl_3 , CoCl_2 , CoBr_2 , or CuCl_2 .³⁹⁰ The metallic halide is an oxidizing agent and becomes reduced. Both aryl and alkyl Grignard reagents can be dimerized by either procedure, though the TlBr method cannot be applied to $\text{R} =$ primary alkyl or to aryl groups with ortho substituents. Aryl Grignard reagents can also be dimerized by treatment with 1,4-dichloro-2-butene, 1,4-dichloro-2-butyne, or 2,3-dichloropropene.³⁹¹ Vinylic and alkynyl Grignard reagents can be coupled (to give 1,3-dienes and 1,3-diynes, respectively) by treatment with thionyl chloride.³⁹² Primary alkyl, vinylic, aryl, and benzylic Grignard reagents give symmetrical dimers in high yield ($\sim 90\%$) when treated with a silver(I) salt, e.g., AgNO_3 , AgBr , AgClO_4 , in the presence of a nitrogen-containing oxidizing agent such as lithium nitrate, methyl nitrate, or NO_2 .³⁹³ This method has been used to close rings of 4, 5, and 6 members.³⁹⁴

The mechanisms of the reactions with metal halides, at least in some cases, probably begin with conversion of RMgX to the corresponding RM (2-35), followed by its decomposition to free radicals.³⁹⁵

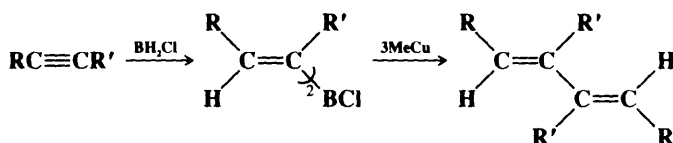
OS VI, 488.

4-34 Coupling of Boranes Alkyl-de-dialkylboration



Alkylboranes can be coupled by treatment with silver nitrate and base.³⁹⁶ Since alkylboranes are easily prepared from olefins (5-12), this is essentially a way of coupling and reducing olefins; in fact, olefins can be hydroborated and coupled in the same flask. For symmetrical coupling ($\text{R} = \text{R}'$) yields range from 60 to 80% for terminal olefins and from 35 to 50% for internal ones. Unsymmetrical coupling has also been carried out,³⁹⁷ but with lower yields. Arylboranes react similarly, yielding biaryls.³⁹⁸ The mechanism is probably of the free-radical type.

Vinylic dimerization can be achieved by treatment of divinylchloroboranes (prepared by addition of BH_2Cl to alkynes; see 5-12) with methylcopper. (*E,E*)-1,3-Dienes are prepared in high yields.³⁹⁹



³⁸⁸For a list of reagents, with references, see Ref. 74, pp. 48-49.

³⁸⁹McKillop; Elsom; Taylor *J. Am. Chem. Soc.* **1968**, *90*, 2423, *Tetrahedron* **1970**, *26*, 4041.

³⁹⁰For reviews, see Kauffmann *Angew. Chem. Int. Ed. Engl.* **1974**, *13*, 291-305 [*Angew. Chem.* *86*, 321-335]; Elsom; Hunt; McKillop *Organomet. Chem. Rev., Sect. A* **1972**, *8*, 135-152; Nigh, Ref. 185, pp. 85-91.

³⁹¹Taylor; Bennett; Heinz; Lashley *J. Org. Chem.* **1981**, *46*, 2194; Cheng; Luo *Tetrahedron Lett.* **1988**, *29*, 1293.

³⁹²Uchida; Nakazawa; Kondo; Iwata; Matsuda *J. Org. Chem.* **1972**, *37*, 3749.

³⁹³Tamura; Kochi *Bull. Chem. Soc. Jpn.* **1972**, *45*, 1120.

³⁹⁴Whitesides; Gutowski *J. Org. Chem.* **1976**, *41*, 2882.

³⁹⁵For a review of the mechanism, see Kashin; Beletskaya *Russ. Chem. Rev.* **1982**, *51*, 503-526.

³⁹⁶Pelter; Smith; Brown *Borane Reagents*; Academic Press: New York, 1988, pp. 306-308.

³⁹⁷Brown; Verbrugge; Snyder *J. Am. Chem. Soc.* **1961**, *83*, 1001.

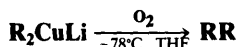
³⁹⁸Breuer; Broster *Tetrahedron Lett.* **1972**, 2193.

³⁹⁹Yamamoto; Yatagai; Maruyama; Sonoda; Murahashi *J. Am. Chem. Soc.* **1977**, *99*, 5652, *Bull. Chem. Soc. Jpn.* **1977**, *50*, 3427. For other methods of dimerizing vinylic boron compounds, see Rao; Kumar; Devaprabhakara *J. Organomet. Chem.* **1979**, *179*, C7; Campbell; Brown *J. Org. Chem.* **1980**, *45*, 549.

In a similar reaction, symmetrical conjugated diynes $\text{RC}\equiv\text{C}-\text{C}\equiv\text{CR}$ can be prepared by reaction of lithium dialkyldialkynylborates $\text{Li}^+ [\text{R}'_2\text{B}(\text{C}\equiv\text{CR})_2]^-$ with iodine.⁴⁰⁰

4-35 Coupling of Other Organometallic Reagents³⁸⁸

De-metallo-coupling



Lithium dialkylcopper reagents can be oxidized to symmetrical dimers by O_2 at -78°C in THF.⁴⁰¹ The reaction is successful for R = primary and secondary alkyl, vinylic, or aryl. Other oxidizing agents, e.g., nitrobenzene, can be used instead of O_2 . Vinylic copper reagents dimerize on treatment with oxygen, or simply on standing at 0°C for several days or at 25°C for several hours, to yield 1,3-dienes.⁴⁰² The finding of retention of configuration for this reaction demonstrates that free-radical intermediates are not involved. Lithium organoaluminates LiAlR_4 are dimerized to RR by treatment with $\text{Cu}(\text{OAc})_2$.⁴⁰³ Terminal vinylic alanes (prepared by 5-13) can be dimerized to 1,3-dienes with CuCl in THF.⁴⁰⁴ Symmetrical 1,3-dienes can also be prepared in high yields by treatment of vinylic mercury chlorides⁴⁰⁵ with LiCl and a rhodium catalyst⁴⁰⁶ and by treatment of vinylic tin compounds with a palladium catalyst.⁴⁰⁷ Arylmercuric salts are converted to biaryls by treatment with copper and a catalytic amount of PdCl_2 .⁴⁰⁸ Vinylic, alkynyl, and aryl tin compounds were dimerized with $\text{Cu}(\text{NO}_3)_2$.⁴⁰⁹ Alkyl- and aryllithium compounds can be dimerized by transition-metal halides in a reaction similar to 4-33.⁴¹⁰ Triarylbiismuth compounds Ar_3Bi react with palladium(0) complexes to give biaryls ArAr .⁴¹¹ Unsymmetrical coupling of vinylic, alkynyl, and arylmercury compounds was achieved in moderate-to-good yields by treatment with alkyl and vinylic dialkylcopper reagents, e.g., $\text{PhCH}=\text{CHHgCl} + \text{Me}_2\text{CuLi} \rightarrow \text{PhCH}=\text{CHMe}$.⁴¹² Unsymmetrical biaryls were prepared by treating a cyanocuprate $\text{ArCu}(\text{CN})\text{Li}$ (prepared from ArLi and CuCN) with an aryllithium $\text{Ar}'\text{Li}$.^{412a}

Halogen as Leaving Group

The conversion of RX to RH can occur by a free-radical mechanism but is treated at 0-76.

⁴⁰⁰Pelter; Smith; Tabata *J. Chem. Soc., Chem. Commun.* **1975**, 857. For extensions to unsymmetrical conjugated diynes, see Pelter; Hughes; Smith; Tabata *Tetrahedron Lett.* **1976**, 4385; Sinclair; Brown *J. Org. Chem.* **1976**, 41, 1078.

⁴⁰¹Whitesides; SanFilippo; Casey; Panek *J. Am. Chem. Soc.* **1967**, 89, 5302. See also Kauffmann; Kuhlmann; Sahm; Schrecken *Angew. Chem. Int. Ed. Engl.* **1968**, 7, 541 [*Angew. Chem.* **80**, 566]; Bertz; Gibson *J. Am. Chem. Soc.* **1986**, 108, 8286.

⁴⁰²Whitesides; Casey; Krieger *J. Am. Chem. Soc.* **1971**, 93, 1379; Walborsky; Banks; Banks; Duraisamy *Organometallics* **1982**, 1, 667; Rao; Periasamy *J. Chem. Soc., Chem. Commun.* **1987**, 495. See also Lambert; Duffley; Dalzell; Razdan *J. Org. Chem.* **1982**, 47, 3350.

⁴⁰³Sato; Mori; Sato *Chem. Lett.* **1978**, 1337.

⁴⁰⁴Zweifel; Miller *J. Am. Chem. Soc.* **1970**, 92, 6678.

⁴⁰⁵For reviews of coupling with organomercury compounds, see Russell *Acc. Chem. Res.* **1989**, 22, 1-8; Larock, Ref. 238, pp. 240-248.

⁴⁰⁶Larock; Bernhardt *J. Org. Chem.* **1977**, 42, 1680. For extension to unsymmetrical 1,3-dienes, see Larock; Riefling *J. Org. Chem.* **1978**, 43, 1468.

⁴⁰⁷Tolstikov; Miftakhov; Danilova; Vel'der; Spirikhin *Synthesis* **1989**, 633.

⁴⁰⁸Kretschmer; Glowinski *J. Org. Chem.* **1976**, 41, 2661. See also Bumagin; Kalinovskii; Beletskaya *J. Org. Chem. USSR* **1982**, 18, 1151; Larock; Bernhardt, Ref. 406.

⁴⁰⁹Ghosal; Luke; Kyler *J. Org. Chem.* **1987**, 52, 4296.

⁴¹⁰Morizur *Bull. Soc. Chim. Fr.* **1964**, 1331.

⁴¹¹Barton; Ozbalik; Ramesh *Tetrahedron* **1988**, 44, 5661.

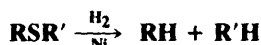
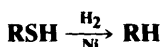
⁴¹²Larock; Leach *Tetrahedron Lett.* **1981**, 22, 3435, *Organometallics* **1982**, 1, 74. For another method, see Larock; Herschberger *Tetrahedron Lett.* **1981**, 22, 2443.

^{412a}Lipshutz; Siegmund; Garcia *J. Am. Chem. Soc.* **1991**, 113, 8161.

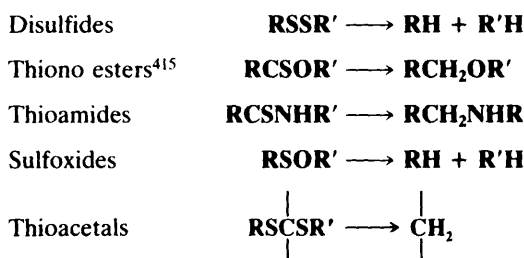
Sulfur as Leaving Group

4-36 Desulfurization with Raney Nickel

Hydro-de-mercapto-substitution, etc.

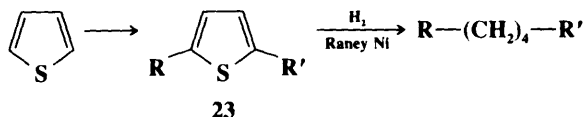


Thiols and thioethers,⁴¹³ both alkyl and aryl, can be desulfurized by hydrogenolysis with Raney nickel.⁴¹⁴ The hydrogen is usually not applied externally, since Raney nickel already contains enough hydrogen for the reaction. Other sulfur compounds can be similarly desulfurized, among them:



The last reaction, which is an indirect way of accomplishing reduction of a carbonyl to a methylene group (see 9-37), can also give the olefin if an α hydrogen is present.⁴¹⁶ In most of the examples given, R can also be aryl. Other reagents⁴¹⁷ have also been used.⁴¹⁸

An important special case of RSR reduction is desulfurization of thiophene derivatives. This proceeds with concomitant reduction of the double bonds. Many compounds have been made by alkylation of thiophene, followed by reduction:



Thiophenes can also be desulfurized to alkenes ($\text{RCH}_2\text{CH}=\text{CHCH}_2\text{R}'$ from 23) with a nickel boride catalyst prepared from nickel(II) chloride and NaBH_4 in methanol.⁴¹⁹ It is possible to reduce just one SR group of a dithioacetal by treatment with borane-pyridine

⁴¹³For a review of the reduction of thioethers, see Block, in Patai *The Chemistry of Functional Groups, Supplement E*, pt. 1; Wiley: New York, 1980, pp. 585-600.

⁴¹⁴For reviews, see Belen'kii, in Belen'kii *Chemistry of Organosulfur Compounds*; Ellis Horwood: Chichester, 1990, pp. 193-228; Pettit; van Tamelen *Org. React.* **1962**, 12, 356-529; Hauptmann; Walter *Chem. Rev.* **1962**, 62, 347-404.

⁴¹⁵See Baxter; Bradshaw *J. Org. Chem.* **1981**, 46, 831.

⁴¹⁶Fishman; Torigoe; Guzik *J. Org. Chem.* **1963**, 28, 1443.

⁴¹⁷For lists of reagents, with references, see Ref. 74, pp. 31-35. For a review with respect to transition-metal reagents, see Luh; Ni *Synthesis* **1990**, 89-103. For some very efficient nickel-containing reagents, see Becker; Fort; Vanderesse; Caubère *J. Org. Chem.* **1989**, 54, 4848.

⁴¹⁸For example, diphosphorus tetraiodide by Suzuki; Tani; Takeuchi *Bull. Chem. Soc. Jpn.* **1985**, 58, 2421; Shigemasa; Ogawa; Sashiwa; Saimoto *Tetrahedron Lett.* **1989**, 30, 1277; $\text{NiBr}_2\text{-Ph}_3\text{P-LiAlH}_4$ by Ho; Lam; Luh *J. Org. Chem.* **1989**, 54, 4474.

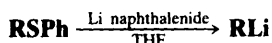
⁴¹⁹Schut; Engberts; Wynberg *Synth. Commun.* **1972**, 2, 415.

in trifluoroacetic acid or in CH_2Cl_2 in the presence of AlCl_3 .⁴²⁰ Phenyl selenides RSePh can be reduced to RH with Ph_3SnH ⁴²¹ and with nickel boride.⁴²²

The exact mechanisms of the Raney nickel reactions are still in doubt, though they are probably of the free-radical type.⁴²³ It has been shown that reduction of thiophene proceeds through butadiene and butene, not through 1-butanethiol or other sulfur compounds, i.e., the sulfur is removed before the double bonds are reduced. This was demonstrated by isolation of the olefins and the failure to isolate any potential sulfur-containing intermediates.⁴²⁴

OS IV, 638; V, 419; VI, 109, 581, 601. See also OS VII, 124, 476.

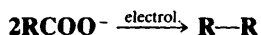
4-37 Conversion of Sulfides to Organolithium Compounds Lithio-de-phenylthio-substitution



Sulfides can be cleaved, with a phenylthio group replaced by a lithium,⁴²⁵ by treatment with lithium or lithium naphthalenide in THF.⁴²⁶ Good yields have been obtained with R = primary, secondary, or tertiary alkyl, or allylic,⁴²⁷ and containing groups such as double bonds or halogens. Dilithio compounds can be made from compounds containing two separated SPh groups, but it is also possible to replace just one SPh from a compound with two such groups on a single carbon, to give an α -lithio sulfide.⁴²⁸ The reaction has also been used to prepare α -lithio ethers and α -lithio organosilanes.⁴²⁵ For some of these compounds lithium 1-(dimethylamino)naphthalenide is a better reagent than either Li or lithium naphthalenide.⁴²⁹ The mechanism is presumably of the free-radical type.

Carbon as Leaving Group

4-38 Decarboxylative Dimerization. The Kolbe Reaction De-carboxylide-coupling



Electrolysis of carboxylate ions, which results in decarboxylation and combination of the resulting radicals, is called the *Kolbe reaction*.⁴³⁰ It is used to prepare symmetrical RR , where R is straight- or branched-chained, except that little or no yield is obtained when there is α branching. The reaction is not successful for R = aryl. Many functional groups

⁴²⁰Kikugawa *J. Chem. Soc., Perkin Trans. I* **1984**, 609.

⁴²¹Clive; Chittattu; Wong *J. Chem. Soc., Chem. Commun.* **1978**, 41.

⁴²²Back *J. Chem. Soc., Chem. Commun.* **1984**, 1417.

⁴²³For a review, see Bonner; Grimm, in Kharasch; Meyers *The Chemistry of Organic Sulfur Compounds*, vol. 2; Pergamon: New York, 1966, pp. 35-71, 410-413. For a review of the mechanism of desulfurization on molybdenum surfaces, see Friend; Roberts *Acc. Chem. Res.* **1988**, *21*, 394-400.

⁴²⁴Owens; Ahmberg *Can. J. Chem.* **1962**, *40*, 941.

⁴²⁵For a review, see Cohen; Bhupathy *Acc. Chem. Res.* **1989**, *22*, 152-161.

⁴²⁶Screttas; Micha-Screttas *J. Org. Chem.* **1978**, *43*, 1064, **1979**, *44*, 713.

⁴²⁷See Cohen; Guo *Tetrahedron* **1986**, *42*, 2803.

⁴²⁸See, for example, Cohen; Sherbine; Matz; Hutchins; McHenry; Willey *J. Am. Chem. Soc.* **1984**, *106*, 3245; Ager *J. Chem. Soc., Perkin Trans. I* **1986**, 183; Ref. 426.

⁴²⁹See Cohen; Matz *Synth. Commun.* **1980**, *10*, 311.

⁴³⁰For reviews, see Schäfer *Top. Curr. Chem.* **1990**, *152*, 91-151, *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 911-934 [*Angew. Chem.* *93*, 978-1000]; Fry *Synthetic Organic Electrochemistry*, 2nd ed.; Wiley: New York, 1989, pp. 238-253; Ebersson; Utley, in Baizer; Lund *Organic Electrochemistry*; Marcel Dekker: New York, 1983, pp. 435-462; Gilde *Methods Free-Radical Chem.* **1972**, *3*, 1-82; Ebersson, in Patai *The Chemistry of Carboxylic Acids and Esters*; Wiley: New York, 1969, pp. 53-101; Vijh; Conway *Chem. Rev.* **1967**, *67*, 623-664.

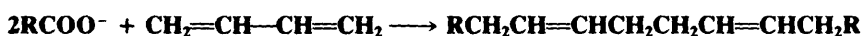
may be present, though many others inhibit the reaction.⁴³⁰ Unsymmetrical RR' have been made by coupling mixtures of acid salts.

A free-radical mechanism is involved:



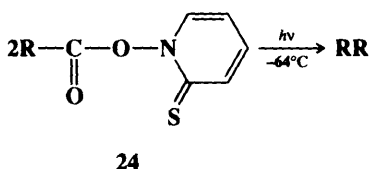
There is much evidence⁴³¹ for this mechanism, including side products (RH , alkenes) characteristic of free-radical intermediates and the fact that electrolysis of acetate ion in the presence of styrene caused some of the styrene to polymerize to polystyrene (such polymerizations can be initiated by free radicals, see p. 744). Other side products (ROH , $RCOOR$) are sometimes found; these stem from further oxidation of the radical $R\cdot$ to the carbocation R^+ .⁴³²

When the reaction is conducted in the presence of 1,3-dienes, additive dimerization can occur:⁴³³



The radical $R\cdot$ adds to the conjugated system to give $RCH_2CH=CHCH_2\cdot$, which dimerizes. Another possible product is $RCH_2CH=CHCH_2R$, from coupling of the two kinds of radicals.⁴³⁴

In a non-electrolytic reaction, which is limited to R = primary alkyl, the thiohydroxamic esters **24** give dimers when irradiated at -64°C in an argon atmosphere:⁴³⁵

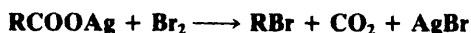


In another non-electrolytic process, arylacetic acids are converted to *vic*-diaryl compounds $2ArCR_2COOH \rightarrow ArCR_2CR_2Ar$ by treatment with sodium persulfate $Na_2S_2O_8$ and a catalytic amount of $AgNO_3$.⁴³⁶ Both of these reactions involve dimerization of free radicals. In still another process, electron-deficient aromatic acyl chlorides are dimerized to biaryls ($2ArCOCl \rightarrow ArAr$) by treatment with a disilane R_3SiSiR_3 and a palladium catalyst.⁴³⁷

OS III, 401; V, 445, 463; VII, 181.

4-39 The Hunsdiecker Reaction

Bromo-de-carboxylation



Reaction of a silver salt of a carboxylic acid with bromine is called the *Hunsdiecker reaction*⁴³⁸ and is a way of decreasing the length of a carbon chain by one unit.⁴³⁹ The reaction is of

⁴³¹For other evidence, see Kraeutler; Jaeger; Bard *J. Am. Chem. Soc.* **1978**, *100*, 4903.

⁴³²See Corey; Bauld; La Londe; Casanova; Kaiser *J. Am. Chem. Soc.* **1960**, *82*, 2645.

⁴³³Lindsey; Peterson *J. Am. Chem. Soc.* **1959**, *81*, 2073; Khrizolitova; Mirkind; Fioshin *J. Org. Chem. USSR* **1968**, *4*, 1640; Bruno; Dubois *Bull. Soc. Chim. Fr.* **1973**, 2270.

⁴³⁴Smith; Gilde *J. Am. Chem. Soc.* **1959**, *81*, 5325, **1961**, *83*, 1355; Schäfer; Pistorius *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 841 [*Angew. Chem.* **84**, 893].

⁴³⁵Barton; Bridon; Fernandez-Picot; Zard *Tetrahedron* **1967**, *43*, 2733.

⁴³⁶Fristad; Klang *Tetrahedron Lett.* **1983**, *24*, 2219.

⁴³⁷Krafft; Rich; McDermott *J. Org. Chem.* **1990**, *55*, 5430.

⁴³⁸This reaction was first reported by the Russian composer-chemist Alexander Borodin: *Liebigs Ann. Chem.* **1861**, *119*, 121.

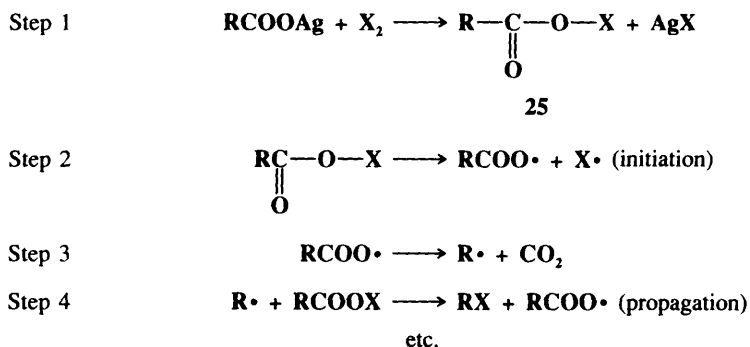
⁴³⁹For reviews, see Wilson *Org. React.* **1957**, *9*, 332-388; Johnson; Ingham *Chem. Rev.* **1956**, *56*, 219-269.

wide scope, giving good results for *n*-alkyl R from 2 to 18 carbons and for many branched R too, producing primary, secondary, and tertiary bromides. Many functional groups may be present as long as they are not α substituted. R may also be aryl. However, if R contains unsaturation, the reaction seldom gives good results. Although bromine is the most often used halogen, chlorine and iodine have also been used.

When iodine is the reagent, the ratio between the reactants is very important and determines the products. A 1:1 ratio of salt to iodine gives the alkyl halide, as above. A 2:1 ratio, however, gives the ester RCOOR. This is called the *Simonini reaction* and is sometimes used to prepare carboxylic esters. The Simonini reaction can also be carried out with lead salts of acids.⁴⁴⁰ A more convenient way to perform the Hunsdiecker reaction is by use of a mixture of the acid and mercuric oxide instead of the salt, since the silver salt must be very pure and dry and such pure silver salts are often not easy to prepare.⁴⁴¹

Other methods for accomplishing the conversion $\text{RCOOH} \rightarrow \text{RX}$ are:⁴⁴² (1) treatment of thallium(I) carboxylates⁴⁴³ with bromine;⁴⁴⁴ (2) treatment of carboxylic acids with lead tetraacetate and halide ions (Cl^- , Br^- , or I^-);⁴⁴⁵ (3) reaction of the acids with lead tetraacetate and N-chlorosuccinimide, which gives tertiary and secondary chlorides in good yields but is not good for R = primary alkyl or phenyl;⁴⁴⁶ (4) the reaction between a diacyl peroxide and CuCl_2 , CuBr_2 , or CuI_2 ⁴⁴⁷ [this reaction also takes place with $\text{Cu}(\text{SCN})_2$, and $\text{Cu}(\text{CN})_2$]; (5) treatment of thiohydroxamic esters (**24**) with CCl_4 , BrCCl_3 (which gives bromination), CHI_3 , or CH_2I_2 in the presence of a radical initiator;⁴⁴⁸ (6) photolysis of benzophenone oxime esters of carboxylic acids in CCl_4 ($\text{RCON}=\text{CPh}_2 \rightarrow \text{RCl}$).⁴⁴⁹ Alkyl fluorides can be prepared in moderate to good yields by treating carboxylic acids RCOOH with XeF_2 .⁴⁵⁰ This method works best for R = primary and tertiary alkyl, and benzylic. Aromatic and vinylic acids do not react.

The mechanism of the Hunsdiecker reaction is believed to be as follows:



⁴⁴⁰Bachman; Kite; Tuccarbasu; Tullman *J. Org. Chem.* **1970**, *35*, 3167.

⁴⁴¹Cristol; Firth *J. Org. Chem.* **1961**, *26*, 280. See also Meyers; Fleming *J. Org. Chem.* **1979**, *44*, 3405, and references cited therein.

⁴⁴²For a list of reagents, with references, see Ref. 74, pp. 381-382.

⁴⁴³These salts are easy to prepare and purify; see Ref. 444.

⁴⁴⁴McKillop; Bromley; Taylor *J. Org. Chem.* **1969**, *34*, 1172; Cambie; Hayward; Jurlina; Rutledge; Woodgate *J. Chem. Soc., Perkin Trans. I* **1981**, 2608.

⁴⁴⁵Kochi *J. Am. Chem. Soc.* **1965**, *87*, 2500; *J. Org. Chem.* **1965**, *30*, 3265. For a review, see Sheldon; Kochi *Org. React.* **1972**, *19*, 279-421, pp. 326-334, 390-399.

⁴⁴⁶Becker; Geisel; Grob; Kuhn *Synthesis* **1973**, 493.

⁴⁴⁷Jenkins; Kochi *J. Org. Chem.* **1971**, *36*, 3095, 3103.

⁴⁴⁸Barton; Crich; Motherwell *Tetrahedron Lett.* **1983**, *24*, 4979; Barton; Lacher; Zard *Tetrahedron* **1987**, *43*, 4321; Stofer; Lion *Bull. Soc. Chim. Belg.* **1987**, *96*, 623; Della; Tsanaktisid *Aust. J. Chem.* **1989**, *42*, 61.

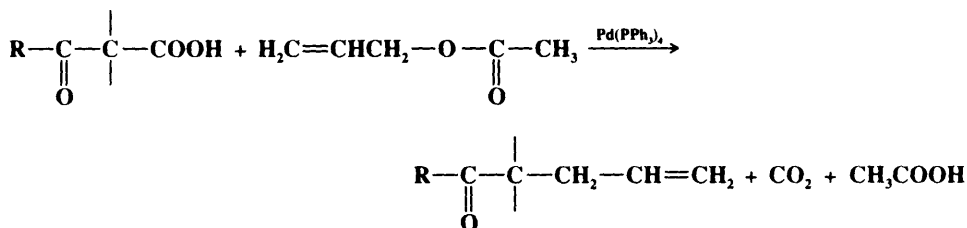
⁴⁴⁹Hasebe; Tsuchiya *Tetrahedron Lett.* **1988**, *29*, 6287.

⁴⁵⁰Patrick; Johri; White; Bertrand; Mokhtar; Kilbourn; Welch **1986**, *Can. J. Chem.* *64*, 138. For another method, see Grakauskas *J. Org. Chem.* **1969**, *34*, 2446.

The first step is not a free-radical process, and its actual mechanism is not known.⁴⁵¹ **25** is an acyl hypophalite and is presumed to be an intermediate, though it has never been isolated from the reaction mixture. Among the evidence for the mechanism is that optical activity at R is lost (except when a neighboring bromine atom is present, see p. 682); if R is neopentyl, there is no rearrangement, which would certainly happen with a carbocation; and the side products, notably RR, are consistent with a free-radical mechanism. There is evidence that the Simonini reaction involves the same mechanism as the Hunsdiecker reaction but that the alkyl halide formed then reacts with excess RCOOAg (**0-24**) to give the ester.⁴⁵² See also **9-13**.

OS **III**, 578; **V**, 126; **VI**, 179. See also OS **VI**, 403.

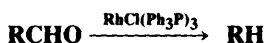
4-40 Decarboxylative Allylation Allyl-de-carboxylation



The COOH group of a β -keto acid is replaced by an allylic group when the acid is treated with an allylic acetate and a palladium catalyst at room temperature.⁴⁵³ The reaction is successful for various substituted allylic groups. The less-highly-substituted end of the allylic group forms the new bond. Thus, both $\text{CH}_2=\text{CHCHMeOAc}$ and $\text{MeCH}=\text{CHCH}_2\text{OAc}$

gave $\text{RCO}-\text{C}(\text{---})-\text{CH}_2\text{CH}=\text{CHMe}$ as the product.

4-41 Decarbonylation of Aldehydes and Acyl Halides Carbonyl-extrusion



Aldehydes, both aliphatic and aromatic, can be decarbonylated⁴⁵⁴ by heating with chlorotris(triphenylphosphine)rhodium⁴⁵⁵ or other catalysts such as palladium.⁴⁵⁶ $\text{RhCl}(\text{Ph}_3\text{P})_3$ is often called *Wilkinson's catalyst*.⁴⁵⁷ In an older reaction aliphatic (but not aromatic) aldehydes are decarbonylated by heating with di-*t*-peroxide or other peroxides,⁴⁵⁸ usually in a solution

⁴⁵¹When Br_2 reacts with aryl R, at low temperature in inert solvents, it is possible to isolate a complex containing both Br_2 and the silver carboxylate: see Bryce-Smith; Isaacs; Tumi *Chem. Lett.* **1984**, 1471.

⁴⁵²Oae; Kashiwagi; Kozuka *Bull. Chem. Soc. Jpn.* **1966**, 39, 2441; Bunce; Murray *Tetrahedron* **1971**, 27, 5323.

⁴⁵³Tsuda; Okada; Nishi; Saegusa *J. Org. Chem.* **1986**, 51, 421.

⁴⁵⁴For reviews, see Collman; Hegedus; Norton; Finke *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987, pp. 768-775; Baird, in Patai *The Chemistry of Functional Groups, Supplement B*, pt. 2; Wiley: New York, 1979, pp. 825-857; Tsuji, in Wender; Pino *Organic Syntheses Via Metal Carbonyls*, vol. 2; Wiley: New York, 1977, pp. 595-654; Tsuji; Ohno *Synthesis* **1969**, 157-169; Bird *Transition Metal Intermediates in Organic Synthesis*; Academic Press: New York, 1967, pp. 239-247.

⁴⁵⁵Tsuji; Ohno *Tetrahedron Lett.* **1965**, 3969; Ohno; Tsuji *J. Am. Chem. Soc.* **1968**, 90, 99; Baird; Nyman; Wilkinson *J. Chem. Soc. A* **1968**, 348.

⁴⁵⁶For a review, see Rylander, Ref. 246, pp. 260-267.

⁴⁵⁷For a review of this catalyst, see Jardine *Prog. Inorg. Chem.* **1981**, 28, 63-202.

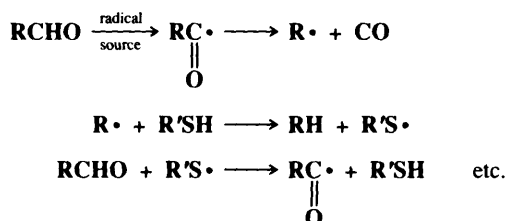
⁴⁵⁸For reviews of free-radical aldehyde decarbonylations, see Vinogradov; Nikishin *Russ. Chem. Rev.* **1971**, 40, 916-932; Schubert; Kintner, in Patai, Ref. 189, pp. 711-735.

containing a hydrogen donor, such as a thiol. The reaction has also been initiated with light, and thermally (without an initiator) by heating at about 500°C.

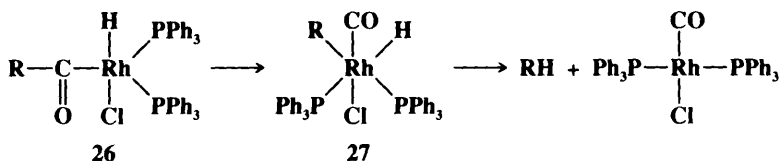
Wilkinson's catalyst has also been reported to decarbonylate aromatic acyl halides at 180°C ($\text{ArCOX} \rightarrow \text{ArX}$).⁴⁵⁹ This reaction has been carried out with acyl iodides,⁴⁶⁰ bromides, and chlorides. Aliphatic acyl halides that lack an α hydrogen also give this reaction,⁴⁶¹ but if an α hydrogen is present, elimination takes place instead (7-19). Aromatic acyl cyanides give aryl cyanides ($\text{ArCOCN} \rightarrow \text{ArCN}$).⁴⁶² Aromatic acyl chlorides and cyanides can also be decarbonylated with palladium catalysts.⁴⁶³

It is possible to decarbonylate acyl halides in another way, to give alkanes ($\text{RCOCl} \rightarrow \text{RH}$). This is done by heating the substrate with tripropylsilane Pr_3SiH in the presence of *t*-butyl peroxide.⁴⁶⁴ Yields are good for R = primary or secondary alkyl and poor for R = tertiary alkyl or benzylic. There is no reaction when R = aryl. (See also the decarbonylation $\text{ArCOCl} \rightarrow \text{ArAr}$ mentioned in 4-38.)

The mechanism of the peroxide- or light-induced reaction seems to be as follows (in the presence of thiols):⁴⁶⁵



The reaction of aldehydes with Wilkinson's catalyst goes through complexes of the form **26** and **27**, which have been trapped.⁴⁶⁶ The reaction has been shown to give retention of



configuration at a chiral R;⁴⁶⁷ and deuterium labeling demonstrates that the reaction is intramolecular: RCOD give RD .⁴⁶⁸ Free radicals are not involved.⁴⁶⁹ The mechanism with acyl halides appears to be more complicated.⁴⁷⁰

For aldehyde decarbonylation by an electrophilic mechanism, see 1-38.

⁴⁵⁹Kampmeier; Rodehorst; Philip *J. Am. Chem. Soc.* **1981**, 103, 1847; Blum *Tetrahedron Lett.* **1966**, 1605; Blum; Oppenheimer; Bergmann *J. Am. Chem. Soc.* **1967**, 89, 2338.

⁴⁶⁰Blum; Rosenman; Bergmann *J. Org. Chem.* **1968**, 33, 1928.

⁴⁶¹Tsuji; Ohno *Tetrahedron Lett.* **1966**, 4713; *J. Am. Chem. Soc.* **1966**, 88, 3452.

⁴⁶²Blum; Oppenheimer; Bergmann, Ref. 459.

⁴⁶³Verbicky; Dellacolella; Williams *Tetrahedron Lett.* **1982**, 23, 371; Murahashi; Naota; Nakajima *J. Org. Chem.* **1986**, 51, 898.

⁴⁶⁴Billingham; Jackson; Malek *J. Chem. Soc., Perkin Trans. 1* **1979**, 1137.

⁴⁶⁵Slaugh *J. Am. Chem. Soc.* **1959**, 81, 2262; Berman; Stanley; Sherman; Cohen *J. Am. Chem. Soc.* **1963**, 85, 4010.

⁴⁶⁶Suggs *J. Am. Chem. Soc.* **1978**, 100, 640; Kampmeier; Harris; Mergelsberg *J. Org. Chem.* **1984**, 49, 621.

⁴⁶⁷Walborsky; Allen *J. Am. Chem. Soc.* **1971**, 93, 5465. See also Tsuji; Ohno *Tetrahedron Lett.* **1967**, 2173.

⁴⁶⁸Prince; Raspin *J. Chem. Soc. A* **1969**, 612; Walborsky; Allen, Ref. 467. See, however, Baldwin; Barden; Pugh; Widdison *J. Org. Chem.* **1987**, 52, 3303.

⁴⁶⁹Kampmeier; Harris; Wedegaertner *J. Org. Chem.* **1980**, 45, 315.

⁴⁷⁰Kampmeier; Rodehorst; Philip, Ref. 459; Kampmeier; Mahalingam; Liu *Organometallics* **1986**, 5, 823; Kampmeier; Liu *Organometallics* **1989**, 8, 2742.

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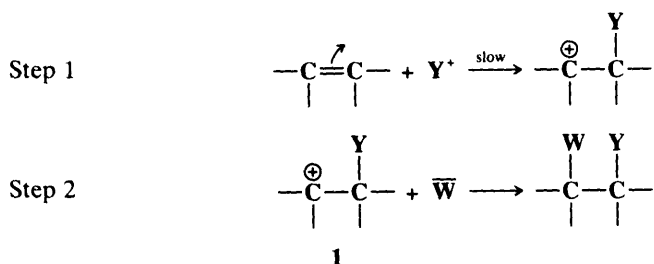
ADDITION TO CARBON-CARBON MULTIPLE BONDS

There are basically four ways in which addition to a double or triple bond can take place. Three of these are two-step processes, with initial attack by a nucleophile, an electrophile, or a free radical. The second step consists of combination of the resulting intermediate with, respectively, a positive species, a negative species, or a neutral entity. In the fourth type of mechanism, attack at the two carbon atoms of the double or triple bond is simultaneous. Which of the four mechanisms is operating in any given case is determined by the nature of the substrate, the reagent, and the reaction conditions. Some of the reactions in this chapter can take place by all four mechanistic types.

MECHANISMS

Electrophilic Addition¹

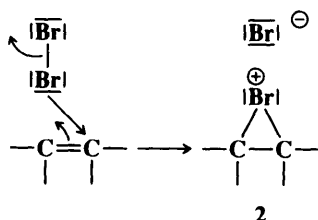
In this mechanism a positive species approaches the double or triple bond and in the first step forms a bond by converting the π pair of electrons into a σ pair:



The IUPAC designation for this mechanism is $A_E + A_N$ (or $A_H + A_N$ if $\text{Y}^+ = \text{H}^+$). As in electrophilic substitution (p. 502), Y need not actually be a positive ion but can be the

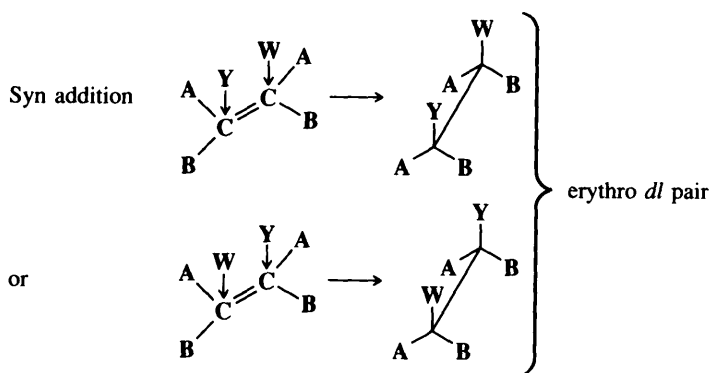
¹For a monograph, see de la Mare; Bolton *Electrophilic Additions to Unsaturated Systems*, 2nd ed.; Elsevier: New York, 1982. For reviews, see Schmid, in Patai *Supplement A: The Chemistry of Double-bonded Functional Groups*, vol. 2, pt. 1; Wiley: New York, 1989, pp. 679-731; Smit *Sov. Sci. Rev. Sect. B* **1985**, 7, 155-236; V'yunov; Ginak *Russ. Chem. Rev.* **1981**, 50, 151-163; Schmid; Garratt, in Patai *Supplement A: The Chemistry of Double-bonded Functional Groups*, vol. 1, pt. 2; Wiley: New York, 1977, pp. 725-912; Freeman *Chem. Rev.* **1975**, 75, 439-490; Bolton, in Bamford; Tipper *Comprehensive Chemical Kinetics*, vol. 9; Elsevier: New York, 1973, pp. 1-86; Dolbier *J. Chem. Educ.* **1969**, 46, 342-344.

positive end of a dipole or an induced dipole, with the negative part breaking off either during the first step or shortly after. The second step is a combination of **1** with a species carrying an electron pair and often bearing a negative charge. This step is the same as the second step of the S_N1 mechanism. Not all electrophilic additions follow the simple mechanism given above. In many brominations it is fairly certain that **1**, if formed at all, very rapidly cyclizes to a bromonium ion (**2**):



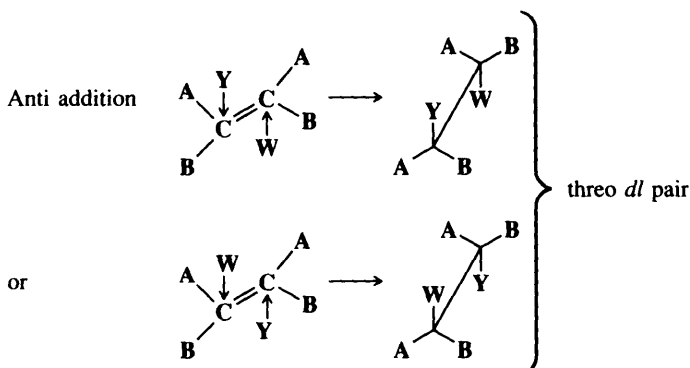
This intermediate is similar to those encountered in the neighboring-group mechanism of nucleophilic substitution (see p. 308). The attack of \bar{W} on an intermediate like **2** is an S_N2 step. Whether the intermediate is **1** or **2**, the mechanism is called $AdE2$ (electrophilic addition, bimolecular).

In investigating the mechanism of addition to a double bond, perhaps the most useful type of information is the stereochemistry of the reaction.² The two carbons of the double bond and the four atoms immediately attached to them are all in a plane (p. 8); there are thus three possibilities. Y and W may enter from the same side of the plane, in which case the addition is stereospecific and *syn*; they may enter from opposite sides for stereospecific *anti* addition; or the reaction may be nonstereospecific. In order to determine which of these possibilities is occurring in a given reaction, the following type of experiment is often done: YW is added to the *cis* and *trans* isomers of an olefin of the form $ABC=CBA$. We may use the *cis* olefin as an example. If the addition is *syn*, the product will be the *erythro dl* pair, because each carbon has a 50% chance of being attacked by Y :



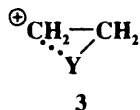
²For a review of the stereochemistry of electrophilic additions to double and triple bonds, see Fahey *Top. Stereochem.* **1968**, 3, 237-342. For a review of the synthetic uses of stereoselective additions, see Bartlett *Tetrahedron* **1980**, 36, 2-72, pp. 3-15.

On the other hand, if the addition is anti, the three *dl* pair will be formed:

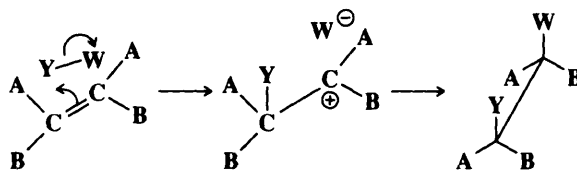


Of course, the *trans* isomer will give the opposite results: the three pair if the addition is syn and the erythro pair if it is anti. The three and erythro isomers have different physical properties. In the special case where $Y = W$ (as in the addition of Br_2), the "erythro pair" is a meso compound. In addition to triple-bond compounds of the type $\text{AC}\equiv\text{CA}$, syn addition results in a *cis* olefin and anti addition in a *trans* olefin. By the definition given on p. 137, addition to triple bonds cannot be stereospecific, though it can be, and often is, stereoselective.

It is easily seen that in reactions involving cyclic intermediates like **2** addition must be anti, since the second step is an $\text{S}_\text{N}2$ step and must occur from the back side. It is not so easy to predict the stereochemistry for reactions involving **1**. If **1** has a relatively long life, the addition should be nonstereospecific, since there will be free rotation about the single bond. On the other hand, there may be some factor that maintains the configuration, in which case W may come in from the same side or the opposite side, depending on the circumstances. For example, the positive charge might be stabilized by an attraction for Y that does not involve a full bond:



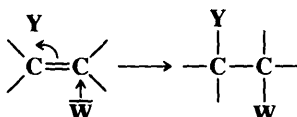
The second group would then come in anti. A circumstance that would favor syn addition would be the formation of an ion pair after the addition of Y :³



Since W is already on the same side of the plane as Y , collapse of the ion pair leads to syn addition.

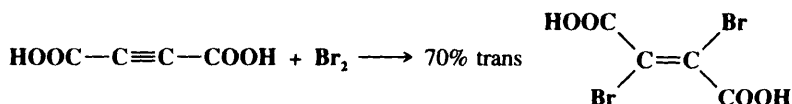
³Dewar *Angew. Chem. Int. Ed. Engl.* **1964**, *3*, 245-249 [*Angew. Chem.* **76**, 320-325]; Heasley; Bower; Dougharty; Easdon; Heasley; Arnold; Carter; Yaeger; Gipe; Shellhamer *J. Org. Chem.* **1980**, *45*, 5150.

Another possibility is that anti addition might, at least in some cases, be caused by the operation of a mechanism in which attack by W and Y are essentially simultaneous but from opposite sides:



This mechanism, called the $\text{A}_{\text{DE}}3$ mechanism (*termolecular addition*, IUPAC $\text{A}_{\text{N}}\text{A}_{\text{E}}$),⁴ has the disadvantage that three molecules must come together in the transition state. However, it is the reverse of the E_{2} mechanism for elimination, for which the transition state is known to possess this geometry (p. 983).

There is much evidence that when the attack is by Br^+ (or a carrier of it), the bromonium ion **2** is often an intermediate and the addition is anti. As long ago as 1911, McKenzie and Fischer independently showed that treatment of maleic acid with bromine gave the *dl* pair of 2,3-dibromosuccinic acid, while fumaric acid (the *trans* isomer) gave the meso compound.⁵ Many similar experiments have been performed since with similar results. For triple bonds, stereoselective anti addition was shown even earlier. Bromination of dicarboxyacetylene gave 70% of the *trans* isomer.⁶



There is other evidence for mechanisms involving **2**. We have already mentioned (p. 312) that bromonium ions have been isolated in stable solutions in nucleophilic substitution reactions involving bromine as a neighboring group. Such ions have also been isolated in reactions involving addition of a Br^+ species to a double bond.⁷ The following is further evidence. If the two bromines approach the double bond from opposite sides, it is very unlikely that they could come from the same bromine molecule. This means that if the reaction is performed in the presence of nucleophiles, some of these will compete in the second step with the bromide liberated from the bromine. It has been found, indeed, that treatment of ethylene with bromine in the presence of chloride ions gives some 1-chloro-2-bromoethane along with the dibromoethane.⁸ Similar results are found when the reaction is carried out in the presence of water (**5-27**) or of other nucleophiles.⁹ Ab initio molecular

⁴For evidence for this mechanism, see, for example, Hammond; Nevitt *J. Am. Chem. Soc.* **1954**, 76, 4121; Bell; Pring *J. Chem. Soc. B* **1966**, 1119; Pincok; Yates *J. Am. Chem. Soc.* **1968**, 90, 5643; Fahey; Lee *J. Am. Chem. Soc.* **1967**, 89, 2780, **1968**, 90, 2124; Fahey; Monahan *J. Am. Chem. Soc.* **1970**, 92, 2816; Fahey; Payne; Lee *J. Org. Chem.* **1974**, 39, 1124; Roberts *J. Chem. Soc., Perkin Trans. 2* **1976**, 1374; Pasto; Gadberry *J. Am. Chem. Soc.* **1978**, 100, 1469; Naab; Staab *Chem. Ber.* **1978**, 111, 2982.

⁵This was done by Fischer *Liebigs Ann. Chem.* **1911**, 386, 374; McKenzie *Proc. Chem. Soc.* **1911**, 150, *J. Chem. Soc.* **1912**, 101, 1196.

⁶Michael *J. Prakt. Chem.* **1892**, 46, 209.

⁷Strating; Wieringa; Wynberg *Chem. Commun.* **1969**, 907; Olah *Angew. Chem. Int. Ed. Engl.* **1973**, 12, 173-212, p. 207 [*Angew. Chem.* 85,183-225]; Slebocka-Tilk; Ball; Brown *J. Am. Chem. Soc.* **1985**, 107, 4504.

⁸Francis *J. Am. Chem. Soc.* **1925**, 47, 2340.

⁹See, for example, Zefirov; Koz'min; Dan'kov; Zhdankin; Kirin *J. Org. Chem. USSR* **1984**, 20, 205.

orbital studies show that **2** is more stable than its open isomer **1** ($Y = \text{Br}$).¹⁰ There is evidence that formation of **2** is reversible.¹¹

However, a number of examples have been found where addition of bromine is not stereospecifically anti. For example, the addition of Br_2 to *cis*- and *trans*-1-phenylpropenes in CCl_4 was nonstereospecific.¹² Furthermore, the stereospecificity of bromine addition to stilbene depends on the dielectric constant of the solvent. In solvents of low dielectric constant, the addition was 90 to 100% anti, but with an increase in dielectric constant, the reaction became less stereospecific, until, at a dielectric constant of about 35, the addition was completely nonstereospecific.¹³ Likewise in the case of triple bonds, stereoselective anti addition was found in bromination of 3-hexyne, but both *cis* and *trans* products were obtained in bromination of phenylacetylene.¹⁴ These results indicate that a bromonium ion is not formed where the open cation can be stabilized in other ways (e.g., addition of Br^+ to 1-phenylpropene gives the ion $\text{Ph}\overset{+}{\text{C}}\text{HCHBrCH}_3$, which is a relatively stable benzylic cation) and that there is probably a spectrum of mechanisms between complete bromonium ion (**2**, no rotation) formation and completely open-cation (**1**, free rotation) formation, with partially bridged bromonium ions (**3**, restricted rotation) in between.¹⁵ We have previously seen cases (e.g., p. 315) where cations require more stabilization from outside sources as they become intrinsically less stable themselves.¹⁶ Further evidence for the open cation mechanism where aryl stabilization is present was reported in an isotope effect study of addition of Br_2 to $\text{ArCH}=\text{CHCHAr}'$ ($\text{Ar} = p$ -nitrophenyl, $\text{Ar}' = p$ -tolyl). The ^{14}C isotope effect for one of the double bond carbons (the one closer to the NO_2 group) was considerably larger than for the other one.¹⁷

Attack by Cl^+ ,¹⁸ I^+ ,¹⁹ and RS^+ ²⁰ is similar to that by Br^+ ; there is a spectrum of mechanisms between cyclic intermediates and open cations. As might be expected from our discussion in Chapter 10 (p. 312), iodonium ions compete with open carbocations more effectively than bromonium ions, while chloronium ions compete less effectively. There is

¹⁰Hamilton; Schaefer *J. Am. Chem. Soc.* **1990**, *112*, 8260.

¹¹Brown; Gedyde; Slebocka-Tilk; Buschek; Kopecky *J. Am. Chem. Soc.* **1984**, *106*, 4515; Bellucci; Bianchini; Chiappe; Marioni; Spagna *J. Am. Chem. Soc.* **1988**, *110*, 546; Ruasse; Motallebi; Galland *J. Am. Chem. Soc.* **1991**, *113*, 3440; Bellucci; Bianchini; Chiappe; Brown; Slebocka-Tilk; *J. Am. Chem. Soc.* **1991**, *113*, 8012; Bennet; Brown; McClung; Klobukowski; Aarts; Santarsiero; Bellucci; Bianchini; *J. Am. Chem. Soc.* **1991**, *113*, 8532.

¹²Fahey; Schneider *J. Am. Chem. Soc.* **1968**, *90*, 4429. See also Rolston; Yates *J. Am. Chem. Soc.* **1969**, *91*, 1469, 1477, 1483.

¹³Buckles; Bader; Thurmaier *J. Org. Chem.* **1962**, *27*, 4523; Heublein *J. Prakt. Chem.* **1966**, [4] *31*, 84. See also Buckles; Miller; Thurmaier *J. Org. Chem.* **1967**, *32*, 888; Heublein; Lauterbach *J. Prakt. Chem.* **1969**, *311*, 91; Ruasse; Dubois *J. Am. Chem. Soc.* **1975**, *97*, 1977. For the dependence of stereospecificity in this reaction on the solvent concentration, see Bellucci; Bianchini; Chiappe; Marioni *J. Org. Chem.* **1990**, *55*, 4094.

¹⁴Pincock; Yates *Can. J. Chem.* **1970**, *48*, 3332.

¹⁵For other evidence for this concept, see Pincock; Yates *Can. J. Chem.* **1970**, *48*, 2944; Heasley; Chamberlain *J. Org. Chem.* **1970**, *35*, 539; Dubois; Toullec; Barbier *Tetrahedron Lett.* **1970**, 4485; Dalton; Davis *Tetrahedron Lett.* **1972**, 1057; Wilkins; Regulski *J. Am. Chem. Soc.* **1972**, *94*, 6016; Sisti; Meyers *J. Org. Chem.* **1973**, *38*, 4431; McManus; Peterson *Tetrahedron Lett.* **1975**, 2753; Abraham; Monasterios *J. Chem. Soc., Perkin Trans. 1* **1973**, 1446; Ruasse; Argile; Dubois *J. Am. Chem. Soc.* **1978**, *100*, 7645; *J. Org. Chem.* **1979**, *44*, 1173; Schmid; Modro; Yates *J. Org. Chem.* **1980**, *45*, 665; Ruasse; Argile *J. Org. Chem.* **1983**, *48*, 202; Cadogan; Cameron; Gosney; Highcock; Newlands *J. Chem. Soc., Chem. Commun.* **1985**, 1751. For a review, see Ruasse *Acc. Chem. Res.* **1990**, *23*, 87-93.

¹⁶In a few special cases, stereospecific syn addition of Br_2 has been found, probably caused by an ion pair mechanism as shown on p. 736; Naac *J. Org. Chem.* **1980**, *45*, 1394.

¹⁷Kokil; Fry *Tetrahedron Lett.* **1986**, *27*, 5051.

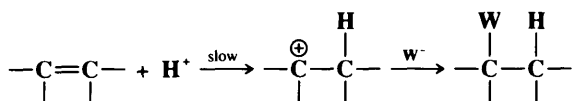
¹⁸Fahey, Ref. 2, pp. 273-277.

¹⁹Hassner; Boerwinkle; Levy *J. Am. Chem. Soc.* **1970**, *92*, 4879.

²⁰For reviews of thiiranium and/or thiirenium ions, see Capozzi; Modena, in Bernardi; Csizmadia; Mangini *Organic Sulfur Chemistry*; Elsevier: New York, 1985, pp. 246-298; Smit, Ref. 1, pp. 180-202; Dittmer; Patwardhan, in Stirling *The Chemistry of the Sulphonium Group*, pt. 1; Wiley: New York, 1981, pp. 387-412; Capozzi; Lucchini; Modena; *Rev. Chem. Intermed.* **1979**, *2*, 347-375; Schmid *Top. Sulfur Chem.* **1977**, *3*, 102-117; Mueller *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 482-492 [*Angew. Chem.* *81*, 475-484]. The specific nature of the 3-membered sulfur-containing ring is in dispute; see Smit; Zefirov; Bodrikov; Krimer *Acc. Chem. Res.* **1979**, *12*, 282-288; Bodrikov; Borisov; Chumakov; Zefirov; Smit *Tetrahedron Lett.* **1980**, *21*, 115; Schmid; Garratt; Dean *Can. J. Chem.* **1987**, *65*, 1172; Schmid; Strukelj; Dalipi *Can. J. Chem.* **1987**, *65*, 1945.

kinetic and spectral evidence that at least in some cases, for example in the addition of Br_2 or ICl , the electrophile forms a π complex with the alkene before a covalent bond is formed.²¹

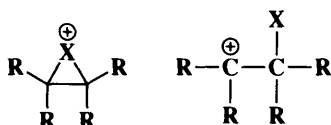
When the electrophile is a proton,²² a cyclic intermediate is not possible, and the mechanism is the simple $\text{A}_\text{H} + \text{A}_\text{N}$ process shown before



This is an A-SE_2 mechanism (p. 374). There is a great deal of evidence²³ for it, including:

1. The reaction is general-acid, not specific-acid-catalyzed, implying rate-determining proton transfer from the acid to the double bond.²⁴

2. The existence of open carbocation intermediates is supported by the contrast in the pattern of alkyl substituent effects²⁵ with that found in brominations, where cyclic intermediates are involved. In the latter case substitution of alkyl groups on $\text{H}_2\text{C}=\text{CH}_2$ causes a cumulative rate acceleration until all four hydrogens have been replaced by alkyl groups,



because each group helps to stabilize the positive charge.²⁶ In addition of HX the effect is not cumulative. Replacement of the two hydrogens on one carbon causes great rate increases (primary \rightarrow secondary \rightarrow tertiary carbocation), but additional substitution on the other carbon produces little or no acceleration.²⁷ This is evidence for open cations when a proton is the electrophile.²⁸

3. Open carbocations are prone to rearrange (Chapter 18). Many rearrangements have been found to accompany additions of HX and H_2O).²⁹

²¹See Norlander; Haky; Landino *J. Am. Chem. Soc.* **1980**, *102*, 7487; Fukuzumi; Kochi *Int. J. Chem. Kinet.* **1983**, *15*, 249; Schmid; Gordon *Can. J. Chem.* **1984**, *62*, 2526, **1986**, *64*, 2171; Bellucci; Bianchini; Ambrosetti *J. Am. Chem. Soc.* **1985**, *107*, 2464; Bellucci; Bianchini; Chiappe; Marion; Ambrosetti; Brown; Slebocka-Tilk *J. Am. Chem. Soc.* **1989**, *111*, 2640.

²²For a review of the addition of HCl , see Sergeev; Smirnov; Rostovshchikova *Russ. Chem. Rev.* **1983**, *52*, 259-274.

²³For other evidence, see Baliga; Whalley *Can. J. Chem.* **1964**, *42*, 1019, **1965**, *43*, 2453; Gold; Kessick *J. Chem. Soc.* **1965**, 6718; Corriu; Guenzet *Tetrahedron* **1970**, *26*, 671; Simandoux; Torck; Hellin; Coussemant *Bull. Soc. Chim. Fr.* **1972**, 4402, 4410; Bernasconi; Boyle *J. Am. Chem. Soc.* **1974**, *96*, 6070; Hampel; Just; Pisanenko; Pritzkow *J. Prakt. Chem.* **1976**, *318*, 930; Allen; Tidwell *J. Am. Chem. Soc.* **1983**, *104*, 3145.

²⁴Kresge; Chiang; Fitzgerald; McDonald; Schmid *J. Am. Chem. Soc.* **1971**, *93*, 4907; Loudon; Noyce *J. Am. Chem. Soc.* **1969**, *91*, 1433; Schubert; Keefe *J. Am. Chem. Soc.* **1972**, *94*, 559; Chiang; Kresge *J. Am. Chem. Soc.* **1985**, *107*, 6363.

²⁵Bartlett; Sargent *J. Am. Chem. Soc.* **1965**, *87*, 1297; Schmid; Garratt *Can. J. Chem.* **1973**, *51*, 2463.

²⁶See, for example, Anantkrishnan; Ingold *J. Chem. Soc.* **1935**, 1396; Swern, in Swern *Organic Peroxides*, vol. 2; Wiley: New York, 1971, pp. 451-454; Nowlan; Tidwell *Acc. Chem. Res.* **1977**, *10*, 252-258.

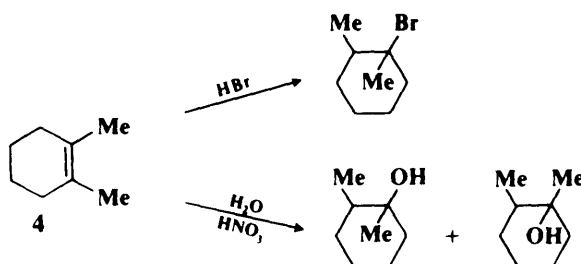
²⁷Bartlett; Sargent, Ref. 25; Riesz; Taft; Boyd *J. Am. Chem. Soc.* **1957**, *79*, 3724.

²⁸A similar result (open cations) was obtained with carbocations Ar_2CH^+ as electrophiles: Mayr; Pock *Chem. Ber.* **1986**, *119*, 2473.

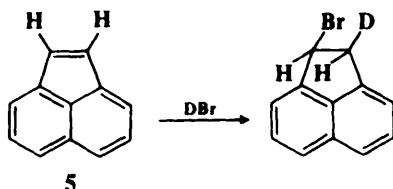
²⁹For example, see Whitmore; Johnston *J. Am. Chem. Soc.* **1933**, *55*, 5020; Fahey; McPherson *J. Am. Chem. Soc.* **1969**, *91*, 3865; Bundel'; Ryabstev; Sorokin; Reutov *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1969**, 1311; Pocker; Stevens *J. Am. Chem. Soc.* **1969**, *91*, 4205; Staab; Wittig; Naab *Chem. Ber.* **1978**, *111*, 2965; Stammann; Griesbaum *Chem. Ber.* **1980**, *113*, 598.

It may also be recalled that vinylic ethers react with proton donors in a similar manner (see 0-6).

The stereochemistry of HX addition is varied. Examples are known of predominant syn, anti, and nonstereoselective addition. It was found that treatment of 1,2-dimethylcyclohexene (**4**) with HBr gave predominant anti addition,³⁰ while addition of water to **4** gave equal amounts of the cis and trans alcohols:³¹

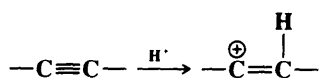


On the other hand, addition of DBr to acenaphthylene (**5**) and to indene and 1-phenylpropene gave predominant syn addition.³²



In fact it has been shown that the stereoselectivity of HCl addition can be controlled by changing the reaction conditions. Addition of HCl to **4** in CH_2Cl_2 at -98°C gave predominantly syn addition, while in ethyl ether at 0°C , the addition was mostly anti.³³

Addition of HX to triple bonds has the same mechanism, though the intermediate in this case is a vinylic cation:³⁴



In all these cases (except for the AdE3 mechanism) we have assumed that formation of the intermediate (**1**, **2**, or **3**) is the slow step and attack by the nucleophile on the intermediate

³⁰Hammond; Nevitt, Ref. 4; See also Fahey; Monahan, Ref. 4; Pasto; Meyer; Lepeska *J. Am. Chem. Soc.* **1974**, 96, 1858.

³¹Collins; Hammond *J. Org. Chem.* **1960**, 25, 911.

³²Dewar; Fahey *J. Am. Chem. Soc.* **1963**, 85, 2245, 2248. For a review of syn addition of HX, see Ref. 3.

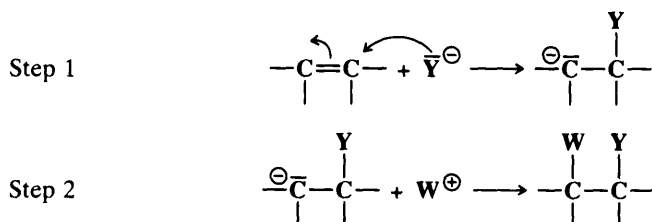
³³Becker; Grob *Synthesis* **1973**, 789. See also Marcuzzi; Melloni; Modena *Tetrahedron Lett.* **1974**, 413; Naab; Staab, Ref. 4.

³⁴For reviews of electrophilic addition to alkynes, including much evidence, see Rappoport *React. Intermed. (Plenum)* **1983**, 3, 427-615, pp. 428-440; Stang; Rappoport; Hanack; Subramanian *Vinyl Cations*; Academic Press: New York, 1979, pp. 24-151; Stang *Prog. Phys. Org. Chem.* **1973**, 10, 205-325; Modena; Tonellato *Adv. Phys. Org. Chem.* **1971**, 9, 185-280, pp. 187-231; Richey; Richey, in Olah; Schleyer *Carbonium Ions*, vol. 2; Wiley: New York, 1970, pp. 906-922.

is rapid, and this is probably true in most cases. However, some additions have been found in which the second step is rate-determining.³⁵

Nucleophilic Addition³⁶

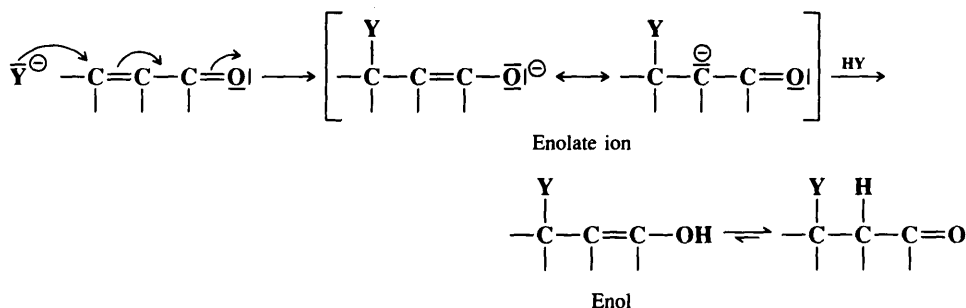
In the first step of nucleophilic addition a nucleophile brings its pair of electrons to one carbon atom of the double or triple bond, creating a carbanion. The second step is combination of this carbanion with a positive species:



This mechanism is the same as the simple electrophilic one shown on p. 734 except that the charges are reversed (IUPAC $A_N + A_E$ or $A_N + A_H$). When the olefin contains a good leaving group (as defined for nucleophilic substitution), substitution is a side reaction (this is nucleophilic substitution at a vinylic substrate, see p. 335).

In the special case of addition of HY to a substrate of the form $-\text{C}=\text{C}-\text{Z}$, where

$\text{Z} = \text{CHO}$, COR ³⁷ (including quinones³⁸), COOR , CONH_2 , CN , NO_2 , SOR , SO_2R ,³⁹ etc., addition nearly always follows a nucleophilic mechanism,⁴⁰ with Y^- bonding with the carbon away from the Z group, e.g.,



³⁵See, for example, Rau; Alcais; Dubois *Bull. Soc. Chim. Fr.* **1972**, 3336; Bellucci; Berti; Ingrosso; Mastrorilli *Tetrahedron Lett.* **1973**, 3911.

³⁶For a review, see Patai; Rappoport, in Patai *The Chemistry of Alkenes*, vol. 1; Wiley: New York, 1964, pp. 469-584.

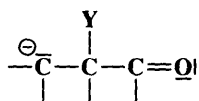
³⁷For reviews of reactions of $\text{C}=\text{C}-\text{C}=\text{O}$ compounds, see, in Patai; Rappoport *The Chemistry of Enones*, pt. 1; Wiley: New York, 1989, the articles by Boyd, pp. 281-315; Duval; G ribaldi, pp. 355-469.

³⁸For reviews of addition reactions of quinones, see Kutyrev; Moskva *Russ. Chem. Rev.* **1991**, 60, 72-88; Finley, in Patai; Rappoport *The Chemistry of the Quinonoid Compounds*, vol. 2, pt. 1; Wiley: New York, 1988, pp. 537-717, pp. 539-589; Finley, in Patai *The Chemistry of the Quinonoid Compounds*, pt. 2; Wiley: New York, 1974, pp. 877-1144.

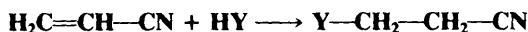
³⁹For a review of vinylic sulfones, see Simpkins *Tetrahedron* **1990**, 46, 6951-6984. For a review of conjugate addition to cycloalkenyl sulfones, see Fuchs; Braish *Chem. Rev.* **1986**, 86, 903-917.

⁴⁰For a review of the mechanism with these substrates, see Bernasconi *Tetrahedron* **1989**, 45, 4017-4090.

Protonation of the enolate ion is chiefly at the oxygen, which is more negative than the carbon, but this produces the enol, which tautomerizes. So although the net result of the reaction is addition to a carbon-carbon double bond, the *mechanism* is 1,4 nucleophilic addition to the $C=C-C=O$ (or similar) system and is thus very similar to the mechanism of addition to carbon-oxygen double and similar bonds (see Chapter 16). When Z is CN or a $C=O$ group, it is also possible for Y^- to attack at *this* carbon, and this reaction sometimes competes. When it happens, it is called 1,2 addition. 1,4 addition to these substrates is also known as *conjugate addition*. Y^- almost never attacks at the 3 position, since the resulting carbanion would have no resonance stabilization:⁴¹

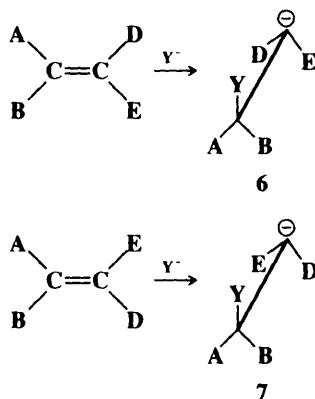


An important substrate of this type is acrylonitrile, and 1,4 addition to it is called *cynoethylation* because the Y is cyanoethylated:



With any substrate, when Y is an ion of the type $Z-\overset{\ominus}{C}R_2$ (Z is as defined above; R may be alkyl, aryl, hydrogen, or another Z), the reaction is called the *Michael reaction* (see 5-17). In this book we will call all other reactions that follow this mechanism *Michael-type additions*. Systems of the type $C=C-C=C-Z$ can give 1,2, 1,4, or 1,6 addition.⁴² Michael-type reactions are reversible, and compounds of the type YCH_2CH_2Z can often be decomposed to YH and $CH_2=CHZ$ by heating, either with or without alkali.

If the mechanism for nucleophilic addition is the simple carbanion mechanism outlined on p. 741, the addition should be nonstereospecific, though it might well be stereoselective (see p. 137 for the distinction). For example, the *E* and *Z* forms of an olefin $ABC=CDE$ would give 6 and 7:



If the carbanion has even a short lifetime, 6 and 7 will assume the most favorable conformation before the attack of W. This is of course the same for both, and when W attacks, the same product will result from each. This will be one of two possible diastereomers, so the reaction will be stereoselective; but since the *cis* and *trans* isomers do not give rise to

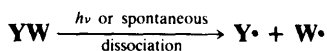
⁴¹For 1,8 addition to a trienone, see Barbot; Kadib-Elban; Miginiac *J. Organomet. Chem.* **1988**, 345, 239.

⁴²However, attack at the 3 position has been reported when the 4 position contains one or two carbanion-stabilizing groups such as $SiMe_3$; Klumpp; Mierop; Vrieling; Brugman; Schakel *J. Am. Chem. Soc.* **1985**, 107, 6740.

different isomers, it will not be stereospecific. Unfortunately, this prediction has not been tested on open-chain olefins. Except for Michael-type substrates, the stereochemistry of nucleophilic addition to double bonds has been studied only in cyclic systems, where only the *cis* isomer exists. In these cases the reaction has been shown to be stereoselective, with *syn* addition reported in some cases⁴³ and *anti* addition in others.⁴⁴ When the reaction is performed on a Michael-type substrate, $C=C-Z$, the hydrogen does not arrive at the carbon directly but only through a tautomeric equilibrium. The product naturally assumes the most thermodynamically stable configuration, without relation to the direction of original attack of *Y*. In one such case (the addition of EtOD and of Me₃CSD to *trans*-MeCH=CHCOOEt) predominant *anti* addition was found; there is evidence that the stereoselectivity here results from the final protonation of the enolate, and not from the initial attack.⁴⁵ For obvious reasons, additions to triple bonds cannot be stereospecific. As with electrophilic additions, nucleophilic additions to triple bonds are usually stereoselective and *anti*,⁴⁶ though *syn* addition⁴⁷ and nonstereoselective addition⁴⁸ have also been reported.

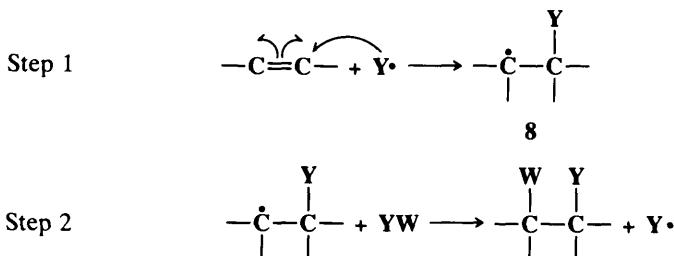
Free-Radical Addition

The mechanism of free-radical addition⁴⁹ follows the pattern discussed in Chapter 14 (pp. 677-678). A radical is generated by



or $R\cdot$ (from some other source) + $YW \longrightarrow RW + Y\cdot$

Propagation then occurs by



⁴³For example, Truce; Levy *J. Org. Chem.* **1963**, 28, 679.

⁴⁴For example, Truce; Levy *J. Am. Chem. Soc.* **1961**, 83, 4641; Zefirov; Yur'ev; Prikazchikova; Bykhovskaya *J. Gen. Chem. USSR* **1963**, 33, 2100.

⁴⁵Mohrig; Fu; King; Warnet; Gustafson *J. Am. Chem. Soc.* **1990**, 112, 3665.

⁴⁶Truce; Simms *J. Am. Chem. Soc.* **1956**, 78, 2756; Shostakovskii; Chekulaeva; Kondrat'eva; Lopatin *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1962**, 2118; Théron; Vessière *Bull. Soc. Chim. Fr.* **1968**, 2994; Bowden; Price *J. Chem. Soc. B* **1970**, 1466, 1472; Raunio; Frey *J. Org. Chem.* **1971**, 36, 345; Truce; Tichenor *J. Org. Chem.* **1972**, 37, 2391.

⁴⁷Truce; Goldhamer; Kruse *J. Am. Chem. Soc.* **1959**, 81, 4931; Dolfini *J. Org. Chem.* **1965**, 30, 1298; Winterfeldt; Preuss *Chem. Ber.* **1966**, 99, 450; Hayakawa; Kamikawaji; Wakita; Kanematsu *J. Org. Chem.* **1984**, 49, 1985.

⁴⁸Gracheva; Laba; Kul'bovskaia; Shostakovskii *J. Gen. Chem. USSR* **1963**, 33, 2431; Truce; Brady *J. Org. Chem.* **1966**, 31, 3543; Prilezhaeva; Vasil'ev; Mikhaleshvili; Bogdanov *Bull. Acad. Sci., USSR, Div. Chem. Sci.* **1970**, 1820.

⁴⁹For a monograph on this subject, see Huyser *Free-Radical Chain Reactions*; Wiley: New York, 1970. Other books with much of interest in this field are Nonhebel; Walton *Free-Radical Chemistry*; Cambridge University Press: London, 1974; Pyor *Free Radicals*; McGraw-Hill: New York, 1965. For reviews, see Giese *Rev. Chem. Intermed.* **1986**, 7, 3-11; *Angew. Chem. Int. Ed. Engl.* **1983**, 22, 753-764 [*Angew. Chem.* 95, 771-782]; Amiel, in Patai; Rappoport *The Chemistry of Functional Groups, Supplement C*, pt. 1; Wiley: New York, 1983, pp. 341-382; Abell, in Bamford; Tipper *Comprehensive Chemical Kinetics*, vol. 18; Elsevier: New York, 1976, pp. 111-165; Abell, in Kochi *Free Radicals*, vol. 2; Wiley: New York, 1973, pp. 63-112; Minisci *Acc. Chem. Res.* **1975**, 8, 165-171; Julia, in Viehe *Acetylenes*; Marcel Dekker: New York, 1969, pp. 335-354; Elad *Org. Photochem.* **1969**, 2, 168-212; Schönberg *Preparative Organic Photochemistry*; Springer: New York, 1968, pp. 155-181; Cadogan; Perkins, in Patai, Ref. 36, pp. 585-632.