

concentrated. This larger cation is much less solubilized by water than K^+ and much more attracted to organic solvents. Though KCN is generally insoluble in organic solvents, the cryptate salt is soluble in many of them. In these cases we do not need an aqueous phase at all but simply add the salt to the organic phase. Suitable cryptands have been used to increase greatly the rates of reactions where F^- , Br^- , I^- , OAc^- , and CN^- are nucleophiles.⁴¹¹ Certain compounds that are not cryptands can act in a similar manner. One example is the podand tris(3,6-dioxaheptyl)amine (**90**), also called TDA-1.⁴¹² Another, not related to the crown ethers, is the pyridyl sulfoxide **91**.⁴¹³

Both of the above-mentioned catalyst types get the anions into the organic phase, but there is another factor as well. There is evidence that sodium and potassium salts of many anions, even if they could be dissolved in organic solvents, would undergo reactions very slowly (dipolar aprotic solvents are exceptions) because in these solvents the anions exist as ion pairs with Na^+ or K^+ and are not free to attack the substrate (p. 350). Fortunately, ion pairing is usually much less with the quaternary ions and with the positive cryptate ions, so the anions in these cases are quite free to attack. Such anions are sometimes referred to as "naked" anions.

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

Although phase transfer catalysis has been most often used for nucleophilic substitutions, it is not confined to these reactions. Any reaction that needs an insoluble anion dissolved in an organic solvent can be accelerated by an appropriate phase transfer catalyst. We shall see some examples in later chapters. In fact, in principle, the method is not even limited to anions, and a small amount of work has been done in transferring cations,⁴¹⁴ radicals, and molecules.⁴¹⁵ The reverse type of phase transfer catalysis has also been reported: transport into the aqueous phase of a reactant that is soluble in organic solvents.⁴¹⁶

The catalysts mentioned above are soluble. Certain cross-linked polystyrene resins, as well as alumina⁴¹⁷ and silica gel, have been used as insoluble phase transfer catalysts. These, called *triphasic catalysts*,⁴¹⁸ have the advantage of simplified product work-up and easy and quantitative catalyst recovery, since the catalyst can easily be separated from the product by filtration.

Another technique used to increase reaction rates is *ultrasound*.⁴¹⁹ In this technique the reaction mixture is subjected to high-energy sound waves, most often 20 KHz, but sometimes higher (a frequency of 20 KHz is about the upper limit of human hearing). When these

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

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

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

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

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

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

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

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

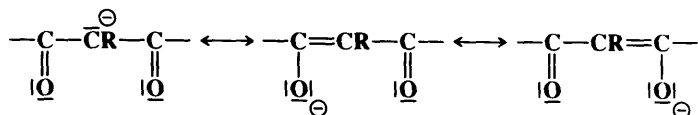
⁴¹⁹For monographs, see Ley; *Low Ultrasound in Synthesis*; Springer: New York, 1989; Mason; Lorimer *Sonochemistry*; Wiley: New York, 1988; Suslick *Ultrasound*; VCH: New York, 1988. For reviews, see Giguere *Org. Synth. Theory Appl.* **1989**, *1*, 103-172; Einhorn; Einhorn; Luche *Synthesis* **1989**,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

waves are passed through a mixture, small bubbles form (*cavitation*). Collapse of these bubbles produces powerful shock waves that greatly increase the temperatures and pressures within these tiny regions, resulting in an increased reaction rate.⁴²⁰ In the common instance where a metal, as a reactant or catalyst, is in contact with a liquid phase, a further effect is that the surface of the metal is cleaned and/or eroded by the ultrasound, allowing the liquid-phase molecules to come into closer contact with the metal atoms. Among the advantages of ultrasound is that it may increase yields, reduce side reactions, and permit the use of lower temperatures and/or pressures. It has been postulated that ultrasound has its best results with reactions that proceed, at least partially, through free-radical intermediates.⁴²¹

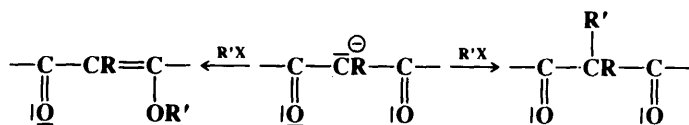
Ambident Nucleophiles. Regioselectivity

Some nucleophiles have a pair of electrons on each of two or more atoms, or canonical forms can be drawn in which two or more atoms bear an unshared pair. In these cases the nucleophile may attack in two or more different ways to give different products. Such reagents are called *ambident nucleophiles*.⁴²² In most cases a nucleophile with two potentially attacking atoms can attack with either of them, depending on conditions, and mixtures are often obtained, though this is not always the case. For example, the nucleophile NCO^- usually gives only isocyanates RNCO and not the isomeric cyanates ROCN .⁴²³ When a reaction can potentially give rise to two or more structural isomers (e.g., ROCN or RNCO) but actually produces only one, the reaction is said to be *regioselective*⁴²⁴ (compare the definitions of stereoselective, p. 137 and enantioselective, p. 119). Some important ambident nucleophiles are:

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



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



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

⁴²⁰Reaction rates can also be increased by running reactions in a microwave oven. For reviews, see Mingos; Baghurst *Chem. Soc. Rev.* **1991**, 20, 1-47; Giguere, Ref. 419.

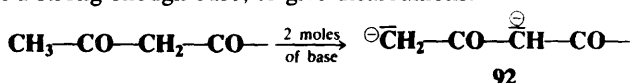
⁴²¹See Einhorn; Einhorn; Dickens; Luche *Tetrahedron Lett.* **1990**, 31, 4129.

⁴²²For a monograph, see Reutov; Beletskaya; Kurts *Ambident Anions*; Plenum: New York, 1983. For a review, see Black *Org. Prep. Proced. Int.* **1989**, 21, 179-217.

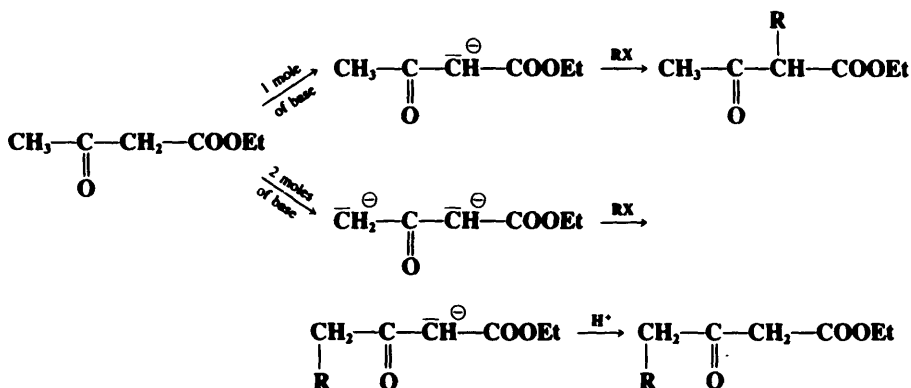
⁴²³Both cyanates and isocyanates have been isolated in treatment of secondary alkyl iodides with NCO^- : Holm; Wentrup *Acta Chem. Scand.* **1966**, 20, 2123.

⁴²⁴This term was introduced by Hassner *J. Org. Chem.* **1968**, 33, 2684.

2. Compounds of the type $\text{CH}_3\text{CO}-\text{CH}_2-\text{CO}-$ can give up two protons, if treated with 2 moles of a strong enough base, to give dicarbanions:



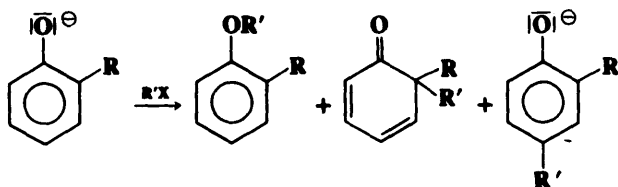
Such ions are ambident nucleophiles, since they have two possible attacking carbon atoms, aside from the possibility of attack by oxygen. In such cases, the attack is virtually always by the more basic carbon.⁴²⁵ Since the hydrogen of a carbon bonded to two carbonyl groups is more acidic than that of a carbon bonded to just one (see Chapter 8), the CH group of **92** is less basic than the CH_2 group, so the latter attacks the substrate. This gives rise to a useful general principle: whenever we desire to remove a proton at a given position for use as a nucleophile but there is a stronger acidic group in the molecule, it may be possible to take off both protons; if it is, then attack is always by the desired position since it is the ion of the weaker acid. On the other hand, if it is desired to attack with the more acidic position, all that is necessary is to remove just one proton.⁴²⁶ For example, ethyl acetoacetate can be alkylated at either the methyl or the methylene group (**0-94**):



3. The CN^- ion. This nucleophile can give nitriles RCN (**0-101**) or isocyanides $\text{RN}\equiv\text{C}$.

4. The nitrite ion. This ion can give nitrite esters $\text{R}-\text{O}-\text{N}=\text{O}$ (**0-32**) or nitro compounds RNO_2 (**0-60**), which are not esters.

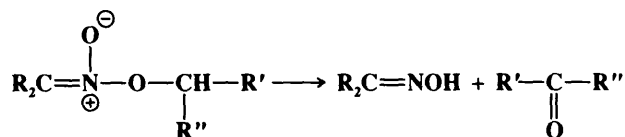
5. Phenoxide ions (which are analogous to enolate ions) can undergo C-alkylation or O-alkylation:



⁴²⁵For an exception, see Trimitsis; Hinkley; TenBrink; Faburada; Anderson; Poli; Christian; Gustafson; Erdman; *Rep J. Org. Chem.* **1963**, 48, 2957.

⁴²⁶The use of this principle was first reported by Hauser; Harris *J. Am. Chem. Soc.* **1958**, 80, 6360. It has since been applied many times. For reviews, see Thompson; Green *Tetrahedron* **1991**, 47, 4223-4285; Kaiser; Petty; Knutson *Synthesis* **1977**, 509-550; Harris; Harris *Org. React.* **1969**, 17, 155-211.

6. Removal of a proton from an aliphatic nitro compound gives a carbanion ($\text{R}_2\text{C}^{\ominus}\text{—NO}_2$) that can be alkylated at oxygen or carbon.⁴²⁷ O-Alkylation gives nitronic esters, which are generally unstable to heat but break down to give an oxime and an aldehyde or ketone.



There are many other ambident nucleophiles.

It would be useful to have general rules as to which atom of an ambident nucleophile will attack a given substrate under a given set of conditions.⁴²⁸ Unfortunately, the situation is complicated by the large number of variables. It might be expected that the more electronegative atom would always attack, but this is often not the case. Where the products are determined by thermodynamic control (p. 214), the principal product is usually the one in which the atom of higher basicity has attacked (i.e., $\text{C} > \text{N} > \text{O} > \text{S}$).⁴²⁹ However, in most reactions, the products are kinetically controlled and matters are much less simple. Nevertheless, the following generalizations can be made, while recognizing that there are many exceptions and unexplained results. As in the discussion of nucleophilicity in general (p. 348), there are two major factors: the polarizability (hard-soft character) of the nucleophile and solvation effects.

1. The principle of hard and soft acids and bases states that hard acids prefer hard bases and soft acids prefer soft bases (p. 263). In an $\text{S}_{\text{N}}1$ mechanism the nucleophile attacks a carbocation, which is a hard acid. In an $\text{S}_{\text{N}}2$ mechanism the nucleophile attacks the carbon atom of a molecule, which is a softer acid. The more electronegative atom of an ambident nucleophile is a harder base than the less electronegative atom. We may thus make the statement: As the character of a given reaction changes from $\text{S}_{\text{N}}1$ -like to $\text{S}_{\text{N}}2$ -like, an ambident nucleophile becomes more likely to attack with its less electronegative atom.⁴³⁰ Therefore, changing from $\text{S}_{\text{N}}1$ to $\text{S}_{\text{N}}2$ conditions should favor C attack by CN^- , N attack by NO_2^- , C attack by enolate or phenoxide ions, etc. As an example, primary alkyl halides are attacked (in protic solvents) by the carbon atom of the anion of $\text{CH}_3\text{COCH}_2\text{COOEt}$, while α -chloro ethers, which react by the $\text{S}_{\text{N}}1$ mechanism, are attacked by the oxygen atom. However, this does not mean that attack is by the less electronegative atom in all $\text{S}_{\text{N}}2$ reactions and by the more electronegative atom in all $\text{S}_{\text{N}}1$ reactions. The position of attack also depends on the nature of the nucleophile, the solvent, the leaving group, and other conditions. The rule merely states that increasing the $\text{S}_{\text{N}}2$ character of the transition state makes attack by the less electronegative atom more likely.

2. All negatively charged nucleophiles must of course have a positive counterion. If this ion is Ag^+ (or some other ion that specifically helps in removing the leaving group, p. 359), rather than the more usual Na^+ or K^+ , then the transition state is more $\text{S}_{\text{N}}1$ -like. Therefore

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

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

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

⁴³⁰This principle, sometimes called *Kornblum's rule*, was first stated by Kornblum; Smiley; Blackwood; Iffland *J. Am. Chem. Soc.* **1955**, 77, 6269.

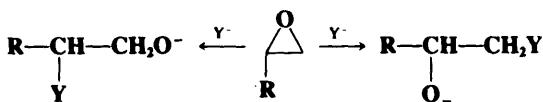
the use of Ag^+ promotes attack at the more electronegative atom. For example, alkyl halides treated with NaCN generally give mostly RCN , but the use of AgCN increases the yield of isocyanides RNC .⁴³¹

3. In many cases the solvent influences the position of attack. The freer the nucleophile, the more likely it is to attack with its more electronegative atom, but the more this atom is encumbered by either solvent molecules or positive counterions, the more likely is attack by the less electronegative atom. In protic solvents, the more electronegative atom is better solvated by hydrogen bonds than the less electronegative atom. In polar aprotic solvents, neither atom of the nucleophile is greatly solvated, but these solvents are very effective in solvating cations. Thus in a polar aprotic solvent the more electronegative end of the nucleophile is freer from entanglement by both the solvent and the cation, so that a change from a protic to a polar aprotic solvent often increases the extent of attack by the more electronegative atom. An example is attack by sodium β -naphthoxide on benzyl bromide, which resulted in 95% O-alkylation in dimethyl sulfoxide and 85% C-alkylation in 2,2,2-trifluoroethanol.⁴³² Changing the cation from Li^+ to Na^+ to K^+ (in nonpolar solvents) also favors O- over C-alkylation⁴³³ for similar reasons (K^+ leaves the nucleophile much freer than Li^+), as does the use of crown ethers, which are good at solvating cations (p. 82).⁴³⁴ Alkylation of the enolate ion of cyclohexanone in the gas phase, where the nucleophile is completely free, showed only O-alkylation and no C-alkylation.⁴³⁵

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

Ambident Substrates

Some substrates (e.g., 1,3-dichlorobutane) can be attacked at two or more positions. We may call these *ambident substrates*. In the example given, there happen to be two leaving groups in the molecule, but there are two kinds of substrates that are inherently ambident (unless symmetrical). One of these, the allylic type, has already been discussed (p. 327). The other is the epoxy (or the similar aziridine or episulfide) substrate.⁴³⁷



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

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

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

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

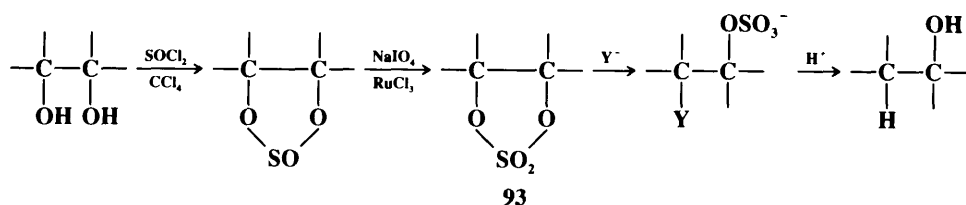
⁴³⁵Jones; Kass; Filley; Barkley; Ellison *J. Am. Chem. Soc.* **1985**, **107**, 109.

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

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

Substitution of the free epoxide, which generally occurs under basic or neutral conditions, usually involves an S_N2 mechanism. Since primary substrates undergo S_N2 attack more readily than secondary, unsymmetrical epoxides are attacked in neutral or basic solution at the less highly substituted carbon, and stereospecifically, with inversion at that carbon. Under acidic conditions, it is the protonated epoxide that undergoes the reaction. Under these conditions the mechanism can be either S_N1 or S_N2 . In S_N1 mechanisms, which favor tertiary carbons, we might expect that attack would be at the more highly substituted carbon, and this is indeed the case. However, even when protonated epoxides react by the S_N2 mechanism, attack is usually at the more highly substituted position.⁴³⁸ Thus, it is often possible to change the direction of ring opening by changing the conditions from basic to acidic or vice versa. In the ring opening of 2,3-epoxy alcohols, the presence of $Ti(O-i-Pr)_4$ increases both the rate and the regioselectivity, favoring attack at C-3 rather than C-2.⁴³⁹ When an epoxide ring is fused to a cyclohexane ring, S_N2 ring opening invariably gives diaxial rather than diequatorial ring opening.⁴⁴⁰

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



REACTIONS

The reactions in this chapter are classified according to the attacking atom of the nucleophile in the order O, S, N, halogen, H, C. For a given nucleophile, reactions are classified by the substrate and leaving group, with alkyl substrates usually considered before acyl ones. Nucleophilic substitutions at a sulfur atom are treated at the end.

Not all the reactions in this chapter are actually nucleophilic substitutions. In some cases the mechanisms are not known with enough certainty even to decide whether a nucleophile, an electrophile, or a free radical is attacking. In other cases (such as **0-76**), conversion of one compound to another can occur by two or even all three of these possibilities, depending on the reagent and the reaction conditions. However, one or more of the nucleophilic mechanisms previously discussed do hold for the overwhelming majority of the reactions in this chapter. For the alkylations, the S_N2 is by far the most common mechanism, as long as R is primary or secondary alkyl. For the acylations, the tetrahedral mechanism is the most common.

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

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

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

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

Oxygen Nucleophiles

A. Attack by OH at an Alkyl Carbon

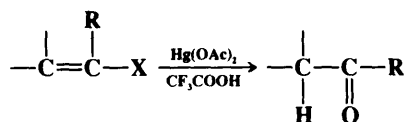
0-1 Hydrolysis of Alkyl Halides

Hydroxy-de-halogenation



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

Vinyl halides are unreactive (p. 341), but they can be hydrolyzed to ketones at room temperature with mercuric trifluoroacetate, or with mercuric acetate in either trifluoroacetic

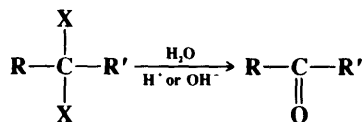


acid or acetic acid containing BF_3 etherate.⁴⁴⁴ Primary bromides and iodides give alcohols when treated with bis(tributyltin)oxide $\text{Bu}_3\text{Sn}-\text{O}-\text{SnBu}_3$ in the presence of silver salts.⁴⁴⁵

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

0-2 Hydrolysis of *gem*-Dihalides

Oxo-de-dihalo-bisubstitution



⁴⁴²It has been proposed that the mechanism of the reaction of primary halides with water is not the ordinary $\text{S}_{\text{N}}2$ mechanism, but that the rate-determining process involves a fluctuation of solvent configuration: Kurz; Kurz *Isr. J. Chem.* **1985**, 26, 339; Kurz; Lee; Love; Rhodes *J. Am. Chem. Soc.* **1986**, 108, 2960.

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

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

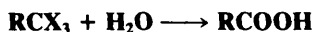
⁴⁴⁵Gingras; Chan *Tetrahedron Lett.* **1989**, 30, 279.

gem-Dihalides can be hydrolyzed with either acid or basic catalysis to give aldehydes or ketones.⁴⁴⁶ Formally, the reaction may be regarded as giving $R-C(OH)XR'$, which is unstable and loses HX to give the carbonyl compound. For aldehydes, strong bases cannot be used, because the product undergoes the aldol reaction (6-39) or the Cannizzaro reaction (9-69).

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

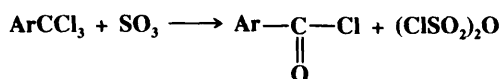
0-3 Hydrolysis of 1,1,1-Trihalides

Hydroxy,oxo-de-trihalo-tersubstitution



This reaction is similar to the previous one. The utility of the method is limited by the lack of availability of trihalides, though these compounds can be prepared by addition of CCl_4 and similar compounds to double bonds (5-33) and by the free-radical halogenation of methyl groups on aromatic rings (4-1). When the hydrolysis is carried out in the presence of an alcohol, a carboxylic ester can be obtained directly.⁴⁴⁷ 1,1-Dichloroalkenes can also be hydrolyzed to carboxylic acids, by treatment with H_2SO_4 . In general 1,1,1-trifluorides do not undergo this reaction,⁴⁴⁸ though exceptions are known.⁴⁴⁹

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



Chloroform is more rapidly hydrolyzed with base than dichloromethane or carbon tetrachloride and gives not only formic acid but also carbon monoxide.⁴⁵¹ Hine⁴⁵² has shown that the mechanism of chloroform hydrolysis is quite different from that of dichloromethane or carbon tetrachloride, though superficially the three reactions appear similar. The first step is the loss of a proton to give CCl_3^- which then loses Cl^- to give dichlorocarbene CCl_2 , which is hydrolyzed to formic acid or carbon monoxide.



This is an example of an $SN1cB$ mechanism (p. 356). The other two compounds react by the normal mechanisms. Carbon tetrachloride cannot give up a proton and dichloromethane is not acidic enough.

OS III, 270; V, 93. Also see OS I, 327.

⁴⁴⁶For a review, see Salomaa, in Patai *The Chemistry of the Carbonyl Group*, vol. 1; Wiley: New York, 1966, pp. 177-210.

⁴⁴⁷See, for example, Le Fave; Scheurer *J. Am. Chem. Soc.* **1950**, 72, 2464.

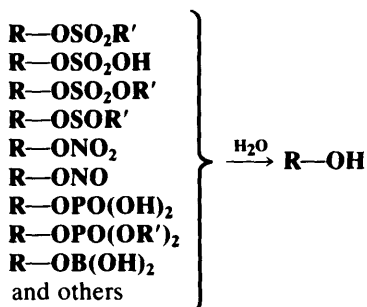
⁴⁴⁸Sheppard; Sharts *Organic Fluorine Chemistry*; W.A. Benjamin: New York, 1969, pp. 410-411; Hudlický, *Chemistry of Organic Fluorine Compounds*, 2nd ed.; Ellis Horwood: Chichester, 1976, pp. 273-274.

⁴⁴⁹See, for example, Kobayashi; Kumadaki *Acc. Chem. Res.* **1978**, 11, 197-204.

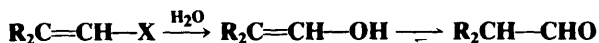
⁴⁵⁰Rondestedt *J. Org. Chem.* **1976**, 41, 3569, 3574, 3576. For another method, see Nakano; Ohkawa; Matsumoto; Nagai *J. Chem. Soc., Chem. Commun.* **1977**, 808.

⁴⁵¹For a review, see Kirmse *Carbene Chemistry*, 2nd ed.; Academic Press: New York, 1971, pp. 129-141.

⁴⁵²Hine *J. Am. Chem. Soc.* **1950**, 72, 2438. Also see le Noble *J. Am. Chem. Soc.* **1965**, 87, 2434.

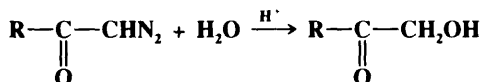
0-4 Hydrolysis of Alkyl Esters of Inorganic Acids**Hydroxy-de-sulfonyloxy-substitution**, etc.

Esters of inorganic acids, including those given above and others, can be hydrolyzed to alcohols. The reactions are most successful when the ester is that of a strong acid, but it can be done for esters of weaker acids by the use of hydroxide ion (a more powerful nucleophile) or acidic conditions (which make the leaving group come off more easily). When vinylic substrates are hydrolyzed, the products are aldehydes or ketones.



These reactions are all considered at one place because they are formally similar, but though some of them involve R—O cleavage and are thus nucleophilic substitutions at a saturated carbon, others involve cleavage of the bond between the inorganic atom and oxygen and are thus nucleophilic substitutions at a sulfur, nitrogen, etc. It is even possible for the same ester to be cleaved at either position, depending on the conditions. Thus benzhydryl *p*-toluenesulfonate ($\text{Ph}_2\text{CHOSOC}_6\text{H}_4\text{CH}_3$) was found to undergo C—O cleavage in HClO_4 solutions and S—O cleavage in alkaline media.⁴⁵³ In general, the weaker the corresponding acid, the less likely is C—O cleavage. Thus, sulfonic acid esters $\text{ROSO}_2\text{R}'$ generally give C—O cleavage,⁴⁵⁴ while nitrous acid esters RONO usually give N—O cleavage.⁴⁵⁵ Esters of sulfonic acids that are frequently hydrolyzed are mentioned on p. 353. For hydrolysis of sulfonic acid esters, see also 0-114.

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

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

Diazo ketones are relatively easy to prepare (see 0-112). When treated with acid, they add a proton to give α -keto diazonium salts, which are hydrolyzed to the alcohols by the $\text{S}_{\text{N}}1$ or $\text{S}_{\text{N}}2$ mechanism.⁴⁵⁶ Relatively good yields of α -hydroxy ketones can be prepared in this

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

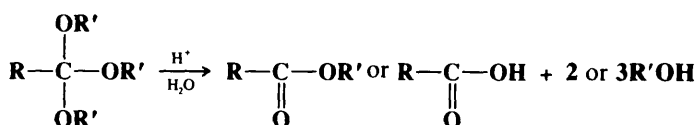
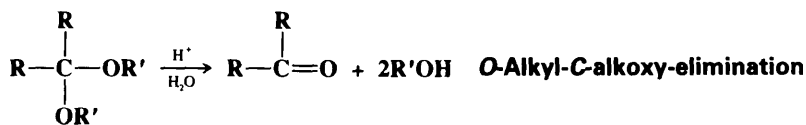
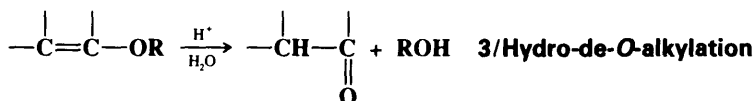
⁴⁵⁴Barnard; Robertson *Can. J. Chem.* **1961**, 39, 881. See also Drabicky; Myhre; Reich; Schmittou *J. Org. Chem.* **1976**, 41, 1472.

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

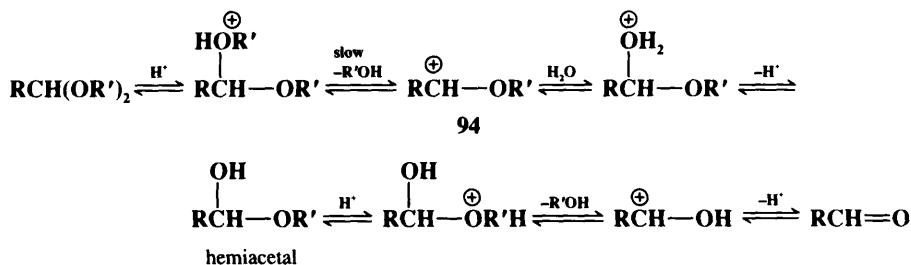
⁴⁵⁶Dahn; Gold *Helv. Chim. Acta* **1963**, 46, 983; Thomas; Leveson *Int. J. Chem. Kinet.* **1983**, 15, 25. For a review of the acid-promoted decomposition of diazo ketones, see Smith; Dieter *Tetrahedron* **1981**, 37, 2407-2439.

way, since the diazonium ion is somewhat stabilized by the presence of the carbonyl group, which discourages N_2 from leaving because that would result in an unstable α -carbonyl carbocation.

0-6 Hydrolysis of Acetals, Enol Ethers, and Similar Compounds⁴⁵⁷



The alkoxyl group OR is not a leaving group, so these compounds must be converted to the conjugate acids before they can be hydrolyzed. Although 100% sulfuric acid and other concentrated strong acids readily cleave simple ethers,⁴⁵⁸ the only acids used preparatively for this purpose are HBr and HI (0-68). However, acetals, ketals, and ortho esters⁴⁵⁹ are easily cleaved by dilute acids. These compounds are hydrolyzed with greater facility because carbocations of the type $RO-\overset{\oplus}{C}$ are greatly stabilized by resonance (p. 170). The reactions therefore proceed by the S_N1 mechanism,⁴⁶⁰ as shown for acetals:⁴⁶¹



This mechanism (which is an S_N1cA or $A1$ mechanism) is the reverse of that for acetal formation by reaction of an aldehyde and an alcohol (6-6). Among the facts supporting the

⁴⁵⁷For reviews, see Bergstrom, in Patai, Ref. 336, pp. 881-902; Cockerill; Harrison, in Patai *The Chemistry of Functional Groups, Supplement A*, pt. 1; Wiley: New York, 1977, pp. 149-329; Cordes; Bull. Chem. Rev. **1974**, 74, 581-603; Cordes *Prog. Phys. Org. Chem.* **1967**, 4, 1-44; Salomaa, Ref. 446, pp. 184-198; Pindur; Müller; Flo; Witzel *Chem. Soc. Rev.* **1987**, 16, 75-87 (ortho esters); Cordes, in Patai, Ref. 197, pp. 632-656 (ortho esters); DeWolfe *Carboxylic Ortho Acid Derivatives*; Academic Press: New York, 1970, pp. 134-146 (ortho esters); Rekasheva *Russ. Chem. Rev.* **1968**, 37, 1009-1022 (enol ethers).

⁴⁵⁸Jaques; Leisten *J. Chem. Soc.* **1964**, 2683. See also Olah; O'Brien *J. Am. Chem. Soc.* **1967**, 89, 1725.

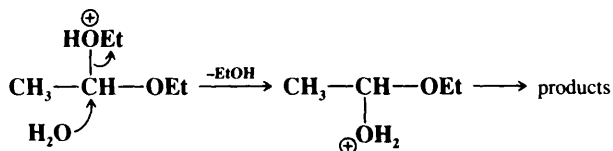
⁴⁵⁹For a review of the reactions of ortho esters, see Pavlova; Davidovich; Rogozhin *Russ. Chem. Rev.* **1986**, 55, 1026-1041.

⁴⁶⁰For a review of the mechanisms of hydrolysis of acetals and thioacetals, see Satchell; Satchell *Chem. Soc. Rev.* **1990**, 19, 55-81.

⁴⁶¹Kreevoy; Taft *J. Am. Chem. Soc.* **1955**, 77, 3146, 5590.

mechanism are:⁴⁶² (1) The reaction proceeds with *specific* H_3O^+ catalysis (see p. 259). (2) It is faster in D_2O . (3) Optically active ROH are not racemized. (4) Even with *t*-butyl alcohol the R—O bond does not cleave, as shown by ^{18}O labeling.⁴⁶³ (5) In the case of acetophenone ketals, the intermediate corresponding to **94** [$\text{ArCMe}(\text{OR})_2^+$] could be trapped with sulfite ions (SO_3^{2-}).⁴⁶⁴ (6) Trapping of this ion did not affect the hydrolysis rate,⁴⁶⁴ so the rate-determining step must come earlier. (7) In the case of 1,1-dialkoxyalkanes, intermediates corresponding to **94** were isolated as stable ions in super-acid solution at -75°C , where their spectra could be studied.⁴⁶⁵ (8) Hydrolysis rates greatly increase in the order $\text{CH}_2(\text{OR}')_2 < \text{RCH}(\text{OR}')_2 < \text{R}_2\text{C}(\text{OR}')_2 < \text{RC}(\text{OR}')_3$, as would be expected for a carbocation intermediate. Formation of **94** is usually the rate-determining step (as marked above), but there is evidence that at least in some cases this step is fast, and the rate-determining step is loss of $\text{R}'\text{OH}$ from the protonated hemiacetal.⁴⁶⁶ Rate-determining addition of water to **94** has also been reported.⁴⁶⁷

While the A1 mechanism shown above operates in most acetal hydrolyses, it has been shown that at least two other mechanisms can take place with suitable substrates.⁴⁶⁸ In one of these mechanisms the second and third of the above steps are concerted, so that the mechanism is $\text{S}_{\text{N}}2\text{cA}$ (or A2). This has been shown, for example, in the hydrolysis of 1,1-diethoxyethane, by isotope effect studies:⁴⁶⁹



In the second mechanism, the first and second steps are concerted. In the case of hydrolysis of 2-(*p*-nitrophenoxy)tetrahydropyran, *general* acid catalysis was shown⁴⁷⁰ demonstrating that the substrate is protonated in the rate-determining step (p. 259). Reactions in which a substrate is protonated in the rate-determining step are called A- $\text{S}_{\text{E}}2$ reactions.⁴⁷¹ However, if protonation of the substrate were all that happens in the slow step, then the proton in the transition state would be expected to lie closer to the weaker base (p. 259). Because the substrate is a much weaker base than water, the proton should be largely transferred. Since the Brønsted coefficient was found to be 0.5, the proton was actually transferred only

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

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

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

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

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

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

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

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

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

⁴⁷¹For a review of A- $\text{S}_{\text{E}}2$ reactions, see Williams; Kreevoy *Adv. Phys. Org. Chem.* **1968**, *6*, 63-101.

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

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

Particularly convenient reagents for acetals are wet silica gel⁴⁷⁴ and Amberlyst-15 (a sulfonic acid-based polystyrene cation exchange resin).⁴⁷⁵ Acetals and ketals can be converted to ketones under nonaqueous conditions by treatment with BF₃ etherate-I⁻ in CHCl₃ or MeCN,⁴⁷⁶ with triphenylphosphine dibromide PPh₃Br₂,⁴⁷⁷ with SmCl₃–Me₃SiCl,⁴⁷⁸ or with Me₃SiI in CH₂Cl₂ or CHCl₃.⁴⁷⁹ They can also be hydrolyzed with LiBF₄ in wet MeCN.⁴⁸⁰

Although acetals, ketals, and ortho esters are easily hydrolyzed by acids, they are extremely resistant to hydrolysis by bases. An aldehyde or ketone can therefore be protected from attack by a base by conversion to the acetal or ketal (**6-6**), and then can be cleaved with acid. Thioacetals, thioketals, *gem*-diamines, and other compounds that contain any two of the groups OR, OCOR, NR₂, NHCOR, SR, and halogen on the same carbon can also be hydrolyzed to aldehydes or ketones, in most cases, by acid treatment. Thioacetals RCH(SR')₂ and thioketals R₂C(SR')₂ are among those compounds generally resistant to acid hydrolysis. Because conversion to these compounds (**6-11**) serves as an important method for protection of aldehydes and ketones, many methods have been devised to cleave them to the parent carbonyl compounds. Among reagents⁴⁸¹ used for this purpose are HgCl₂,⁴⁸² H₂O₂–HCl,⁴⁸³ *t*-BuBr–Me₂SO,⁴⁸⁴ Me₂SO–HCl–dioxane,⁴⁸⁵ Cu(NO₃)₂ on clay (clay-cop),⁴⁸⁶ CuSO₄ on silica gel,⁴⁸⁷ *m*-chloroperoxybenzoic acid and CF₃COOH in CH₂Cl₂,⁴⁸⁸ GaCl₃–H₂O,⁴⁸⁹ phenyl dichlorophosphate–DMF–NaI,⁴⁹⁰ bis(trifluoroacetoxy)iodobenzene (CF₃CO₂)₂IPh,⁴⁹¹ diphosphorus tetraiodide P₂I₄ in Ac₂O,⁴⁹² and benzeneseleninic anhydride (PhSeO)₂O.⁴⁹³ Electrochemical methods have also been used.⁴⁹⁴

⁴⁷²See Bergstrom; Cashen; Chiang; Kresge *J. Org. Chem.* **1979**, *44*, 1639; Ahmad; Bergstrom; Cashen; Chiang; Kresge; McClelland; Powell *J. Am. Chem. Soc.* **1979**, *101*, 2669; Chiang; Kresge; Lahti; Weeks *J. Am. Chem. Soc.* **1983**, *105*, 6852; Santry; McClelland *J. Am. Chem. Soc.* **1983**, *105*, 6138; Fife; Przysas *J. Chem. Soc., Perkin Trans. 2* **1987**, 143.

⁴⁷³See, for example, Kirby *Acc. Chem. Res.* **1984**, *17*, 305-311; Bouab; Lamaty; Moreau *Can. J. Chem.* **1985**, *63*, 816. See, however, Ratcliffe; Mootoo; Andrews; Fraser-Reid *J. Am. Chem. Soc.* **1989**, *111*, 7661.

⁴⁷⁴Huet; Lechevallier; Pellet; Conia *Synthesis* **1978**, 63.

⁴⁷⁵Coppola *Synthesis* **1984**, 1021.

⁴⁷⁶Mandal; Shrotri; Ghogare *Synthesis* **1986**, 221.

⁴⁷⁷Wagner; Heitz; Mioskowski *J. Chem. Soc., Chem. Commun.* **1989**, 1619.

⁴⁷⁸Ukaji; Koumoto; Fujisawa *Chem. Lett.* **1989**, 1623.

⁴⁷⁹Jung; Andrus; Ornstein *Tetrahedron Lett.* **1977**, 4175. See also Balme; Goré *J. Org. Chem.* **1983**, *48*, 3336.

⁴⁸⁰Lipshutz; Harvey *Synth. Commun.* **1982**, *12*, 267.

⁴⁸¹For references to other reagents, see Gröbel; Seebach *Synthesis* **1977**, 357-402, pp. 359-367; Cussans; Ley; Barton *J. Chem. Soc., Perkin Trans. 1* **1980**, 1654.

⁴⁸²Corey; Erickson *J. Org. Chem.* **1971**, *36*, 3553. For a mechanistic study, see Satchell; Satchell *J. Chem. Soc., Perkin Trans. 2* **1987**, 513.

⁴⁸³Olah; Narang; Salem *Synthesis* **1980**, 657, 659.

⁴⁸⁴Olah; Mehrotra; Narang *Synthesis* **1982**, 151.

⁴⁸⁵Prato; Quintily; Scorrano; Sturaro *Synthesis* **1982**, 679.

⁴⁸⁶Laszlo; Cornélis *Aldrichimica Acta* **1988**, *21*, 97-103, p. 101.

⁴⁸⁷Caballero; Gros *J. Chem. Res. (S)* **1989**, 320.

⁴⁸⁸Cossy *Synthesis* **1987**, 1113.

⁴⁸⁹Saigo; Hashimoto; Kihara; Umehara; Hasegawa *Chem. Lett.* **1990**, 831.

⁴⁹⁰Liu; Wiszniewski *Tetrahedron Lett.* **1988**, *29*, 5471.

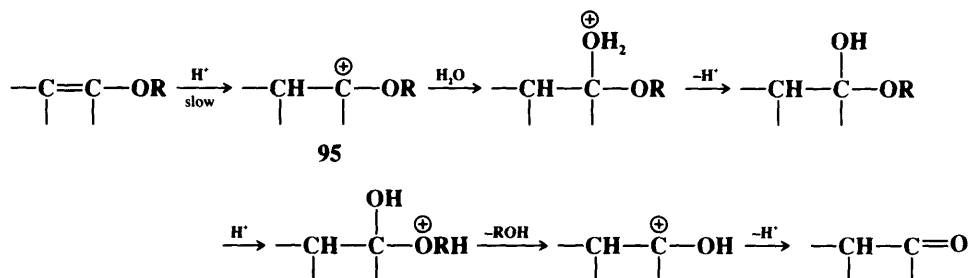
⁴⁹¹Stork; Zhao *Tetrahedron Lett.* **1989**, *30*, 287.

⁴⁹²Shigemasa; Ogawa; Sashiwa; Saimoto *Tetrahedron Lett.* **1989**, *30*, 1277.

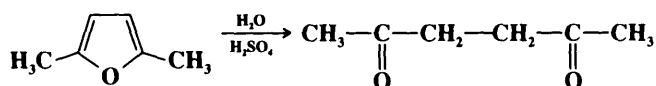
⁴⁹³Cussans; Ley; Barton, Ref. 481.

⁴⁹⁴See Platen; Steckhan *Chem. Ber.* **1984**, *117*, 1679; Schulz-von Itter; Steckhan *Tetrahedron* **1987**, *43*, 2475.

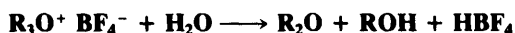
Enol ethers are readily hydrolyzed by acids; the rate-determining step is protonation of the substrate. However, protonation does not take place at the oxygen but at the β carbon,⁴⁹⁵ because that gives rise to the stable carbocation **95**.⁴⁹⁶ After that the mechanism is similar to the A1 mechanism given above for the hydrolysis of acetals.



Among the facts supporting this mechanism (which is an A-SE2 mechanism because the substrate is protonated in the rate-determining step) are: (1) ^{18}O labeling shows that in ROCH=CH_2 it is the vinyl-oxygen bond and not the RO bond that cleaves;⁴⁹⁷ (2) the reaction is subject to general acid catalysis;⁴⁹⁸ (3) there is a solvent isotope effect when D_2O is used.⁴⁹⁸ Enamines are also hydrolyzed by acids (see **6-2**); the mechanism is similar. Ketene dithioacetals $\text{R}_2\text{C=C}(\text{SR}')_2$ also hydrolyze by a similar mechanism, except that the initial protonation step is partially reversible.⁴⁹⁹ Furans represent a special case of enol ethers that are cleaved by acid to give 1,4 diones. Thus



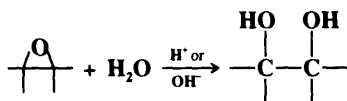
Oxonium ions are cleaved by water to give an alcohol and an ether:



OS **I**, 67, 205; **II**, 302, 305, 323; **III**, 37, 127, 465, 470, 536, 541, 641, 701, 731, 800; **IV**, 302, 499, 660, 816, 903; **V**, 91, 292, 294, 703, 716, 937, 967, 1088; **VI**, 64, 109, 312, 316, 361, 448, 496, 683, 869, 893, 905, 996; **VII**, 12, 162, 241, 249, 251, 263, 271, 287, 381, 495; **68**, 25, 92; **69**, 31, 55, 148.

0-7 Hydrolysis of Epoxides

(3) OC-*seco*-hydroxy-de-alkoxy-substitution



⁴⁹⁵Jones; Wood *J. Chem. Soc.* **1964**, 5400; Okuyama; Fueno; Furukawa *Bull. Chem. Soc. Jpn.* **1970**, 43, 3256; Kreevoy; Eliason *J. Phys. Chem.* **1969**, 72, 1313; Lienhard; Wang *J. Am. Chem. Soc.* **1969**, 91, 1146; Kresge; Chen *J. Am. Chem. Soc.* **1972**, 94, 2818; Burt; Chiang; Kresge; Szilagyi *Can. J. Chem.* **1984**, 62, 74.

⁴⁹⁶See Chwang; Kresge; Wiseman *J. Am. Chem. Soc.* **1979**, 101, 6972.

⁴⁹⁷Kiprianova; Rekasheva *Dokl. Akad. Nauk SSSR* **1962**, 142, 589.

⁴⁹⁸Fife *J. Am. Chem. Soc.* **1965**, 87, 1084; Salomaa; Kankaanperä; Lajunen *Acta Chem. Scand.* **1966**, 20, 1790; Kresge; Chiang *J. Chem. Soc. B* **1967**, 53, 58; Kresge; Yin *Can. J. Chem.* **1987**, 65, 1753.

⁴⁹⁹For a review, see Okuyama *Acc. Chem. Res.* **1986**, 19, 370-376.

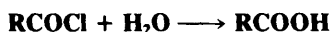
The hydrolysis of epoxides is a convenient method for the preparation of *vic*-diols. The reaction is catalyzed by acids or bases (see discussion of the mechanism on p. 369). Among acid catalysts the reagent of choice is perchloric acid, since side reactions are minimized with this reagent.⁵⁰⁰ Dimethyl sulfoxide is a superior solvent for the alkaline hydrolysis of epoxides.⁵⁰¹

OS V, 414.

B. Attack by OH at an Acyl Carbon

0-8 Hydrolysis of Acyl Halides

Hydroxy-de-halogenation



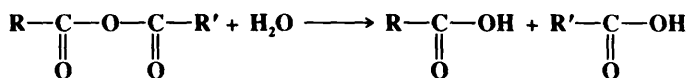
Acyl halides are so reactive that hydrolysis is easily carried out. In fact, most simple acyl halides must be stored under anhydrous conditions lest they react with water in the air. Consequently, water is usually a strong enough nucleophile for the reaction, though in difficult cases hydroxide ion may be required. The reaction is seldom synthetically useful, because acyl halides are normally prepared from acids. The reactivity order is $\text{F} < \text{Cl} < \text{Br} < \text{I}$.⁵⁰² If a carboxylic acid is used as the nucleophile, an exchange may take place (see 0-74). The mechanism⁵⁰² of hydrolysis can be either $\text{S}_{\text{N}}1$ or tetrahedral, the former occurring in highly polar solvents and in the absence of strong nucleophiles.⁵⁰³ There is also evidence for the $\text{S}_{\text{N}}2$ mechanism in some cases.⁵⁰⁴

Hydrolysis of acyl halides is not usually catalyzed by acids, except for acyl fluorides, where hydrogen bonding can assist in the removal of F.⁵⁰⁵

OS II, 74.

0-9 Hydrolysis of Anhydrides

Hydroxy-de-acyloxy-substitution



Anhydrides are somewhat more difficult to hydrolyze than acyl halides, but here too water is usually a strong enough nucleophile. The mechanism is usually tetrahedral. Only under acid catalysis does the $\text{S}_{\text{N}}1$ mechanism occur and seldom even then.⁵⁰⁶ Anhydride hydrolysis can also be catalyzed by bases. Of course, OH^- attacks more readily than water, but other bases can also catalyze the reaction. This phenomenon, called *nucleophilic catalysis* (p. 334), is actually the result of two successive tetrahedral mechanisms. For example, pyridine catalyzes the hydrolysis of acetic anhydride in this manner.⁵⁰⁷

⁵⁰⁰Fieser; Fieser *Reagents for Organic Synthesis*, vol. 1; Wiley: New York, 1967, p. 796.

⁵⁰¹Berti; Macchia; Macchia *Tetrahedron Lett.* **1965**, 3421.

⁵⁰²For a review, see Talbot, Ref. 197, pp. 226-257. For a review of the mechanisms of reactions of acyl halides with water, alcohols, and amines, see Kivinen, in Patai *The Chemistry of Acyl Halides*; Wiley: New York, 1972, pp. 177-230.

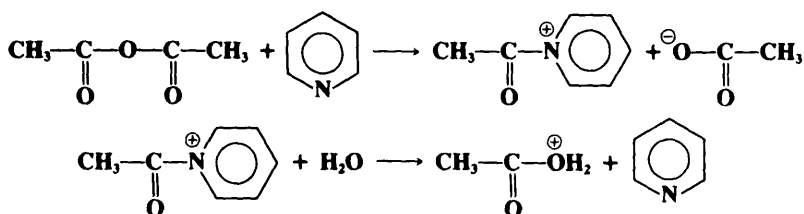
⁵⁰³Bender; Chen *J. Am. Chem. Soc.* **1963**, 85, 30. See also Song; Jencks *J. Am. Chem. Soc.* **1989**, 111, 8470; Bentley; Koo; Norman *J. Org. Chem.* **1991**, 56, 1604.

⁵⁰⁴Bentley; Carter; Harris, Ref. 198; Guthrie; Pike, Ref. 198. See also Lee; Sung; Uhm; Ryu *J. Chem. Soc., Perkin Trans. 2* **1989**, 1697.

⁵⁰⁵Bevan; Hudson *J. Chem. Soc.* **1953**, 2187; Satchell *J. Chem. Soc.* **1963**, 555.

⁵⁰⁶Satchell *Q. Rev., Chem. Soc.* **1963**, 17, 160-203, pp. 172-173. For a review of the mechanism, see Talbot, Ref. 197, pp. 280-287.

⁵⁰⁷Butler; Gold *J. Chem. Soc.* **1961**, 4362; Fersht; Jencks *J. Am. Chem. Soc.* **1970**, 92, 5432, 5442; Deady; Finlayson *Aust. J. Chem.* **1983**, 36, 1951.

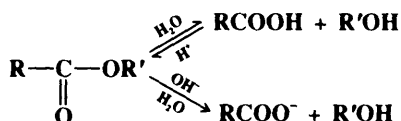


Many other nucleophiles similarly catalyze the reaction.

OS I, 408; II, 140, 368, 382; IV, 766; V, 8, 813.

0-10 Hydrolysis of Carboxylic Esters

Hydroxy-de-alkoxylation



Ester hydrolysis is usually catalyzed by acids or bases. Since OR is a much poorer leaving group than halide or OCOR, water alone does not hydrolyze most esters. When bases catalyze the reaction, the attacking species is the more powerful nucleophile OH^- . This reaction is called *saponification* and gives the salt of the acid. Acids catalyze the reaction by making the carbonyl carbon more positive and therefore more susceptible to attack by the nucleophile. Both reactions are equilibrium reactions, so they are practicable only when there is a way of shifting the equilibrium to the right. Since formation of the salt does just this, ester hydrolysis is almost always done for preparative purposes in basic solution, unless the compound is base-sensitive. Ester hydrolysis can also be catalyzed⁵⁰⁸ by metal ions, by cyclodextrins,⁵⁰⁹ by enzymes,⁵¹⁰ and by nucleophiles (see 0-9).¹⁹⁷ Among other compounds used to cleave carboxylic esters have been methanesulfonic acid,⁵¹¹ guanidine,⁵¹² Dowex-50,⁵¹³ Me_3SiI ,⁵¹⁴ $\text{MeSiCl}_3\text{--NaI}$,⁵¹⁵ and KOSiMe_3 .⁵¹⁶ Phenolic esters can be similarly cleaved; in fact the reaction is usually faster for these compounds.⁵¹⁷ Lactones also undergo the reaction⁵¹⁸ (though if the lactone is five- or six-membered, the hydroxy acid often spontaneously relactonizes) and thiol esters (RCOSR') give thiols $\text{R}'\text{SH}$. Sterically hindered esters are hydrolyzed with difficulty (p. 340), though this can be accomplished at room temperature with "anhydrous hydroxide," generated via the reaction of 2 moles of *t*-BuOK with 1 mole

⁵⁰⁸For a list of catalysts and reagents that have been used to convert carboxylic esters to acids, with references, see Larock *Comprehensive Organic Transformations*; VCH: New York, 1989, pp. 981-985.

⁵⁰⁹See Bender; Komiyama *Cyclodextrin Chemistry*; Springer: New York, 1978, pp. 34-41. The mechanism is shown in Saenger *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 344-362 [*Angew. Chem.* **92**, 343-361].

⁵¹⁰For reviews of ester hydrolysis catalyzed by pig liver esterase, see Zhu; Tedford *Tetrahedron* **1990**, *46*, 6587-6611; Ohno; Otsuka *Org. React.* **1989**, *37*, 1-55. For reviews of enzymes as catalysts in synthetic organic chemistry, see Wong *Chemtracts: Org. Chem.* **1990**, *3*, 91-111, *Science* **1989**, *244*, 1145-1152; Whitesides; Wong *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 617-638 [*Angew. Chem.* **97**, 617-638].

⁵¹¹Loev *Chem. Ind. (London)* **1964**, 193.

⁵¹²Kunesch; Miet; Poisson *Tetrahedron Lett.* **1987**, *28*, 3569.

⁵¹³Basu; Sarkar; Ranu *Synth. Commun.* **1989**, *19*, 627.

⁵¹⁴Ho; Olah *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 774 [*Angew. Chem.* **88**, 847]; Jung; Lyster *J. Am. Chem. Soc.* **1977**, *99*, 968. For a review of this reagent, see Olah; Narang *Tetrahedron* **1982**, *38*, 2225-2277.

⁵¹⁵Olah; Husain; Singh; Mehrotra *J. Org. Chem.* **1983**, *48*, 3667.

⁵¹⁶Laganis; Chenard *Tetrahedron Lett.* **1984**, *25*, 5831.

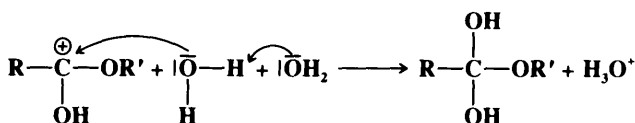
⁵¹⁷For a method of hydrolyzing phenolic esters in the presence of other esters, see Blay; Cardona; Garcia; Pedro *Synthesis* **1989**, 438.

⁵¹⁸For a review of the mechanisms of lactone hydrolysis, see Kaiser; Kézdy *Prog. Bioorg. Chem.* **1976**, *4*, 239-267, pp. 254-265.

of water.⁵¹⁹ Hindered esters can also be cleaved with *n*-propyllithium.⁵²⁰ For esters insoluble in water the rate of two-phase ester saponification can be greatly increased by the application of ultrasound.⁵²¹ Phase-transfer techniques have also been applied.⁵²²

Ingold⁵²³ has classified the acid- and base-catalyzed hydrolyses of esters (and the formation of esters, since these are reversible reactions and thus have the same mechanisms) into eight possible mechanisms (Table 10.14), depending on the following criteria: (1) acid- or base-catalyzed, (2) unimolecular or bimolecular, and (3) acyl cleavage or alkyl cleavage.⁵²⁵ All eight of these are S_N1, S_N2, or tetrahedral mechanisms. The acid-catalyzed mechanisms are shown with reversible arrows. They are not only reversible but symmetrical; that is, the mechanisms for ester formation are exactly the same as for hydrolysis, except that H replaces R. Internal proton transfers, such as shown for **B** and **C**, may not actually be direct but may take place through the solvent. There is much physical evidence to show that esters are initially protonated on the carbonyl and not on the alkyl oxygen (Chapter 8, Ref. 17). We have nevertheless shown the AAC1 mechanism as proceeding through the ether-protonated intermediate **A**, since it is difficult to envision OR' as a leaving group here. It is of course possible for a reaction to proceed through an intermediate even if only a tiny concentration is present. The designations AAC1, etc., are those of Ingold. The AAC2 and AAC1 mechanisms are also called A2 and A1, respectively. It may be noted that the AAC1 mechanism is actually the same as the S_N1cA mechanism for this type of substrate and that AAL2 is analogous to S_N2cA. Some authors use A1 and A2 to refer to all types of nucleophilic substitution in which the leaving group first acquires a proton. The base-catalyzed reactions are not shown with reversible arrows, since they are reversible only in theory and not in practice. Hydrolyses taking place under neutral conditions are classified as B mechanisms.

Of the eight mechanisms, seven have actually been observed in hydrolysis of carboxylic esters. The one that has not been observed is the BAC1 mechanism.⁵²⁶ The most common mechanisms are the BAC2 for basic catalysis and the AAC2⁵²⁷ for acid catalysis, that is, the two tetrahedral mechanisms. Both involve acyl-oxygen cleavage. The evidence is: (1) hydrolysis with H₂¹⁸O results in the ¹⁸O appearing in the acid and not in the alcohol;⁵²⁸ (2) esters with chiral R' groups give alcohols with *retention* of configuration;⁵²⁹ (3) allylic R' gives no allylic rearrangement;⁵³⁰ (4) neopentyl R' gives no rearrangement;⁵³¹ all these facts indicate that the O—R' bond is not broken. It has been concluded that two molecules of water are required in the AAC2 mechanism.



⁵¹⁹Gassman; Schenk *J. Org. Chem.* **1977**, 42, 918.

⁵²⁰Lion; Dubois; MacPhee; Bonzougou *Tetrahedron* **1979**, 35, 2077.

⁵²¹Moon; Duchin; Cooney *Tetrahedron Lett.* **1979**, 3917.

⁵²²Dehmlo; Naranjo *J. Chem. Res., (S)* **1979**, 238; Loupy; Pedoussaut; Sansoulet *J. Org. Chem.* **1986**, 51, 740.

⁵²³Ingold, Ref. 366, pp. 1129-1131.

⁵²⁴As given here, the IUPAC designations for BAC1 and BAL1 are the same, but Rule A.2 adds further symbols so that they can be distinguished: Su-AL for BAL1 and Su-AC for BAC1. See the IUPAC rules: Guthrie *Pure Appl. Chem.* **1989**, 61, 23-56, p. 49.

⁵²⁵For reviews of the mechanisms of ester hydrolysis and formation, see Kirby, in Bamford; Tipper, Ref. 178, vol. 10, 1972, pp. 57-207; Euranto, in Patai, Ref. 197, pp. 505-588.

⁵²⁶This is an S_N1 mechanism with OR' as leaving group, which does not happen.

⁵²⁷For a discussion of this mechanism with specific attention to the proton transfers involved, see Zimmermann; Rudolph *Angew. Chem. Int. Ed. Engl.* **1965**, 4, 40-49 [*Angew. Chem.* 77, 65-74].

⁵²⁸For one of several examples, see Polanyi; Szabo *Trans. Faraday Soc.* **1934**, 30, 508.

⁵²⁹Holmberg *Ber.* **1912**, 45, 2997.

⁵³⁰Ingold; Ingold *J. Chem. Soc.* **1932**, 758.

⁵³¹Norton; Quayle *J. Am. Chem. Soc.* **1940**, 62, 1170.

TABLE 10.14 Classification of the eight mechanisms for ester hydrolysis and formation^{52,3}

Name		Type	Mechanism
Ingold	IUPAC ^{52,4}		
Acid catalysts			
AAC1	$A_h + D_N + A_N + D_h$	SN1	$\text{R}-\text{C}(=\text{O})-\text{OR}' \xrightleftharpoons{\text{H}^+} \text{R}-\text{C}(=\text{O})-\text{OR}'^+ \xrightleftharpoons[\text{R'OH}]{\text{slow}} \text{R}-\text{C}(=\text{O})-\text{OH}_2^+ \xrightleftharpoons[\text{slow}]{\text{H}_2\text{O}} \text{R}-\text{C}(=\text{O})-\text{OH} \xrightleftharpoons[\text{H}^+]{\text{R}-\text{C}(=\text{O})-\text{OH}} \text{R}-\text{C}(=\text{O})-\text{OH}$
			A
AAC2	$A_h + A_N + A_h D_h + D_N + D_h$	Tetra-hedral	$\text{R}-\text{C}(=\text{O})-\text{OR}' \xrightleftharpoons{\text{H}^+} \text{R}-\text{C}(=\text{O})-\text{OR}'^+ \xrightleftharpoons[\text{slow}]{\text{H}_2\text{O}} \text{R}-\text{C}(\text{OH})(\text{OR}')-\text{OH}_2^+ \xrightleftharpoons[\text{R'OH}]{\text{slow}} \text{R}-\text{C}(\text{OH})(\text{OR}')-\text{OH} \xrightleftharpoons[\text{H}^+]{\text{R}-\text{C}(\text{OH})(\text{OR}')-\text{OH}} \text{R}-\text{C}(=\text{O})-\text{OH}$
			B C
AAL1	$A_h + D_N + A_N + D_h$	SN1	$\text{R}-\text{C}(=\text{O})-\text{OR}' \xrightleftharpoons{\text{H}^+} \text{R}-\text{C}(=\text{O})-\text{OR}'^+ \xrightleftharpoons[\text{slow}]{\text{H}_2\text{O}} \text{R}-\text{C}(=\text{O})-\text{OH} \xrightleftharpoons[\text{H}^+]{\text{R}-\text{C}(=\text{O})-\text{OH}} \text{R}-\text{C}(=\text{O})-\text{OH}$
AAL2	$A_h + A_h D_N + D_h$	SN2	$\text{R}-\text{C}(=\text{O})-\text{OR}' \xrightleftharpoons{\text{H}^+} \text{R}-\text{C}(=\text{O})-\text{OR}'^+ \xrightleftharpoons[\text{H}^+]{\text{H}_2\text{O}} \text{R}-\text{C}(\text{OH})(\text{OR}')-\text{OH} \xrightleftharpoons[\text{R'OH}]{\text{H}^+} \text{R}-\text{C}(=\text{O})-\text{OH}$
BAC1	$D_N + A_N + A_h D_h$	SN1	$\text{R}-\text{C}(=\text{O})-\text{OR}' \xrightarrow[\text{slow}]{\text{OH}^-} \text{R}-\text{C}(=\text{O})-\text{OR}'^- \xrightarrow{\text{OH}^-} \text{R}-\text{C}(=\text{O})-\text{OH} + \text{OR}'^- \longrightarrow \text{R}-\text{C}(=\text{O})-\text{O}^- + \text{R'OH}$
BAC2	$A_N + D_N + A_h D_h$	Tetra-hedral	$\text{R}-\text{C}(=\text{O})-\text{OR}' \xrightarrow[\text{slow}]{\text{OH}^-} \text{R}-\text{C}(\text{OH})(\text{OR}')-\text{O}^- \longrightarrow \text{R}-\text{C}(=\text{O})-\text{OH} + \text{OR}'^- \longrightarrow \text{R}-\text{C}(=\text{O})-\text{O}^- + \text{R'OH}$
BAL1	$D_N + A_N + A_h D_h$	SN1	$\text{R}-\text{C}(=\text{O})-\text{OR}' \xrightarrow[\text{slow}]{\text{OH}^-} \text{R}-\text{C}(=\text{O})-\text{O}^- + \text{R}' \xrightarrow[\text{H}_2\text{O}]{\text{R'OH}} \text{R}-\text{C}(=\text{O})-\text{OH}$
BAL2	$A_h D_N$	SN2	$\text{R}-\text{C}(=\text{O})-\text{OR}' \xrightarrow[\text{slow}]{\text{OH}^-} \text{R}-\text{C}(=\text{O})-\text{O}^- + \text{R'OH}$
Basic catalysts			

If this is so, the protonated derivatives **B** and **C** would not appear at all. This conclusion stems from a value of w (see p. 257) of about 5, indicating that water acts as a proton donor here as well as a nucleophile.⁵³² Termolecular processes are rare, but in this case the two water molecules are already connected by a hydrogen bond. (A similar mechanism, called BAC3, also involving two molecules of water, has been found for esters that hydrolyze without a catalyst.⁵³³ Such esters are mostly those containing halogen atoms in the R group.)

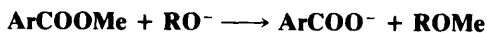
The other mechanism involving acyl cleavage is the AAC1 mechanism. This is rare, being found only where R is very bulky, so that bimolecular attack is sterically hindered, and only in ionizing solvents. The mechanism has been demonstrated for esters of 2,4,6-trimethylbenzoic acid (mesitoic acid). This acid depresses the freezing point of sulfuric acid four times as much as would be predicted from its molecular weight, which is evidence for the equilibrium



In a comparable solution of benzoic acid the freezing point is depressed only twice the predicted amount, indicating only a normal acid-base reaction. Further, a sulfuric acid solution of methyl mesitoate when poured into water gave mesitoic acid, while a similar solution of methyl benzoate similarly treated did not.⁵³⁴ The AAC1 mechanism is also found when acetates of phenols or of primary alcohols are hydrolyzed in concentrated (more than 90%) H_2SO_4 (the mechanism under the more usual dilute acid conditions is the normal AAC2).⁵³⁵

The mechanisms involving alkyl-oxygen cleavage are ordinary $\text{S}_{\text{N}}1$ and $\text{S}_{\text{N}}2$ mechanisms in which OCOR (an acyloxy group) or its conjugate acid is the leaving group. Two of the four mechanisms, the BAL1 and AAL1 mechanisms, occur most readily when R' comes off as a stable carbocation, that is, when R' is tertiary alkyl, allylic, benzylic, etc. For acid catalysis, most esters with this type of alkyl group (especially tertiary alkyl) cleave by this mechanism, but even for these substrates, the BAL1 mechanism occurs only in neutral or weakly basic solution, where the rate of attack by OH^- is so slowed that the normally slow (by comparison) unimolecular cleavage takes over. These two mechanisms have been established by kinetic studies, ^{18}O labeling, and isomerization of R'.⁵³⁶ Secondary and benzylic acetates hydrolyze by the AAC2 mechanism in dilute H_2SO_4 , but in concentrated acid the mechanism changes to AAL1.⁵³⁵ Despite its designation, the BAL1 mechanism is actually uncatalyzed (as is the unknown BAC1 mechanism).

The two remaining mechanisms, BAL2 and AAL2, are very rare, the BAL2 because it requires OH^- to attack an alkyl carbon when an acyl carbon is also available, and the AAL2 because it requires water to be a nucleophile in an $\text{S}_{\text{N}}2$ process. Both have been observed, however. The BAL2 has been seen in the hydrolysis of β -lactones under neutral conditions⁵³⁷ (because cleavage of the C—O bond in the transition state opens the four-membered ring and relieves strain), the alkaline hydrolysis of methyl 2,4,6-tri-*t*-butyl benzoate,⁵³⁸ and in the unusual reaction⁵³⁹



⁵³²Martin *J. Am. Chem. Soc.* **1962**, *84*, 4130. See also Lane; Cheung; Dorsey *J. Am. Chem. Soc.* **1968**, *90*, 6492; Yates; McClelland *J. Am. Chem. Soc.* **1967**, *89*, 2686; Yates *Acc. Chem. Res.* **1971**, *6*, 136-144; Huskey; Warren; Hogg *J. Org. Chem.* **1981**, *46*, 59.

⁵³³Euranto; Kanerva; Cleve *J. Chem. Soc., Perkin Trans. 2* **1984**, 2085; Neuvonen *J. Chem. Soc., Perkin Trans. 2* **1986**, 1141; Euranto; Kanerva *Acta Chem. Scand., Ser. B* **1988**, 42 717.

⁵³⁴Treffers; Hammett *J. Am. Chem. Soc.* **1937**, *59*, 1708. For other evidence for this mechanism, see Bender; Chen *J. Am. Chem. Soc.* **1963**, *85*, 37.

⁵³⁵Yates, Ref. 532; Al-Shalchi; Selwood; Tillett *J. Chem. Res. (S)* **1985**, 10.

⁵³⁶For discussions, see Kirby, Ref. 525, pp. 86-101; Ingold, Ref. 366, pp. 1137-1142, 1157-1163.

⁵³⁷Cowdrey; Hughes; Ingold; Masterman; Scott *J. Chem. Soc.* **1937**, 1264; Long; Purchase *J. Am. Chem. Soc.* **1950**, *73*, 3267.

⁵³⁸Barclay; Hall; Cooke *Can. J. Chem.* **1962**, *40*, 1981.

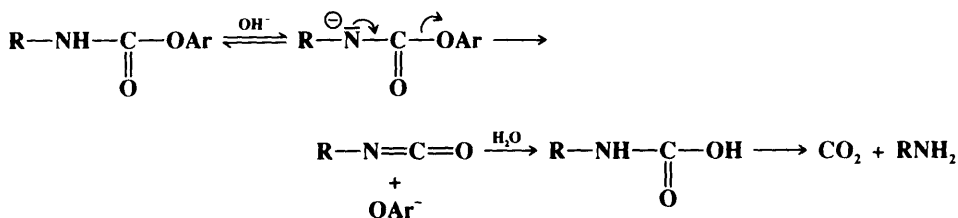
⁵³⁹Sneen; Rosenberg *J. Org. Chem.* **1961**, *26*, 2099. See also Müller; Siegfried *Helv. Chim. Acta* **1974**, *57*, 987.

When it does occur, the BAL2 mechanism is easy to detect, since it is the only one of the base-catalyzed mechanisms that requires inversion at R'. However, in the last example given, the mechanism is evident from the nature of the product, since the ether could have been formed in no other way. The AAL2 mechanism has been reported in the acid cleavage of γ -lactones.^{539a}

To sum up the acid-catalysis mechanisms, AAC2 and AAL1 are the common mechanisms, the latter for R' that give stable carbocations, the former for practically all the rest. AAC1 is rare, being found mostly with strong acids and sterically hindered R. AAL2 is even rarer. For basic catalysis, BAC2 is almost universal; BAL1 occurs only with R' that give stable carbocations and then only in weakly basic or neutral solutions; BAL2 is very rare; and BAC1 has never been observed.

The above results pertain to reactions in solution. In the gas phase⁵⁴⁰ reactions can take a different course, as illustrated by the reaction of carboxylic esters with MeO^- , which in the gas phase was shown to take place only by the BAL2 mechanism,⁵⁴¹ even with aryl esters,⁵⁴² where this means that an $\text{S}_{\text{N}}2$ mechanism takes place at an aryl substrate. However, when the gas-phase reaction of aryl esters was carried out with MeO^- ions, each of which was solvated with a single molecule of MeOH or H_2O , the BAC2 mechanism was observed.⁵⁴²

In the special case of alkaline hydrolysis of N-substituted aryl carbamates, there is another mechanism⁵⁴³ involving elimination-addition:⁵⁴⁴



This mechanism does not apply to unsubstituted or N,N-disubstituted aryl carbamates, which hydrolyze by the normal mechanisms. Carboxylic esters substituted in the α position by an electron-withdrawing group (e.g., CN or COOEt) can also hydrolyze by a similar mechanism involving a ketene intermediate.⁵⁴⁵ These elimination-addition mechanisms usually are referred to as E1cB mechanisms, because that is the name given to the elimination portion of the mechanism (p. 991).

The acid-catalyzed hydrolysis of enol esters $\text{RCOOCR}'=\text{CR}_2'$ can take place either by the normal AAC2 mechanism or by a mechanism involving initial protonation on the double-bond carbon, similar to the mechanism for the hydrolysis of enol ethers given in 0-6,⁵⁴⁶

^{539a}Moore; Schwab *Tetrahedron Lett.* **1991**, 32, 2331.

⁵⁴⁰Takashima; José; do Amaral; Riveros *J. Chem. Soc. Chem. Commun.* **1983**, 1255.

⁵⁴¹Comisarow *Can. J. Chem.* **1977**, 55, 171.

⁵⁴²Fukuda; McIver *J. Am. Chem. Soc.* **1979**, 101, 2498.

⁵⁴³For a review of elimination-addition mechanisms at a carbonyl carbon, see Williams; Douglas *Chem. Rev.* **1975**, 75, 627-649.

⁵⁴⁴Bender; Homer *J. Org. Chem.* **1965**, 30, 3975; Williams *J. Chem. Soc., Perkin Trans. 2* **1972**, 808, **1973**, 1244; Hegarty; Frost *J. Chem. Soc., Perkin Trans. 2* **1973**, 1719; Menger; Glass *J. Org. Chem.* **1974**, 39, 2469; Sartoré; Bergon; Calmon *J. Chem. Soc., Perkin Trans. 2* **1977**, 650; Moravcová; Večeřa *Collect. Czech. Chem. Commun.* **1977**, 42, 3048; Broxton; Chung *J. Org. Chem.* **1986**, 51, 3112.

⁵⁴⁵Casanova; Werner; Kiefer *J. Am. Chem. Soc.* **1967**, 89, 2411; Holmquist; Bruice *J. Am. Chem. Soc.* **1969**, 91, 2993, 3003; Campbell; Lawrie *Chem. Commun.* **1971**, 355; Kirby; Lloyd *J. Chem. Soc., Perkin Trans. 2* **1976**, 1762; Broxton; Duddy *J. Org. Chem.* **1981**, 46, 1186; Inoue; Bruice *J. Am. Chem. Soc.* **1982**, 104, 1644, *J. Org. Chem.* **1983**, 48, 3559, **1986**, 51, 959; Alborz; Douglas *J. Chem. Soc., Perkin Trans. 2* **1982**, 331; Thea; Cevasco; Guanti; Kashefi-Naini; Williams *J. Org. Chem.* **1985**, 50, 1867; Isaacs; Najem *Can. J. Chem.* **1986**, 64, 1140, *J. Chem. Soc., Perkin Trans. 2* **1988**, 557.

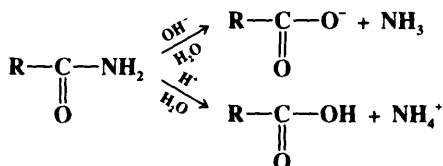
⁵⁴⁶Alkynyl esters also hydrolyze by this mechanism; see Allen; Kitamura; Roberts; Stang; Tidwell *J. Am. Chem. Soc.* **1988**, 110, 622.

depending on reaction conditions.⁵⁴⁷ In either case, the products are the carboxylic acid RCOOH and the aldehyde or ketone R₂CHCOR'.

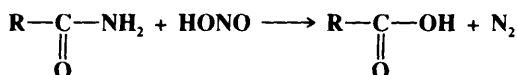
OS I, 351, 360, 366, 379, 391, 418, 523; II, 1, 5, 53, 93, 194, 214, 258, 299, 416, 422, 474, 531, 549; III, 3, 33, 101, 209, 213, 234, 267, 272, 281, 300, 495, 510, 526, 531, 615, 637, 652, 705, 737, 774, 785, 809 (but see OS V, 1050), 833, 835; IV, 15, 55, 169, 317, 417, 444, 532, 549, 555, 582, 590, 608, 616, 628, 630, 633, 635, 804; V, 8, 445, 509, 687, 762, 887, 985, 1031; VI, 75, 121, 560, 690, 824, 913, 1024; VII, 4, 190, 210, 297, 319, 323, 356, 411; 65, 203; 66, 37, 87, 173; 67, 76, 170; 68, 175, 198; 69, 1, 19. Ester hydrolyses with concomitant decarboxylation are listed at reaction 2-40.

0-11 Hydrolysis of Amides

Hydroxy-de-amination



Unsubstituted amides (RCONH₂) can be hydrolyzed with either acidic or basic catalysis, the products being, respectively, the free acid and the ammonium ion or the salt of the acid and ammonia. N-Substituted (RCONHR') and N,N-disubstituted (RCONR'₂) amides can be hydrolyzed analogously, with the primary or secondary amine, respectively (or their salts), being obtained instead of ammonia. Lactams, imides, cyclic imides, hydrazides, etc., also undergo the reaction. Water alone is not sufficient to hydrolyze most amides, since NH₂ is even a poorer leaving group than OR.⁵⁴⁸ Prolonged heating is often required, even with acidic or basic catalysts.⁵⁴⁹ In difficult cases, nitrous acid, NOCl, N₂O₄,⁵⁵⁰ or a similar compound can be used (unsubstituted amides only⁵⁵¹).



These reactions involve a diazonium ion (see 2-49) and are much faster than ordinary hydrolysis; for benzamide the nitrous acid reaction took place 2.5×10^7 times faster than ordinary hydrolysis.⁵⁵² Another procedure for difficult cases involves treatment with aqueous sodium peroxide.⁵⁵³ In still another method, the amide is treated with water and *t*-BuOK at room temperature.⁵⁵⁴ The strong base removes the proton from **96**, thus preventing the reaction marked k_{-1} . Amide hydrolysis can also be catalyzed by nucleophiles (see p. 334).

⁵⁴⁷See, for example, Noyce; Pollack *J. Am. Chem. Soc.* **1969**, *91*, 119, 7158; Monthéard; Camps; Chatzopoulos; Benzaid *Bull. Soc. Chim. Fr.* **1984**, 11-109. For a discussion, see Euranto *Pure Appl. Chem.* **1977**, *49*, 1009-1020.

⁵⁴⁸The very low rate of amide hydrolysis by water alone has been measured: Kahne; Still *J. Am. Chem. Soc.* **1988**, *110*, 7529.

⁵⁴⁹For a list of catalysts and reagents that have been used to hydrolyze amides, with references, see Ref. 508, pp. 988-989.

⁵⁵⁰Kim; Kim; Park *Tetrahedron Lett.* **1990**, *31*, 3893.

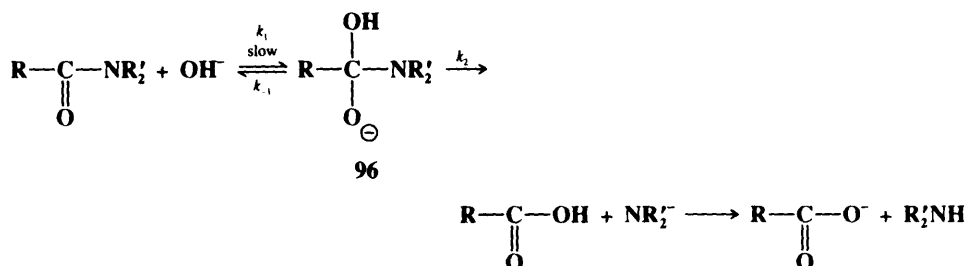
⁵⁵¹N-Substituted amides can be converted to N-nitrosoamides, which are more easily hydrolyzable than the original amide. For example, see Rull; Serratos; Vilarrasa *Tetrahedron Lett.* **1977**, 4549. For another method of hydrolyzing N-substituted amides, see Flynn; Zelle; Grieco *J. Org. Chem.* **1983**, *48*, 2424.

⁵⁵²Ladenheim; Bender *J. Am. Chem. Soc.* **1960**, *82*, 1895.

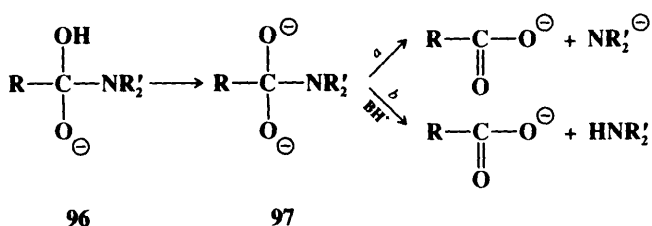
⁵⁵³Vaughan; Robbins *J. Org. Chem.* **1975**, *40*, 1187.

⁵⁵⁴Gassman; Hodgson; Balchunis *J. Am. Chem. Soc.* **1976**, *98*, 1275.

The same framework of eight possible mechanisms that was discussed for ester hydrolysis can also be applied to amide hydrolysis.⁵⁵⁵ Both the acid- and base-catalyzed hydrolyses are essentially irreversible, since salts are formed in both cases. For basic catalysis⁵⁵⁶ the mechanism is BAC2.



There is much evidence for this mechanism, similar to that discussed for ester hydrolysis. In certain cases, kinetic studies have shown that the reaction is second order in OH^- , indicating that **96** can lose a proton to give **97**.⁵⁵⁷ Depending on the nature of R' , **97** can



cleave directly to give the two negative ions (path *a*) or become N-protonated prior to or during the act of cleavage (path *b*), in which case the products are obtained directly and a final proton transfer is not necessary.⁵⁵⁸ Studies of the effect, on the rate of hydrolysis and on the ratio k_{-1}/k_2 , of substituents on the aromatic rings in a series of amides CH_3CONHAr led to the conclusion that path *a* is taken when Ar contains electron-withdrawing substituents and path *b* when electron-donating groups are present.⁵⁵⁹ The presence of electron-withdrawing groups helps stabilize the negative charge on the nitrogen, so that NR'_2^- can be a leaving group (path *a*). Otherwise, the C—N bond does not cleave until the nitrogen is protonated (either prior to or in the act of cleavage), so that the leaving group, *even in the base-catalyzed reaction*, is not NR'_2^- but the conjugate HNR'_2 (path *b*). Though we have shown formation of **96** as the rate-determining step in the BAC2 mechanism, this is true

⁵⁵⁵For reviews, see O'Connor *Q. Rev., Chem. Soc.* **1970**, 24, 553-564; Talbot, *Ref.* 197, pp. 257-280; Challis; Challis, in Zabicky *The Chemistry of Amides*; Wiley: New York, 1970, pp. 731-857.

⁵⁵⁶For a comprehensive list of references, see DeWolfe; Newcomb *J. Org. Chem.* **1971**, 36, 3870.

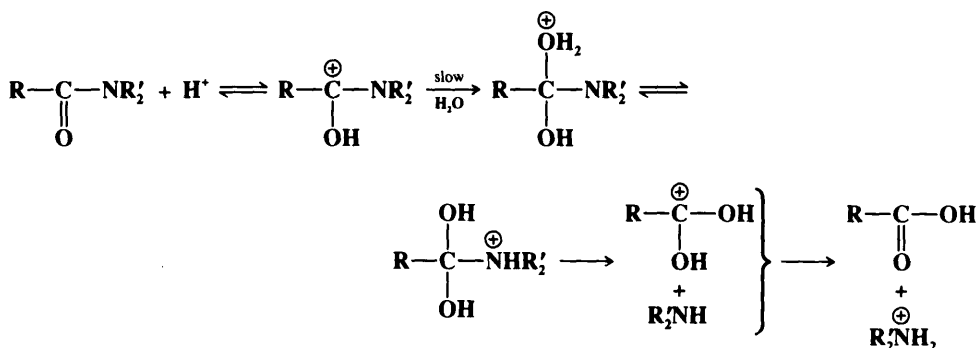
⁵⁵⁷Biechler; Taft *J. Am. Chem. Soc.* **1957**, 79, 4927. For evidence that a similar intermediate can arise in base-catalyzed ester hydrolysis, see Khan; Olagbemiro *J. Org. Chem.* **1982**, 47, 3695.

⁵⁵⁸Eriksson; Holst *Acta Chem. Scand.* **1966**, 20, 1892; Eriksson *Acta Chem. Scand.* **1968**, 22, 892, *Acta Pharm. Suec.* **1969**, 6, 139-162.

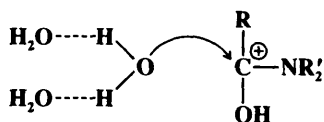
⁵⁵⁹Bender; Thomas *J. Am. Chem. Soc.* **1961**, 83, 4183; Pollack; Bender *J. Am. Chem. Soc.* **1970**, 92, 7190; Kershner; Schowen *J. Am. Chem. Soc.* **1971**, 93, 2014; Schowen; Hopper; Bazikian *J. Am. Chem. Soc.* **1972**, 94, 3095. See also Ref. 556; Gani; Viout *Tetrahedron Lett.* **1972**, 5241; Menger; Donohue *J. Am. Chem. Soc.* **1973**, 95, 432; Pollack; Dumsha *J. Am. Chem. Soc.* **1973**, 95, 4463; Kijima; Sekiguchi *J. Chem. Soc., Perkin Trans. 2* **1987**, 1203.

only at high base concentrations. At lower concentrations of base, the cleavage of **96** or **97** becomes rate-determining.⁵⁶⁰

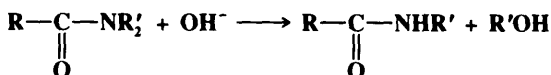
For acid catalysis, matters are less clear. The reaction is generally second order, and it is known that amides are primarily protonated on the oxygen (Chapter 8, Ref. 17). Because of these facts it has been generally agreed that most acid-catalyzed amide hydrolysis takes place by the AAC2 mechanism.



Further evidence for this mechanism is that a small but detectable amount of ¹⁸O exchange (see p. 332) has been found in the acid-catalyzed hydrolysis of benzamide.⁵⁶¹ (¹⁸O exchange has also been detected for the base-catalyzed process,⁵⁶² in accord with the BAC2 mechanism). Kinetic data have shown that three molecules of water are involved in the rate-determining step,⁵⁶³ suggesting that, as in the AAC2 mechanism for ester hydrolysis (**0-10**), additional water molecules take part in a process such as



The four mechanisms involving alkyl—N cleavage (the AL mechanisms) do not apply to this reaction. They are not possible for unsubstituted amides, since the only N—C bond is the acyl bond. They are possible for N-substituted and N,N-disubstituted amides, but in these cases they give entirely different products and are not amide hydrolyses at all.



This reaction, while rare, has been observed for various N-*t*-butyl amides in 98% sulfuric acid, where the mechanism was the AAL1 mechanism,⁵⁶⁴ and for certain amides containing

⁵⁶⁰Schowen; Jayaraman; Kershner *J. Am. Chem. Soc.* **1966**, *88*, 3373. See also Gani; Viout *Tetrahedron* **1976**, *32*, 1669, 2883; Bowden; Bromley *J. Chem. Soc., Perkin Trans. 2* **1990**, 2103.

⁵⁶¹McClelland *J. Am. Chem. Soc.* **1975**, *97*, 5281; Bennet; Šlebocka-Tilk; Brown; Guthrie; Jodhan *J. Am. Chem. Soc.* **1990**, *112*, 8497.

⁵⁶²Bender; Thomas, Ref. 559; Bunton; Nayak; O'Connor *J. Org. Chem.* **1968**, *33*, 572; Šlebocka-Tilk; Bennet; Hogg; Brown *J. Am. Chem. Soc.* **1991**, *113*, 1288; Ref. 561.

⁵⁶³Moodie; Wale; Whaite *J. Chem. Soc.*, **1963**, 4273; Yates; Stevens *Can. J. Chem.* **1965**, *43*, 529; Yates; Riordan *Can. J. Chem.* **1965**, *43*, 2328.

⁵⁶⁴Lacey *J. Chem. Soc.* **1960**, 1633; Druet; Yates *Can. J. Chem.* **1984**, *62*, 2401.

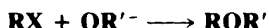
an azo group, where a $BAL1$ mechanism was postulated.⁵⁶⁵ Of the two first-order acyl cleavage mechanisms, only the $AAC1$ has been observed, in concentrated sulfuric acid solutions.⁵⁶⁶ Of course, the diazotization of unsubstituted amides might be expected to follow this mechanism, and there is evidence that this is true.⁵⁵²

OS I, 14, 111, 194, 201, 286; **II**, 19, 25, 28, 49, 76, 208, 330, 374, 384, 457, 462, 491, 503, 519, 612; **III**, 66, 88, 154, 256, 410, 456, 586, 591, 661, 735, 768, 813; **IV**, 39, 42, 55, 58, 420, 441, 496, 664; **V**, 27, 96, 341, 471, 612, 627; **VI**, 56, 252, 507, 951, 967; **VII**, 4, 287; **65**, 119, 173; **67**, 52; **68**, 83; **69**, 55.

The oxidation of aldehydes to carboxylic acids can proceed by a nucleophilic mechanism, but more often it does not. The reaction is considered in Chapter 14 (4-6). Basic cleavage of β -keto esters and the haloform reaction could be considered at this point, but they are also electrophilic substitutions and are treated in Chapter 12 (2-43 and 2-44).

C. Attack by OR at an Alkyl Carbon

0-12 Alkylation with Alkyl Halides. The Williamson Reaction Alkoxy-de-halogenation



The *Williamson reaction*, discovered in 1850, is still the best general method for the preparation of unsymmetrical ethers or, for that matter, symmetrical ones.⁵⁶⁷ The reaction can also be carried out with aromatic R' , though C-alkylation is sometimes a side reaction (see p. 366).⁵⁶⁸ The normal method involves treatment of the halide with alkoxide or aroxide ion prepared from an alcohol or phenol, but it is also possible to mix the halide and alcohol or phenol directly with solid KOH in Me_2SO ⁵⁶⁹ or with HgO and HBf_4 in CH_2Cl_2 .⁵⁷⁰ The reaction is not successful for tertiary R (because of elimination), and low yields are obtained with secondary R. Many other functional groups can be present in the molecule without interference. Ethers with one tertiary group *can* be prepared by treatment of an alkyl halide or sulfate ester (0-14) with a tertiary alkoxide $R'O^-$, which is prepared by removal of a proton from a tertiary alcohol with methylsulfinyl carbanion.⁵⁷¹ or with a copper(I) tertiary alkoxide.⁵⁷² Di-*t*-butyl ether was prepared in high yield by direct attack by *t*-BuOH on the *t*-butyl cation (at $-80^\circ C$ in SO_2ClF).⁵⁷³ Di-*t*-alkyl ethers in general have proved difficult to make, but they can be prepared in low-to-moderate yields by treatment of a tertiary halide with Ag_2CO_3 or Ag_2O .⁵⁷⁴ Active halides such as Ar_3CX may react directly with the alcohol without the need for the more powerful nucleophile alkoxide ion.⁵⁷⁵ Even tertiary halides have been converted to ethers in this way, with no elimination.⁵⁷⁶ The mechanism in these cases is of course $SN1$. *t*-Butyl halides can be converted to aryl *t*-butyl ethers by treatment

⁵⁶⁵Stodola *J. Org. Chem.* **1972**, 37, 178.

⁵⁶⁶Duffy; Leisten *J. Chem. Soc.* **1960**, 545, 853; Barnett; O'Connor *J. Chem. Soc., Chem. Commun.* **1972**, 525. *J. Chem. Soc., Perkin Trans. 2* **1972**, 2378.

⁵⁶⁷For a review, see Feuer; Hooz, in Patai, Ref. 333, pp. 446-450, 460-468.

⁵⁶⁸For a list of reagents used to convert alcohols and phenols to ethers, see Ref. 508, pp. 446-448.

⁵⁶⁹Benedict; Bianchi; Cate *Synthesis* **1979**, 428; Johnstone; Rose *Tetrahedron* **1979**, 35, 2169. See also Loupy; Sansoulet; Vaziri-Zand *Bull. Soc. Chim. Fr.* **1987**, 1027.

⁵⁷⁰Barluenga; Alonso-Cires; Campos; Asensio *Synthesis* **1983**, 53.

⁵⁷¹Sjöberg; Sjöberg *Acta Chem. Scand.* **1972**, 26, 275.

⁵⁷²Whitesides; Sadowski; Lilburn *J. Am. Chem. Soc.* **1974**, 96, 2829.

⁵⁷³Olah; Halpern; Lin *Synthesis* **1975**, 315. For another synthesis of di-*t*-butyl ether, see Masada; Yonemitsu; Hirota *Tetrahedron Lett.* **1979**, 1315.

⁵⁷⁴Masada; Sakajiri *Bull. Chem. Soc. Jpn.* **1978**, 51, 866.

⁵⁷⁵For a review of reactions in which alcohols serve as nucleophiles, see Salomaa; Kankaanperä; Pihlaja, in Patai *The Chemistry of the Hydroxyl Group*, pt. 1; Wiley: New York, 1971, pp. 454-466.

⁵⁷⁶Biordi; Moelwyn-Hughes, *J. Chem. Soc.* **1962**, 4291.

with phenols and an amine such as pyridine.⁵⁷⁷ Aryl alkyl ethers can be prepared from alkyl halides by treatment with an aryl acetate (instead of a phenol) in the presence of K_2CO_3 and a crown ether.⁵⁷⁸

gem-Dihalides react with alkoxides to give acetals, and 1,1,1-trihalides give ortho esters.⁵⁷⁹ Both aryl alkyl and dialkyl ethers can be efficiently prepared with the use of phase transfer catalysis (p. 362)⁵⁸⁰ and with micellar catalysis.⁵⁸¹

Hydroxy groups can be protected⁵⁸² by reaction of their salts with chloromethyl methyl ether.



This protecting group is known as MOM (methoxymethyl) and such compounds are called MOM ethers. The resulting acetals are stable to bases and are easily cleaved with mild acid treatment (0-6). Another protecting group, the 2-methoxyethoxymethyl group (the MEM group), is formed in a similar manner: $RO^- + MeOCH_2CH_2OCH_2Cl \longrightarrow ROCH_2OCH_2CH_2OMe$. Both MOM and MEM groups can be cleaved with dialkyl- and diarylboron halides such as Me_2BBr .⁵⁸³ Phenacyl bromides ($ArCOCH_2Br$) have also been used to protect hydroxy groups.⁵⁸⁴ The resulting ethers can easily be hydrolyzed with zinc and acetic acid.

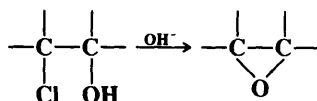
Aryl cyanates⁵⁸⁵ can be prepared by reaction of phenols with cyanogen halides in the presence of a base: $ArO^- + ClCN \longrightarrow ArOCN + Cl^-$.⁵⁸⁶ This reaction has also been applied to certain alkyl cyanates.⁵⁸⁷

Though most Williamson reactions proceed by the S_N2 mechanism, there is evidence (see p. 308) that in some cases the SET mechanism can take place, especially with alkyl iodides.⁵⁸⁸

OS **I**, 75, 205, 258, 296, 435; **II**, 260; **III**, 127, 140, 209, 418, 432, 544; **IV**, 427, 457, 558, 590, 836; **V**, 251, 258, 266, 403, 424, 684; **VI**, 301, 361, 395, 683; **VII**, 34, 386, 435; **65**, 68, 173; **68**, 92; **69**, 148.

0-13 Epoxide Formation

(3)OC-cyclo-Alkoxy-de-halogenation



⁵⁷⁷Masada; Oishi *Chem. Lett.* 57, 1978. For another method, see Camps; Coll; Moretó, *Synthesis* **1982**, 186.

⁵⁷⁸Banerjee; Gupta; Singh *J. Chem. Soc., Chem. Commun.* **1982**, 815.

⁵⁷⁹For a review of the formation of ortho esters by this method, see DeWolfe, Ref. 457, pp. 12-18.

⁵⁸⁰For reviews, see Starks; Liotta, Ref. 404, pp. 128-138; Weber; Gokel *Phase Transfer Catalysis in Organic Synthesis*, Ref. 404, pp. 73-84. For the use of phase transfer catalysis to convert, selectively, one OH group of a diol or triol to an ether, see de la Zerda; Barak; Sasson *Tetrahedron* **1989**, 45, 1533.

⁵⁸¹Juršić *Tetrahedron* **1988**, 44, 6677.

⁵⁸²For other protecting groups for OH, see Greene, *Protective Groups in Organic Synthesis*; Wiley: New York, 1981, pp. 10-113; Corey; Gras; Ulrich *Tetrahedron Lett.* **1976**, 809 and references cited therein.

⁵⁸³Guindon; Yoakim; Morton *J. Org. Chem.* **1984**, 49, 3912. For other methods, see Williams; Sakdarat *Tetrahedron Lett.* **1983**, 24, 3965; Hanessian; Delorme; Dufresne *Tetrahedron Lett.* **1984**, 25, 2515; Rigby; Wilson *Tetrahedron Lett.* **1984**, 25, 1429.

⁵⁸⁴Hendrickson; Kandall *Tetrahedron Lett.* **1970**, 343.

⁵⁸⁵For reviews of alkyl and aryl cyanates, see Jensen; Holm in Patai *The Chemistry of Cyanates and Their Thio Derivatives*, pt. 1; Wiley: New York, 1977, pp. 569-618; Grigat; Pütter *Angew. Chem. Int. Ed. Engl.* **1967**, 6, 206-218 [*Angew. Chem.* 79, 219-231].

⁵⁸⁶Grigat; Pütter *Chem. Ber.* **1964**, 97, 3012; Martin; Bauer *Org. Synth.* VII, 435.

⁵⁸⁷Kauer; Henderson *J. Am. Chem. Soc.* **1964**, 86, 4732.

⁵⁸⁸Ashby; Bae; Park; Depriest; Su *Tetrahedron Lett.* **1984**, 25, 5107.

This is a special case of **0-12**. The base removes the proton from the OH group and the epoxide then attacks in an internal S_N2 reaction.⁵⁸⁹ Many epoxides have been made in this way.⁵⁹⁰ The method can also be used to prepare larger cyclic ethers: five- and six-membered rings. Additional treatment with base yields the glycol (**0-7**).

OS **I**, 185, 233; **II**, 256; **III**, 835; **VI**, 560; **VII**, 164, 356; **66**, 160.

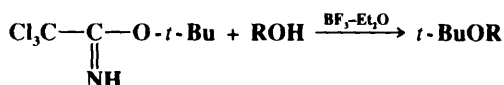
0-14 Alkylation with Inorganic Esters

Alkoxy-de-sulfonyloxy-substitution



The reaction of alkyl sulfates with alkoxide ions is quite similar to **0-12** in mechanism and scope. Other inorganic esters can also be used. One of the most common usages of the reaction is the formation of methyl ethers of alcohols and phenols by treatment of alkoxides or aroxides with methyl sulfate. The alcohol or phenol can be methylated directly, by treatment with dimethyl sulfate and alumina in cyclohexane.⁵⁹¹ Carboxylic esters sometimes give ethers when treated with alkoxides (B_{AL}2 mechanism, p. 381) in a very similar process (see also **0-23**).

t-Butyl ethers can be prepared by treating the compound *t*-butyl 2,2,2-trichloroacetimidate with an alcohol or phenol in the presence of boron trifluoride etherate.⁵⁹²



OS **I**, 58, 537; **II**, 387, 619; **III**, 127, 564, 800; **IV**, 588; **VI**, 737, 859, **VII**, 41. Also see OS **V**, 431.

0-15 Alkylation with Diazo Compounds

Hydro,alkoxy-de-diazo-bisubstitution



Reaction with alcohols is general for diazo compounds, but it is most often performed with diazomethane to produce methyl ethers or with diazo ketones to produce α-keto ethers, since these kinds of diazo compounds are most readily available. With diazomethane⁵⁹³ the method is expensive and requires great caution. It is used chiefly to methylate alcohols and phenols that are expensive or available in small amounts, since the conditions are mild and high yields are obtained. Hydroxy compounds react better as their acidity increases; ordinary alcohols do not react at all unless a catalyst such as HBF₄⁵⁹⁴ or silica gel⁵⁹⁵ is present. The more acidic phenols react very well in the absence of a catalyst. Oximes, and ketones that

⁵⁸⁹See, for example, Swain; Ketley; Bader *J. Am. Chem. Soc.* **1959**, *81*, 2353; Knipe *J. Chem. Soc., Perkin Trans. 2* **1973**, 589.

⁵⁹⁰For a review, see Berti *Top. Stereochem.* **1973**, *7*, 93-251, pp. 187-209.

⁵⁹¹Ogawa; Ichimura; Chihara; Teratani; Taya *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2481.

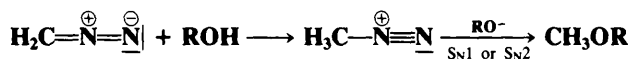
⁵⁹²Armstrong; Brackenridge; Jackson; Kirk *Tetrahedron Lett.* **1988**, *29*, 2483.

⁵⁹³For a review of diazomethane, see Pizey *Synthetic Reagents*, vol. 2; Wiley: New York, 1974, pp. 65-142.

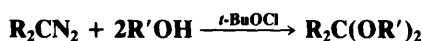
⁵⁹⁴Neeman; Caserio; Roberts; Johnson *Tetrahedron* **1959**, *6*, 36.

⁵⁹⁵Ohno; Nishiyama; Nagase *Tetrahedron Lett.* **1979**, 4405; Ogawa; Hagiwara; Chihara; Teratani; Taya *Bull. Chem. Soc. Jpn.* **1987**, *60*, 627.

have substantial enolic contributions, give O-alkylation to form, respectively, O-alkyl oximes and enol ethers. The mechanism⁵⁹⁶ is as in 0-5:



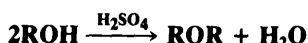
Diazoalkanes can also be converted to ethers by thermal or photochemical cleavage in the presence of an alcohol. These are carbene or carbenoid reactions.⁵⁹⁷ Similar intermediates are involved when diazoalkanes react with alcohols in the presence of *t*-BuOCl to give acetals.⁵⁹⁸



OS V, 245. Also see OS V, 1099.

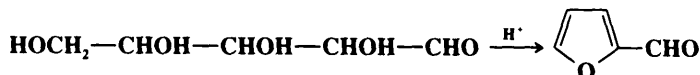
0-16 Dehydration of Alcohols

Alkoxy-de-hydroxylation



The dehydration of alcohols to form ethers⁵⁹⁹ is analogous to 0-12 and 0-14, but the species from which the leaving group departs is ROH_2^+ or ROSO_2OH . The former is obtained directly on treatment of alcohols with sulfuric acid and may go, by an $\text{S}_{\text{N}1}$ or $\text{S}_{\text{N}2}$ pathway, directly to the ether if attacked by another molecule of alcohol. On the other hand, it may, again by either an $\text{S}_{\text{N}1}$ or $\text{S}_{\text{N}2}$ route, be attacked by the nucleophile HSO_4^- , in which case it is converted to ROSO_2OH , which in turn may be attacked by an alcohol molecule to give ROR . Elimination is always a side reaction and, in the case of tertiary alkyl substrates, completely predominates. Good yields of ethers were obtained by heating diarylcarbinols $[\text{ArAr}'\text{CHOH} \rightarrow (\text{ArAr}'\text{CH})_2\text{O}]$ with TsOH in the solid state.⁶⁰⁰

The ether prepared is symmetrical. Mixed ethers can be prepared if one group is tertiary alkyl and the other primary or secondary, since the latter group is not likely to compete with the tertiary group in the formation of the carbocation, while a tertiary alcohol is a very poor nucleophile.⁶⁰¹ If one group is not tertiary, the reaction of a mixture of two alcohols leads to all three possible ethers. Diols can be converted to cyclic ethers,⁶⁰² though the reaction is most successful for five-membered rings. Thus, 1,6-hexanediol gives mostly 2-ethyltetrahydrofuran. However, 5-, 6-, and 7-membered rings have been prepared with $\text{AlPO}_4\text{-Al}_2\text{O}_3$,⁶⁰³ with BuSnCl_3 ,⁶⁰⁴ and with a Nafion-H acid catalyst⁶⁰⁵ (the last-named reagent was also used to make an 8-membered ring). This reaction is also important in preparing furfural derivatives from aldoses, with concurrent elimination:



⁵⁹⁶Kreevoy; Thomas *J. Org. Chem.* **1977**, 42, 3979. See also McGarrity; Smyth *J. Am. Chem. Soc.* **1980**, 102, 7303.

⁵⁹⁷Bethell; Howard *J. Chem. Soc. B* **1969**, 745; Bethell; Newall; Whittaker *J. Chem. Soc. B* **1971**, 23; Noels; Demonceau; Petiniot; Hubert; Teyssié *Tetrahedron* **1982**, 38, 2733.

⁵⁹⁸Baganz; May *Angew. Chem. Int. Ed. Engl.* **1966**, 5, 420 [*Angew. Chem.* 78, 448].

⁵⁹⁹For a review, see Ref. 567, pp. 457-460, 468-470.

⁶⁰⁰Toda; Takumi; Akehi *J. Chem. Soc., Perkin Trans. 2* **1990**, 1270.

⁶⁰¹See, for example, Jenner *Tetrahedron Lett.* **1988**, 29, 2445.

⁶⁰²For a list of reagents, with references, see Ref. 508, pp. 449-450.

⁶⁰³Costa; Riego *Synth. Commun.* **1987**, 17, 1373.

⁶⁰⁴Tagliavini; Marton; Furlani *Tetrahedron* **1989**, 45, 1187.

⁶⁰⁵Olah; Fung; Malhotra *Synthesis* **1981**, 474.

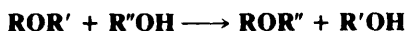
Phenols and primary alcohols form ethers when heated with dicyclohexylcarbodiimide⁶⁰⁶ (see 0-22). 1,2-Diols can be converted to epoxides by treatment with dimethylformamide dimethyl acetal [(MeO)₂CHNMe₂],⁶⁰⁷ with diethyl azodicarboxylate [EtOOCN=NCOOEt] and Ph₃P,⁶⁰⁸ with a dialkoxytriphenylphosphorane,⁶⁰⁹ or with TsCl-NaOH-PhCH₂NEt₃⁺ Cl⁻.⁶¹⁰

OS I, 280; II, 126; IV, 25, 72, 266, 350, 393, 534; V, 539, 1024; VI, 887; 69, 205. Also see OS V, 721.

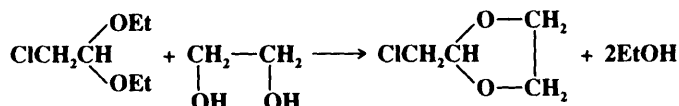
0-17 Transetherification

Hydroxy-de-alkoxylation

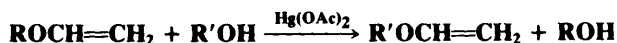
Alkoxy-de-hydroxylation



The exchange of one alkoxy group for another is very rare for *ethers*, though it has been accomplished with reactive R, for example, diphenylmethyl with *p*-toluenesulfonic acid as a catalyst,⁶¹¹ and by treatment of alkyl aryl ethers with alkoxide ions: ROAr + R'O⁻ → ROR' + ArO⁻.⁶¹² However, acetals and ortho esters undergo transesterification readily,⁶¹³ for example,⁶¹⁴



because, as we have seen (0-6), departure of the leaving group from an acetal gives a particularly stable carbocation. These are equilibrium reactions, and most often the equilibrium is shifted by removing the lower-boiling alcohol by distillation. Enol ethers can be prepared by treating an alcohol with an enol ester or a different enol ether, with mercuric acetate as a catalyst,⁶¹⁵ e.g.,



1,2-Diketones can be converted to α-keto enol ethers by treatment with an alkoxytrimethylsilane ROSiMe₃.⁶¹⁶

OS VI, 298, 491, 584, 606, 869; VII, 334; 65, 32; 68, 92. Also see OS V, 1080, 1096.

⁶⁰⁶Vowinkel *Chem. Ber.* **1962**, 95, 2997, **1963**, 96, 1702, **1966**, 99, 42.

⁶⁰⁷Neumann *Chimia* **1969**, 23, 267.

⁶⁰⁸Guthrie; Jenkins; Yamasaki; Skelton; White *J. Chem. Soc., Perkin Trans. I* **1981**, 2328 and references cited therein. For a review of diethyl azodicarboxylate-Ph₃P, see Mitsunobu *Synthesis* **1981**, 1-28.

⁶⁰⁹Robinson; Barry; Kelly; Evans *J. Am. Chem. Soc.* **1985**, 107, 5210; Kelly; Evans *J. Org. Chem.* **1986**, 51, 5490. See also Hendrickson; Hussoin *Synlett* **1990**, 423.

⁶¹⁰Szeja *Synthesis* **1985**, 983.

⁶¹¹Pratt; Draper *J. Am. Chem. Soc.* **1949**, 71, 2846.

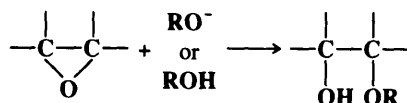
⁶¹²Zoltewicz; Sale *J. Org. Chem.* **1970**, 35, 3462.

⁶¹³For reviews, see Ref. 575, pp. 458-463; DeWolfe, Ref. 457, pp. 18-29, 146-148.

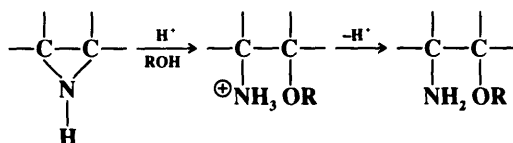
⁶¹⁴McElvain; Curry *J. Am. Chem. Soc.* **1948**, 70, 3781.

⁶¹⁵Watanabe; Conlon *J. Am. Chem. Soc.* **1957**, 79, 2828; Büchi; White *J. Am. Chem. Soc.* **1964**, 86, 2884. For a review, see Shostakovskii; Trofimov; Atavin; Lavrov *Russ. Chem. Rev.* **1968**, 37, 907-919. For a discussion of the mechanism, see Garcev *J. Org. Chem. USSR* **1982**, 18, 36.

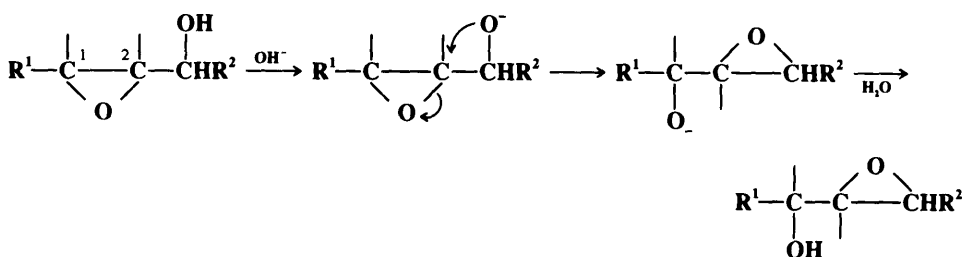
⁶¹⁶Ponaras; Meah *Tetrahedron Lett.* **1986**, 27, 4953.

0-18 Alcoholysis of Epoxides**(3) OC-seco-Alkoxy-de-alkoxylation**

This reaction is analogous to **0-7**. It may be acid, base, or alumina⁶¹⁷ catalyzed, and may occur by either an S_N1 or S_N2 mechanism. Many of the β-hydroxy ethers produced in this way are valuable solvents, for example, diethylene glycol, Cellosolve, etc. Aziridines can similarly be converted to β-amino ethers.⁶¹⁸



In the *Payne rearrangement*, a 2,3-epoxy alcohol is converted to an isomeric one, by treatment with aqueous base:⁶¹⁹



The reaction results in inverted configuration at C-2. Of course, the product can also revert to the starting material by the same pathway, so a mixture of epoxy alcohols is generally obtained.

0-19 Alkylation with Oxonium Salts**Alkoxy-de-hydroxylation**

Oxonium ions are excellent alkylating agents, and ethers can be conveniently prepared by treating them with alcohols or phenols.⁶²⁰ Quaternary ammonium salts can sometimes also be used.⁶²¹

OS 65, 140; 66, 29.

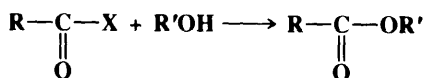
⁶¹⁷See Posner; Rogers *J. Am. Chem. Soc.* **1977**, 99, 8208, 8214.

⁶¹⁸For a review, see Dermer; Ham, Ref. 437, pp. 224-227, 256-257.

⁶¹⁹Payne *J. Org. Chem.* **1962**, 27, 3819; Behrens; Ko; Sharpless; Walker *J. Org. Chem.* **1985**, 50, 5687.

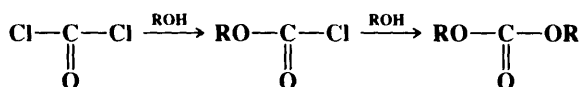
⁶²⁰Granik; Pyatin; Glushkov, Ref. 339, p. 749.

⁶²¹For an example, see Vogel; Büchi *Org. Synth.* 66, 29.

D. Attack by OR at an Acyl Carbon**0-20 Alcoholysis of Acyl Halides****Alkoxy-de-halogenation**

The reaction between acyl halides and alcohols or phenols is the best general method for the preparation of carboxylic esters. The reaction is of wide scope, and many functional groups do not interfere. A base is frequently added to combine with the HX formed. When aqueous alkali is used, this is called the *Schotten-Baumann procedure*, but pyridine is also frequently used. Both R and R' may be primary, secondary, or tertiary alkyl or aryl. Enolic esters can also be prepared by this method, though C-acylation competes in these cases. In difficult cases, especially with hindered acids or tertiary R', the alkoxide can be used instead of the alcohol.⁶²² Activated alumina has also been used as a catalyst, for tertiary R'.⁶²³ Thallium salts of phenols give very high yields of phenolic esters.⁶²⁴ Phase transfer catalysis has been used for hindered phenols.⁶²⁵

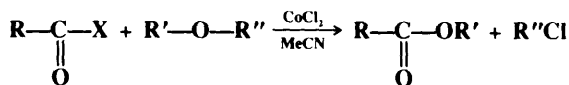
When phosgene is the acyl halide, haloformic esters or carbonates can be obtained.



An important example is the preparation of carbobenzoxoy chloride (PhCH₂OCOCl) from phosgene and benzyl alcohol. This compound is widely used for protection of amino groups during peptide synthesis (see 0-52).

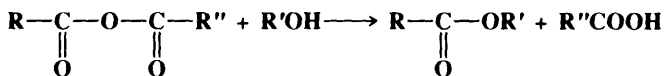
As with 0-8, the mechanism can be S_N1 or tetrahedral.⁵⁰² Pyridine catalyzes the reaction by the nucleophilic catalysis route (see 0-9).

Acyl halides can also be converted to carboxylic acids by using ethers instead of alcohols, in MeCN in the presence of certain catalysts such as cobalt(II) chloride.⁶²⁶



This is a method for the cleavage of ethers (see also 0-68).

OS **I**, 12; **III**, 142, 144, 167, 187, 623, 714; **IV**, 84, 263, 478, 479, 608, 616, 788; **V**, 1, 166, 168, 171; **VI**, 199, 259, 312, 824. **VII**, 190; **65**, 203; **69**, 1.

0-21 Alcoholysis of Anhydrides**Alkoxy-de-acyloxy-substitution**

⁶²²For an example, see Kaiser; Woodruff, *J. Org. Chem.* **1970**, 35, 1198.

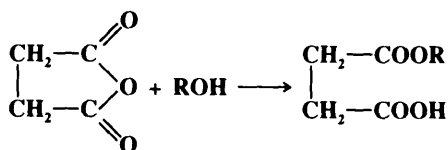
⁶²³Nagasawa; Yoshitake; Amiya; Ito *Synth. Commun.* **1990**, 20, 2033.

⁶²⁴Taylor, McLay; McKillop *J. Am. Chem. Soc.* **1968**, 90, 2422.

⁶²⁵Illi, *Tetrahedron Lett.* **1979**, 2431. For another method, see Nekhoroshev; Ivakhnenko; Okhlobystin *J. Org. Chem. USSR* **1977**, 13, 608.

⁶²⁶See Ahmad; Iqbal *Chem. Lett.* **1987**, 953, and references cited therein.

The scope of this reaction is similar to that of **0-20**. Though anhydrides are somewhat less reactive than acyl halides, they are often used to prepare carboxylic esters. Acids, Lewis acids, and bases are often used as catalysts—most often, pyridine.⁶²⁷ Catalysis by pyridine is of the nucleophilic type (see **0-9**). 4-(N,N-Dimethylamino)pyridine is a better catalyst than pyridine and can be used in cases where pyridine fails.⁶²⁸ A nonbasic catalyst is cobalt(II) chloride.⁶²⁹ Formic anhydride is not a stable compound but esters of formic acid can be prepared by treating alcohols⁶³⁰ or phenols⁶³¹ with acetic-formic anhydride. Cyclic anhydrides give monoesterified dicarboxylic acids, for example,

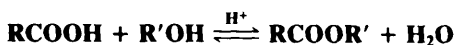


Alcohols can also be acylated by mixed organic-inorganic anhydrides, such as acetic-phosphoric anhydride $\text{MeCOOPO}(\text{OH})_2$ ⁶³² (see **0-33**).

OS **I**, 285, 418; **II**, 69, 124; **III**, 11, 127, 141, 169, 237, 281, 428, 432, 690, 833; **IV**, 15, 242, 304; **V**, 8, 459, 591, 887; **VI**, 121, 245, 560, 692; **67**, 76; **69**, 19.

0-22 Esterification of Carboxylic Acids

Alkoxy-de-hydroxylation



The esterification of carboxylic acids with alcohols⁶³³ is the reverse of **0-11** and can be accomplished only if a means is available to drive the equilibrium to the right.⁶³⁴ There are many ways of doing this, among which are: (1) addition of an excess of one of the reactants, usually the alcohol; (2) removal of the ester or the water by distillation; (3) removal of water by azeotropic distillation; and (4) removal of water by use of a dehydrating agent or a molecular sieve. When R' is methyl, the most common way of driving the equilibrium is by adding excess MeOH; when R' is ethyl, it is preferable to remove water by azeotropic distillation.⁶³⁵ The most common catalysts are H_2SO_4 and TsOH, though some reactive acids (e.g., formic,⁶³⁶ trifluoroacetic⁶³⁷) do not require a catalyst. Besides methyl and ethyl, R' may be other primary or secondary alkyl groups, but tertiary alcohols usually give carbonations and elimination. Phenols can sometimes be used to prepare phenolic esters, but yields are generally very low.

⁶²⁷For a list of catalysts, with references, see Ref. 508, pp. 980-981.

⁶²⁸For reviews, see Scriven *Chem. Soc. Rev.* **1983**, 12, 129-161; Höfle; Steglich; Vorbrüggen *Angew. Chem. Int. Ed. Engl.* **1978**, 17, 569-583 [*Angew. Chem.* **90**, 602-615].

⁶²⁹Ahmad; Iqbal *J. Chem. Soc., Chem. Commun.* **1987**, 114.

⁶³⁰For example, see Stevens; van Es *Recl. Trav. Chim. Pays-Bas*, **1964**, 83, 1287; van Es; Stevens *Recl. Trav. Chim. Pays-Bas* **1965**, 84, 704.

⁶³¹For example, see Stevens; van Es *Recl. Trav. Chim. Pays-Bas* **1964**, 83, 1294; Sōfuku; Muramatsu; Hagitani *Bull. Chem. Soc. Jpn.* **1967**, 40, 2942.

⁶³²Fatiadi *Carbohydr. Res.* **1968**, 6, 237.

⁶³³For a review of some methods, see Haslam *Tetrahedron* **1980**, 36, 2409-2433.

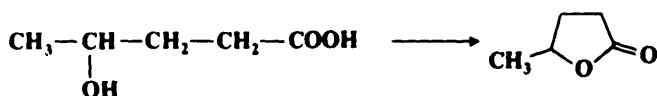
⁶³⁴For a list of reagents, with references, see Ref. 508, pp. 966-972.

⁶³⁵Newman *An Advanced Organic Laboratory Course*; Macmillan: New York, 1972, pp. 8-10.

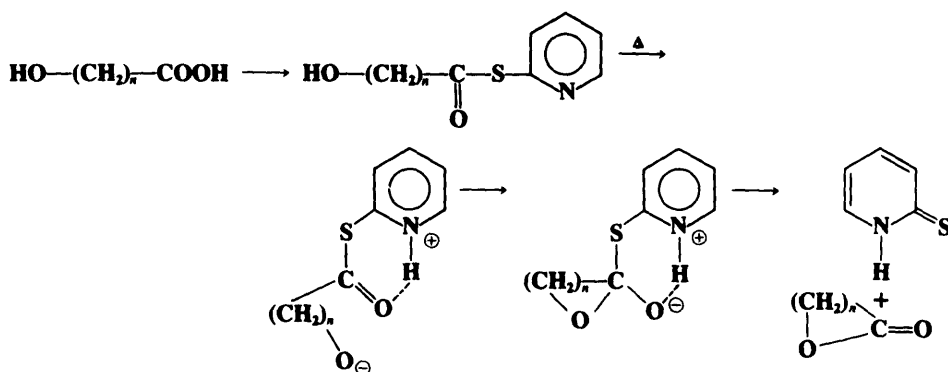
⁶³⁶Formates can be prepared if diisopropyl ether is used to remove water by azeotropic distillation: Werner, *J. Chem. Res. (S)* **1980**, 196.

⁶³⁷Johnston; Knipe; Watts *Tetrahedron Lett.* **1979**, 4225.

γ - and δ -hydroxy acids are easily lactonized by treatment with acids, or often simply on standing, but larger and smaller lactone rings cannot be made in this manner, because



polyester formation occurs more readily.⁶³⁸ Often the conversion of a group such as keto or halogen, γ or δ to a carboxyl group, to a hydroxyl group gives the lactone directly, since the hydroxy acid cyclizes too rapidly for isolation. β -Substituted β -hydroxy acids can be converted to β -lactones by treatment with benzenesulfonyl chloride in pyridine at 0 to 5°C.⁶³⁹ ϵ -Lactones (seven-membered rings) have been made by cyclization of ϵ -hydroxy acids at high dilution.⁶⁴⁰ Macrocyclic lactones⁶⁴¹ can be prepared indirectly in very good yields by conversion of the hydroxy acids to 2-pyridinethiol esters and adding these to refluxing xylene.⁶⁴²



A closely related method, which often gives higher yields, involves treatment of the hydroxy acids with 1-methyl- or 1-phenyl-2-halopyridinium salts, especially 1-methyl-2-chloropyridinium iodide (*Mukaiyama's reagent*).⁶⁴³ Another method uses organotin oxides.⁶⁴⁴

⁶³⁸For a review of the synthesis of lactones and lactams, see Wolfe; Ogliaruso, in Patai *The Chemistry of Acid Derivatives*, pt. 2; Wiley: New York, 1979, pp. 1062-1330. For a list of methods for converting hydroxy acids to lactones, with references, see Ref. 508, pp. 941-943.

⁶³⁹Adam; Baeza; Liu *J. Am. Chem. Soc.* **1972**, *94*, 2000. For other methods of converting β -hydroxy acids to β -lactones, see Merger *Chem. Ber.* **1968**, *101*, 2413; Blume *Tetrahedron Lett.* **1969**, 1047.

⁶⁴⁰Lardelli; Lamberti; Weller; de Jonge *Recl. Trav. Chim. Pays-Bas* **1967**, *86*, 481.

⁶⁴¹For reviews on the synthesis of macrocyclic lactones, see Nicolaou *Tetrahedron* **1977**, *33*, 683-710; Back *Tetrahedron* **1977**, *33*, 3041-3059; Masamune; Bates; Corcoran *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 585-607 [*Angew. Chem.* **89**, 602-624].

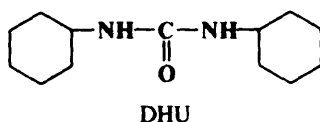
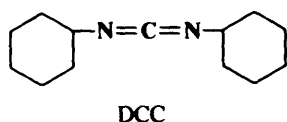
⁶⁴²Corey; Nicolaou; Melvin *J. Am. Chem. Soc.* **1975**, *97*, 653, 655; Corey; Brunelle; Stork *Tetrahedron Lett.* **1976**, 3405; Corey; Brunelle; *Tetrahedron Lett.* **1976**, 3409; Wollenberg; Nimitz; Gokcek *Tetrahedron Lett.* **1980**, *21*, 2791; Thalmann; Oertle; Gerlach *Org. Synth. VII*, 470. See also Schmidt; Heermann *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 308 [*Angew. Chem.* **91**, 330].

⁶⁴³For a review of reactions with this and related methods, see Mukaiyama *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 707-721 [*Angew. Chem.* **91**, 798-812].

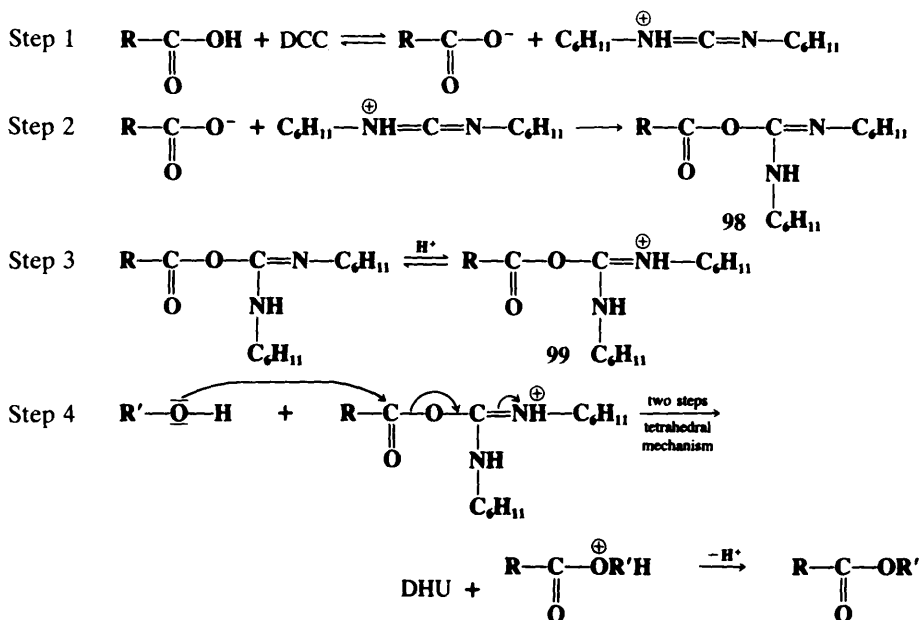
⁶⁴⁴Steliou; Szczygielska-Nowosielska; Favre; Poupart; Hanessian *J. Am. Chem. Soc.* **1980**, *102*, 7578; Steliou; Poupart *J. Am. Chem. Soc.* **1983**, *105*, 7130. For some other methods, see Masamune; Kamata; Schilling *J. Am. Chem. Soc.* **1975**, *97*, 3515; Scott; Naples *Synthesis* **1976**, 738; Kurihara; Nakajima; Mitsunobu *Tetrahedron Lett.* **1976**, 2455; Corey; Brunelle; Nicolaou *J. Am. Chem. Soc.* **1977**, *99*, 7359; Vorbrüggen; Krolkiewicz *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 876 [*Angew. Chem.* **89**, 914]; Nimitz; Wollenberg *Tetrahedron Lett.* **1978**, 3523; Inanaga; Hirata; Saeki; Katsuki; Yamaguchi *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989; Venkataraman; Wagle *Tetrahedron Lett.* **1980**, *21*, 1893; Schmidt; Dietsche *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 771 [*Angew. Chem.* **93**, 786]; Taniguchi; Kinoshita; Inomata; Kotake *Chem. Lett.* **1984**, 1347; Cossy; Pete *Bull. Soc. Chim. Fr.* **1988**, 989.

Esterification is catalyzed by acids (not bases) in ways that were discussed on p. 379.⁵²⁵ The mechanisms are usually AAC2, but AAC1 and AAL1 have also been observed.⁶⁴⁵ Certain acids, such as 2,6-di-ortho-substituted benzoic acids, cannot be esterified by the AAC2 mechanism because of steric hindrance (p. 340). In such cases, esterification can be accomplished by dissolving the acid in 100% H_2SO_4 (forming the ion RCO^+) and pouring the solution into the alcohol (AAC1 mechanism). The reluctance of hindered acids to undergo the normal AAC2 mechanism can sometimes be put to advantage when, in a molecule containing two COOH groups, only the less hindered one is esterified. The AAC1 pathway cannot be applied to unhindered carboxylic acids.

Another way to esterify a carboxylic acid is to treat it with an alcohol in the presence of a dehydrating agent.⁶³⁴ One of these is dicyclohexylcarbodiimide (DCC), which is converted



in the process to dicyclohexylurea (DHU). The mechanism⁶⁴⁶ has much in common with the nucleophilic catalysis mechanism; the acid is converted to a compound with a better leaving group. However, the conversion is not by a tetrahedral mechanism (as it is in nucleophilic catalysis), since the $\text{C}-\text{O}$ bond remains intact during this step:



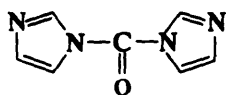
Evidence for this mechanism was the preparation of O-acylureas similar to **98** and the finding that when catalyzed by acids they react with alcohols to give esters.⁶⁴⁷

⁶⁴⁵For a review of aspects of the mechanism, see Ref. 575, pp. 466-481.

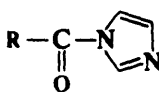
⁶⁴⁶Smith; Moffatt; Khorana *J. Am. Chem. Soc.* **1958**, *80*, 6204; Balcom; Petersen *J. Org. Chem.* **1989**, *54*, 1922.

⁶⁴⁷Dolleschall; Lempert *Tetrahedron Lett.* **1963**, 1195.

However, there are limitations to the use of DCC; yields are variable and N-acylureas are side products. Many other dehydrating agents⁶⁴⁸ have been used, including an alkyl chloroformate and Et₃N,⁶⁴⁹ pyridinium salts-Bu₃N,⁶⁴³ phenyl dichlorophosphate PhOPOCl₂,⁶⁵⁰ DCC and an aminopyridine,⁶⁵¹ 2-chloro-1,3,5-trinitrobenzene and pyridine,⁶⁵² di-2-pyridyl carbonate,⁶⁵³ polystyryl diphenylphosphine,⁶⁵⁴ (trimethylsilyl)ethoxyacetylene,⁶⁵⁵ 1,1'-carbonylbis(3-methylimidazolium) triflate (CBMIT),⁶⁵⁶ Amberlyst-15,⁶⁵⁷ diethyl azodicarboxylate EtOOCN=NCOOEt and Ph₃P⁶⁵⁸ (when these reagents are used the procedure is called the *Mitsunobu esterification reaction*⁶⁵⁹), chlorosulfonyl isocyanate ClSO₂NCO,⁶⁶⁰ chlorosilanes,⁶⁶¹ MeSO₂Cl-Et₃N,⁶⁶² Ph₃P-CCl₄-



100



101

Et₃N,⁶⁶³ and N,N'-carbonyldiimidazole (**100**).⁶⁶⁴ In the latter case easily alcoholized imidazolides (**101**) are intermediates. BF₃ promotes the esterification by converting the acid to RCO⁺ BF₃OH⁻, so the reaction proceeds by an AAC1 type of mechanism. The use of BF₃-etherate is simple and gives high yields.⁶⁶⁵ Carboxylic esters can also be prepared by treating carboxylic acids with *t*-butyl ethers and acid catalysts.⁶⁶⁶



Carboxylic acids can be converted to *t*-butyl esters by treatment with *t*-butyl 2,2,2-trichloroacetimidate (see **0-14**) and BF₃-Et₂O.⁵⁹²

OS **I**, 42, 138, 237, 241, 246, 254, 261, 451; **II**, 260, 264, 276, 292, 365, 414, 526; **III**, 46, 203, 237, 381, 413, 526, 531, 610; **IV**, 169, 178, 302, 329, 390, 398, 427, 506, 532, 635, 677; **V**, 80, 762, 946; **VI**, 471, 797; **VII**, 93, 99, 210, 319, 356, 386, 470; **66**, 22, 142; **67**, 76. Also see OS **III**, 536, 742.

⁶⁴⁸For a list of many of these with references, see Arrieta; García; Lago; Palomo *Synth. Commun.* **1983**, 13, 471.

⁶⁴⁹Kim; Lee; Kim *J. Org. Chem.* **1985**, 50, 560.

⁶⁵⁰Liu; Chan; Lee *Tetrahedron Lett.* **1978**, 4461. García; Arrieta; Palomo *Synth. Commun.* **1982**, 12, 681. See also Ueda; Oikawa *J. Org. Chem.* **1985**, 50, 760.

⁶⁵¹Hassner; Alexanian *Tetrahedron Lett.* **1978**, 4475; Neises; Steglich *Angew. Chem. Int. Ed. Engl.* **1978**, 17, 522 [*Angew. Chem.* 90, 556]; Boden; Keck *J. Org. Chem.* **1985**, 50, 2394.

⁶⁵²Takimoto; Inanaga; Katsuki; Yamaguchi *Bull. Chem. Soc. Jpn.* **1981**, 54, 1470. See also Kim; Yang *Synth. Commun.* **1981**, 11, 121; Takimoto; Abe; Kodera; Ohta *Bull. Chem. Soc. Jpn.* **1983**, 56, 639.

⁶⁵³Kim; Lee; Ko *Tetrahedron Lett.* **1984**, 25, 4943. For a review of 2-pyridyl reagents, see Kim *Org. Prep. Proced. Int.* **1988**, 20, 145-172.

⁶⁵⁴Caputo; Corrado; Ferreri; Palumbo *Synth. Commun.* **1986**, 16, 1081.

⁶⁵⁵Kita; Akai; Yamamoto; Taniguchi; Tamura *Synthesis* **1989**, 334.

⁶⁵⁶Saha; Schultz; Rapoport *J. Am. Chem. Soc.* **1989**, 111, 4856.

⁶⁵⁷Petrini; Ballini; Marcantoni; Rosini *Synth. Commun.* **1988**, 18, 847.

⁶⁵⁸Mitsunobu; Yamada *Bull. Chem. Soc. Jpn.* **1967**, 40, 2380; Camp; Jenkins *Aust. J. Chem.* **1988**, 41, 1835.

⁶⁵⁹For discussions of the mechanism, see Varasi; Walker; Maddox *J. Org. Chem.* **1987**, 52, 4235; Hughes; Reamer; Bergan; Grabowski *J. Am. Chem. Soc.* **1988**, 110, 6487; Crich; Dyker; Harris *J. Org. Chem.* **1989**, 54, 257; Camp; Jenkins *J. Org. Chem.* **1989**, 54, 3045, 3049.

⁶⁶⁰Keshavamurthy; Vankar; Dhar *Synthesis* **1982**, 506. For a review of ClSO₂NCO, see Dhar; Murthy *Synthesis* **1988**, 437-450.

⁶⁶¹Nakao; Oka; Fukumoto *Bull. Chem. Soc. Jpn.* **1981**, 54, 1267; Brook; Chan *Synthesis* **1983**, 201.

⁶⁶²Chandrasekaran; Turner *Synth. Commun.* **1982**, 12, 727.

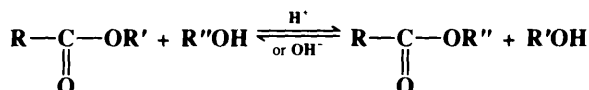
⁶⁶³Hashimoto; Furukawa *Bull. Chem. Soc. Jpn.* **1981**, 54, 2227; Ramaiah *J. Org. Chem.* **1985**, 50, 4991.

⁶⁶⁴For a review, see Staab; Rohr *Newer Methods Prep. Org. Chem.* **1968**, 5, 61-108. See also Morton; Mangroo; Gerber *Can. J. Chem.* **1988**, 66, 1701.

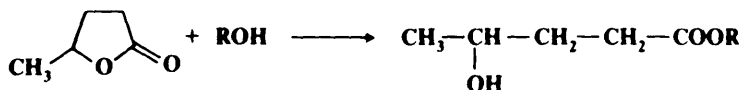
⁶⁶⁵For examples, see Marshall; Erickson; Folsom *Tetrahedron Lett.* **1970**, 4011; Kadaba *Synthesis* **1972**, 628, *Synth. Commun.* **1974**, 4, 167.

⁶⁶⁶Derevitskaya; Klimov; Kochetkov *Tetrahedron Lett.* **1970**, 4269. See also Mohacs *Synth. Commun.* **1982**, 12, 453.

0-23 Alcoholysis of Carboxylic Esters. Transesterification
Alkoxy-de-alkoxylation

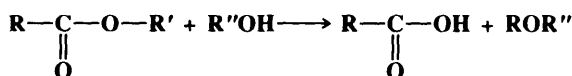


Transesterification is catalyzed⁶⁶⁷ by acids or bases.⁶⁶⁸ It is an equilibrium reaction and must be shifted in the desired direction. In many cases low-boiling esters can be converted to higher-boiling ones by the distillation of the lower-boiling alcohol as fast as it is formed. This reaction has been used as a method for the acylation of a primary OH in the presence of a secondary OH: The diol is treated with ethyl acetate in the presence of Woelm neutral alumina.⁶⁶⁹ Regioselectivity has also been accomplished by using enzymes (lipases) as catalysts.⁶⁷⁰ Lactones are easily opened by treatment with alcohols to give open-chain hydroxy esters:



Transesterification has been carried out with phase-transfer catalysis, without an added solvent.⁶⁷¹ In another procedure, RCOOR' are converted to RCOOR'' by treatment of the ester and an alcohol $\text{R}''\text{OH}$ with $n\text{-BuLi}$, which converts the $\text{R}''\text{OH}$ to $\text{R}''\text{OLi}$.⁶⁷²

Transesterification occurs by mechanisms⁶⁷³ that are identical with those of ester hydrolysis—except that ROH replaces HOH —that is, by the acyl-oxygen fission mechanisms. When alkyl fission takes place, the products are the *acid* and the *ether*:



Therefore, transesterification reactions frequently fail when R' is tertiary, since this type of substrate most often reacts by alkyl-oxygen cleavage. In such cases, the reaction is of the Williamson type with OCOR as the leaving group (see 0-14).

With enol esters, the free alcohol is the enol of a ketone, so such esters easily undergo the reaction



⁶⁶⁷For a list of catalysts, with references, see Ref. 508, pp. 985-987.

⁶⁶⁸For some methods of transesterification under neutral conditions, see Bittner, Barneis; *Felix Tetrahedron Lett.* **1975**, 3871; Hashimoto; Furukawa; Kuroda *Tetrahedron Lett.* **1980**, 21, 2857; Olah; Narang; Salem; Gupta *Synthesis* **1981**, 142; Otera; Yano; Kawabata; Nozaki *Tetrahedron Lett.* **1986**, 27, 2383; Imwinkelried; Schiess; Seebach *Org. Synth.* **65**, 230.

⁶⁶⁹Posner; Oda *Tetrahedron Lett.* **1981**, 22, 5003; Rana; Barlow; Matta *Tetrahedron Lett.* **1981**, 22, 5007. See also Costa; Riego *Can. J. Chem.* **1987**, 65, 2327.

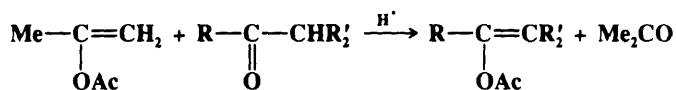
⁶⁷⁰Therisod; Klivanov *J. Am. Chem. Soc.* **1987**, 109, 3977. See also Wang; Lalonde; Momongan; Bergbreiter; Wong *J. Am. Chem. Soc.* **1988**, 110, 7200.

⁶⁷¹Barry; Bram; Petit *Tetrahedron Lett.* **1988**, 29, 4567. See also Nishiguchi; Taya *J. Chem. Soc., Perkin Trans. 1* **1990**, 172.

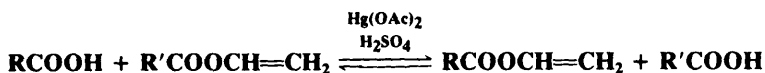
⁶⁷²Meth-Cohn *J. Chem. Soc., Chem. Commun.* **1986**, 695.

⁶⁷³For a review, see Koskikallio, in Patai, Ref. 197, pp. 103-136.

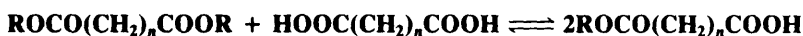
Hence, enol esters such as isopropenyl acetate are good acylating agents for alcohols.⁶⁷⁴ Isopropenyl acetate can also be used to convert other ketones to the corresponding enol acetates in an exchange reaction:⁶⁷⁵



Enol esters can also be prepared in the opposite type of exchange reaction, catalyzed by mercuric acetate⁶⁷⁶ or Pd(II) chloride,⁶⁷⁷ e.g.,



A closely related reaction is equilibration of a dicarboxylic acid and its diester to produce monoesters:



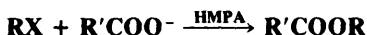
OS II, 5, 122, 360; III, 123, 146, 165, 231, 281, 581, 605; IV, 10, 549, 630, 977; V, 155, 545, 863; VI, 278; VII, 4, 164, 411; 65, 98, 230; 67, 170; 68, 77, 92, 155, 210. See also OS VII, 87; 66, 108.

Alcoholysis of amides is possible but is seldom performed,⁶⁷⁸ except for the imidazolidine type of amide (101).

E. Attack by OCOR at an Alkyl Carbon

0-24 Alkylation of Carboxylic Acid Salts

Acyloxy-de-halogenation



Sodium salts of carboxylic acids, including hindered acids such as mesitoic, rapidly react with primary and secondary bromides and iodides at room temperature in dipolar aprotic solvents, especially HMPA, to give high yields of carboxylic esters.⁶⁷⁹ The mechanism is S_N2. Another method uses phase transfer catalysis.⁶⁸⁰ With this method good yields of esters have been obtained from primary, secondary, benzylic, allylic, and phenacyl halides.⁶⁸¹ In another procedure, which is applicable to long-chain primary halides, the dry carboxylate salt and the halide, impregnated on alumina as a solid support, are subjected to irradiation by microwaves in a commercial microwave oven.⁶⁸² In still another method, carboxylic acids

⁶⁷⁴Jeffery; Satchell *J. Chem. Soc.* **1962**, 1906; Rothman; Hecht; Pfeffer; Silbert *J. Org. Chem.* **1972**, 37, 3551.

⁶⁷⁵For examples, see Deghenghi; Engel *J. Am. Chem. Soc.* **1960**, 82, 3201; House; Trost *J. Org. Chem.* **1965**, 30, 2502.

⁶⁷⁶For example, see Hopff; Osman *Tetrahedron* **1968**, 24, 2205, 3887; Mondal; van der Meer; German; Heikens *Tetrahedron* **1974**, 30, 4205.

⁶⁷⁷Henry *J. Am. Chem. Soc.* **1971**, 93, 3853, *Acc. Chem. Res.* **1973**, 6, 16-24.

⁶⁷⁸For example, see Czarnik *Tetrahedron Lett.* **1984**, 25, 4875. For a list of references, see Ref. 508, pp. 989-990.

⁶⁷⁹Parker, *Adv. Org. Chem.* **1965**, 5, 1-46, p. 37; Alvarez; Watt *J. Org. Chem.* **1968**, 33, 2143; Mehta *Synthesis* **1972**, 262; Shaw; Kunerth *J. Org. Chem.* **1974**, 39, 1968; Larock *J. Org. Chem.* **1974**, 39, 3721; Pfeffer; Silbert *J. Org. Chem.* **1976**, 41, 1373.

⁶⁸⁰For reviews of phase transfer catalysis of this reaction, see Starks; Liotta, Ref. 404, pp. 140-155; Weber; Gokel *Phase Transfer Catalysis in Organic Synthesis*, Ref. 404, pp. 85-95.

⁶⁸¹For an alternative method for phenacyl halides, see Clark; Miller *Tetrahedron Lett.* **1977**, 599.

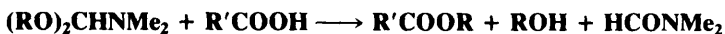
⁶⁸²Bram; Loupy; Majdoub; Gutierrez; Ruiz-Hitzky *Tetrahedron* **1990**, 46, 5167. See also Barry; Bram; Decodts; Loupy; Orange; Petit; Sansoulet *Synthesis* **1985**, 40; Arrad; Sasson *J. Am. Chem. Soc.* **1988**, 110, 185; Dakka; Sasson; Khawaled; Bram; Loupy *J. Chem. Soc., Chem. Commun.* **1991**, 853.

have been esterified by treatment with primary or secondary halides in benzene in the presence of DBU (p. 1023).⁶⁸³ In most cases good yields of esters can be obtained only with one of these methods. Without phase transfer catalysts and in protic solvents, the reaction is useful only for fairly active R, such as benzylic, allylic, etc. (S_N1 mechanism), but not for tertiary alkyl, since elimination occurs instead.⁶⁸⁴ Sodium salts are often used, but potassium, silver, cesium,⁶⁸⁵ and substituted ammonium salts have also been used. Lactones can be prepared from halo acids by treatment with base (see 0-22). This has most often been accomplished with γ and δ lactones, but macrocyclic lactones (e.g., 11 to 17 members) have also been prepared in this way.⁶⁸⁶

Cooper(I) carboxylates give esters with primary (including neopentyl without rearrangement), secondary, and tertiary alkyl, allylic, and vinylic halides.⁶⁸⁷ A simple S_N mechanism is obviously precluded in this case. Vinylic halides can be converted to vinylic acetates by treatment with sodium acetate if palladium(II) chloride is present.⁶⁸⁸

A carboxylic acid (not the salt) can be the nucleophile if F⁻ is present.⁶⁸⁹ Dihalides have been converted to diesters by this method.⁶⁸⁹ A COOH group can be conveniently protected by reaction of its ion with a phenacyl bromide (ArCOCH₂Br).⁵⁸⁴ The resulting ester is easily cleaved when desired with zinc and acetic acid. Dialkyl carbonates can be prepared without phosgene (see 0-20) by phase-transfer catalyzed treatment of primary alkyl halides with dry KHCO₃ and K₂CO₃.⁶⁹⁰

Other leaving groups can also be replaced by OCOR. Alkyl chlorosulfites (ROSOCI) and other derivatives of sulfuric, sulfonic, and other inorganic acids can be treated with carboxylate ions to give the corresponding esters. The use of dimethyl sulfate⁶⁹¹ or trimethyl phosphate⁶⁹² allows sterically hindered COOH groups to be methylated. With certain substrates, carboxylic acids are strong enough nucleophiles for the reaction. Examples of such substrates are trialkyl phosphites P(OR)₃⁶⁹³ and acetals of dimethylformamide.⁶⁹⁴



This is an S_N2 process, since inversion is found at R. Another good leaving group is NTs₂; ditosylamines react quite well with acetate ion in dipolar aprotic solvents.⁶⁹⁵ RNTs₂ + OAc⁻ → ROAc. Ordinary primary amines have been converted to acetates and benzoates by the Katritzky pyrylium-pyridinium method (p. 354).⁶⁹⁶ Quaternary ammonium salts can be cleaved by heating with AcO⁻ in an aprotic solvent.⁶⁹⁷ Oxonium ions can also be used as substrates.⁶⁹⁸ R₃O⁺ + R'COO⁻ → R'COOR + R₂O.

⁶⁸³Ono; Yamada; Saito; Tanaka; Kaji *Bull. Chem. Soc. Jpn.* **1978**, *51*, 2401; *Mal Synth. Commun.* **1986**, *16*, 331.

⁶⁸⁴See, however, Moore; Foglia; McGahan *J. Org. Chem.* **1979**, *44*, 2425.

⁶⁸⁵See Kruizinga; Strijveen; Kellogg *J. Org. Chem.* **1981**, *46*, 4321; Dijkstra; Kruizinga; Kellogg *J. Org. Chem.* **1987**, *52*, 4230.

⁶⁸⁶For example, see Galli; Mandolini *Org. Synth.* **VI**, 698; Kruizinga; Kellogg *J. Chem. Soc. Chem. Commun.* **1979**, 286; *J. Am. Chem. Soc.* **1981**, *103*, 5183; Regen; Kimura *J. Am. Chem. Soc.* **1982**, *104*, 2064; Kimura; Regen *J. Org. Chem.* **1983**, *48*, 1533.

⁶⁸⁷Lewin; Goldberg *Tetrahedron Lett.* **1972**, 491; Klumpp; Bos; Schakel; Schmitz; Vrielink *Tetrahedron Lett.* **1975**, 3429.

⁶⁸⁸Kohll; van Helden *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 481; Volger *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 501; Yamaji; Fujiwara; Asano; Teranishi *Bull. Chem. Soc. Jpn.* **1973**, *46*, 90.

⁶⁸⁹Clark; Emsley; Hoyte *J. Chem. Soc. Perkin Trans. 1* **1977**, 1091. See also Barluenga; Alonso-Cires; Campos; Asensio *Synthesis* **1983**, 649.

⁶⁹⁰Lissel; Dehmloew *Chem. Ber.* **1981**, *114*, 1210.

⁶⁹¹Grundy; James; Pattenden *Tetrahedron Lett.* **1972**, 757.

⁶⁹²Harris; Patel *Chem. Ind. (London)* **1973**, 1002.

⁶⁹³Szmuszkowicz *Org. Prep. Proceed. Int.* **1972**, *4*, 51.

⁶⁹⁴Vorbrüggen *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 211 [*Angew. Chem.* **75**, 296]; Brechbühler; Büchi; Hatz; Schreiber; Eschenmoser *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 212 [*Angew. Chem.* **75**, 296].

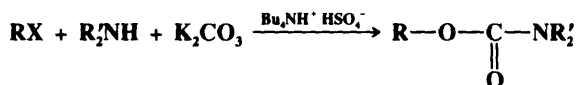
⁶⁹⁵Andersen; Uh *Synth. Commun.* **1972**, *2*, 297; Curtis; Schwartz; Hartman; Pick; Kolar; Baumgarten *Tetrahedron Lett.* **1977**, 1969.

⁶⁹⁶See Katritzky; Gruntz; Kenny; Rezende; Sheikh *J. Chem. Soc., Perkin Trans 1* **1979**, 430.

⁶⁹⁷Wilson; Joule *Tetrahedron* **1968**, *24*, 5493.

⁶⁹⁸Raber; Gariano; Brod; Gariano; Guida; Guida; Herbst *J. Org. Chem.* **1979**, *44*, 1149.

In a variation of this reaction, alkyl halides can be converted to carbamates, by treatment with a secondary amine and K_2CO_3 under phase transfer conditions.⁶⁹⁹

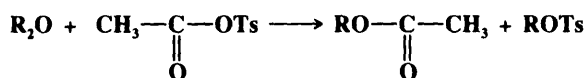


OS II, 5; III, 650; IV, 582; V, 580; VI, 273, 576, 698.

0-25 Cleavage of Ethers with Acetic Anhydride
Acyloxy-de-alkoxylation



Dialkyl ethers can be cleaved by treatment with anhydrous ferric chloride in acetic anhydride.⁷⁰⁰ In this reaction both R groups are converted to acetates. Yields are moderate to high. Ethers can also be cleaved by the mixed anhydride acetyl tosylate:⁷⁰¹



Epoxides give β -hydroxyalkyl carboxylates when treated with a carboxylic acid or a carboxylate ion and a suitable catalyst.⁷⁰²

OS 67, 114.

0-26 Alkylation of Carboxylic Acids with Diazo Compounds
Hydro,acyloxy-de-diazo-bisubstitution



Carboxylic acids can be converted to esters with diazo compounds in a reaction essentially the same as 0-15. In contrast to alcohols, carboxylic acids undergo the reaction quite well at room temperature, since the reactivity of the reagent increases with acidity. The reaction is used where high yields are important or where the acid is sensitive to higher temperatures. Because of availability, the diazo compounds most often used are diazomethane⁵⁹³ (for methyl esters)

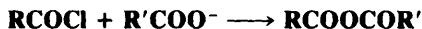


and diazo ketones. The mechanism is as shown in 0-15.

OS V, 797.

F. Attack by OCOR at an Acyl Carbon

0-27 Acylation of Carboxylic Acids with Acyl Halides
Acyloxy-de-halogenation



⁶⁹⁹Gómez-Parra; Sánchez; Torres *Synthesis* **1985**, 282, *J. Chem. Soc., Perkin Trans. 2* **1987**, 695. For another method, with lower yields, see Yoshida; Ishii; Yamashita *Chem. Lett.* **1984**, 1571.

⁷⁰⁰Ganem; Small *J. Org. Chem.* **1974**, 39, 3728.

⁷⁰¹Karger; Mazur *J. Am. Chem. Soc.* **1968**, 90, 3878. See also Coffi-Nketsia; Kergomard; Tautou *Bull. Soc. Chim. Fr.* **1967**, 2788.

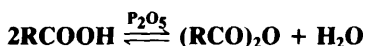
⁷⁰²See Otera; Matsuzaki *Synthesis* **1986**, 1019; Deardorff; Myles *Org. Synth.* 67, 114.

Unsymmetrical as well as symmetrical anhydrides are often prepared by the treatment of an acyl halide with a carboxylic acid salt. If a metallic salt is used, Na^+ , K^+ , or Ag^+ are the most common cations, but more often pyridine or another tertiary amine is added to the free acid and the salt thus formed is treated with the acyl halide. Mixed formic anhydrides are prepared from sodium formate and an aryl halide, by use of a solid-phase copolymer of pyridine-1-oxide.⁷⁰³ Symmetrical anhydrides can be prepared by reaction of the acyl halide with aqueous NaOH or NaHCO_3 under phase transfer conditions.⁷⁰⁴

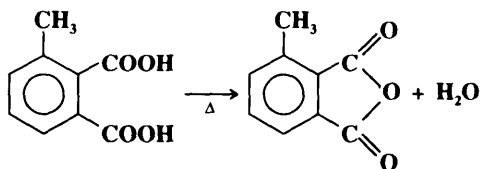
OS III, 28, 422, 488; IV, 285; VI, 8, 910; 66, 132. See also OS VI, 418.

0-28 Acylation of Carboxylic Acids with Carboxylic Acids

Acyloxy-de-hydroxylation

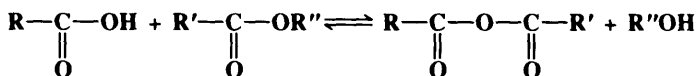


Anhydrides can be formed from two molecules of an ordinary carboxylic acid only if a dehydrating agent is present so that the equilibrium can be driven to the right. Common dehydrating agents⁷⁰⁵ are acetic anhydride, trifluoroacetic anhydride, dicyclohexylcarbodiimide,⁷⁰⁶ methoxyacetylene,⁷⁰⁷ and P_2O_5 . Among other reagents used have been trimethylsilylethoxyacetylene $\text{Me}_3\text{SiC}\equiv\text{COEt}$,⁷⁰⁸ tetracyanoethylene and a base,⁷⁰⁹ 1,1,1-trichloro-3,3,3-trifluoroacetone and pyridine,⁷¹⁰ diphenyl phosphorochloridate $(\text{PhO})_2\text{POCl}$,⁷¹¹ and phenyl N-phenylphosphoramidochloridate $(\text{PhO})(\text{PhNH})\text{POCl}$.⁷¹¹ The method is very poor for the formation of mixed anhydrides, which in any case generally undergo disproportionation to the two simple anhydrides when they are heated. However, simple heating of dicarboxylic acids does give cyclic anhydrides, provided that the ring formed contains five, six, or seven members, e.g.,



Malonic acid and its derivatives, which would give four-membered cyclic anhydrides, do not give this reaction when heated but undergo decarboxylation (2-40) instead.

Carboxylic acids exchange with amides and esters; these methods are sometimes used to prepare anhydrides if the equilibrium can be shifted, e.g.,



⁷⁰³Fife; Zhang *J. Org. Chem.* **1986**, 51, 3744. See also Fife; Zhang *Tetrahedron Lett.* **1986**, 27, 4933, 4937. For a review of acetic formic anhydride see Strazzolini; Giumanini; Cauci *Tetrahedron* **1990**, 46 1081-1118.

⁷⁰⁴Plusquellec; Roulleau; Lefevre; Brown *Tetrahedron* **1988**, 44, 2471; Wang; Hu; Cui *J. Chem. Res. (S)* **1990**, 84.

⁷⁰⁵For lists of other dehydrating agents with references, see Ref. 508, pp. 965-966; Ogliaruso; Wolfe, in Patai, Ref. 638, pt. 1, pp. 437-438.

⁷⁰⁶For example, see Schüssler; Zahn *Chem. Ber.* **1962**, 95, 1076; Rammler; Khorana *J. Am. Chem. Soc.* **1963**, 85, 1997. See also Hata; Tajima; Mukaiyama *Bull. Chem. Soc. Jpn.* **1968**, 41, 2746.

⁷⁰⁷See, for example, Eglinton; Jones; Shaw; Whiting *J. Chem. Soc.* **1954**, 1860; Arens; Doornbos *Recl. Trav. Chim. Pays-Bas* **1955**, 74, 79.

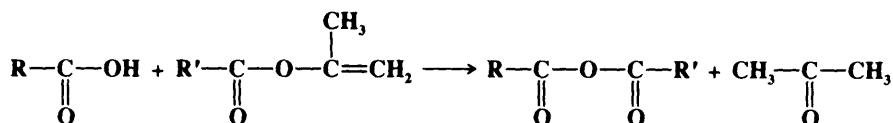
⁷⁰⁸Kita; Akai; Yoshigi; Nakajima; Yasuda; Tamura *Tetrahedron Lett.* **1984**, 25, 6027.

⁷⁰⁹Voisin; Gastambide *Tetrahedron Lett.* **1985**, 26, 1503.

⁷¹⁰Abdel-Baky; Giese *J. Org. Chem.* **1986**, 51, 3390.

⁷¹¹Mestres; Palomo *Synthesis* **1981**, 218.

Enolic esters are especially good for this purpose, because the equilibrium is shifted by formation of the ketone.



Carboxylic acids also exchange with anhydrides; indeed, this is how acetic anhydride acts as a dehydrating agent in this reaction.

Anhydrides can be formed from certain carboxylic acid salts; for example, by treatment of trimethylammonium carboxylates with phosgene:⁷¹²



or of thallium(I) carboxylates with thionyl chloride,⁶²⁴ or of sodium carboxylates with CCl_4 and a catalyst such as CuCl or FeCl_2 .⁷¹³

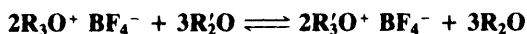
OS I, 91, 410; II, 194, 368, 560; III, 164, 449; IV, 242, 630, 790; V, 8, 822. Also see OS VI, 757; VII, 506.

G. Other Oxygen Nucleophiles

0-29 Formation of Oxonium Salts



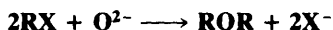
Alkyl halides can be alkylated by ethers or ketones to give oxonium salts, if a very weak, negatively charged nucleophile is present to serve as a counterion and a Lewis acid is present to combine with X^- .⁷¹⁴ A typical procedure consists of treating the halide with the ether or the ketone in the presence of AgBF_4 or AgSbF_6 . The Ag^+ serves to remove X^- and the BF_4^- or SbF_6^- acts as the counterion. Another method involves treatment of the halide with a complex formed between the oxygen compound and a Lewis acid, e.g., $\text{R}_2\text{O}-\text{BF}_3 + \text{RF} \rightarrow \text{R}_3\text{O}^+ \text{BF}_4^-$, though this method is most satisfactory when the oxygen and halogen atoms are in the same molecule so that a cyclic oxonium ion is obtained. Ethers and oxonium ions also undergo exchange reactions:



OS V, 1080, 1096, 1099; VI, 1019.

0-30 Reaction of Halides with Oxide Ion

Oxy-de-dihalo-aggre-substitution

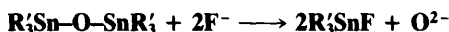


⁷¹²Rinderknecht; Ma *Helv. Chim. Acta* **1964**, 47, 152. See also Nangia; Chandrasekaran *J. Chem. Res.*, (S) **1984**, 100.

⁷¹³Weiss; Havelka; Nefedov *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1978**, 27, 193.

⁷¹⁴Meerwein; Hederich; Wunderlich *Arch. Pharm.* **1958**, 291/63, 541. For a review, see Perst, Ref. 84, pp. 22-39.

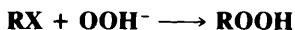
Alkyl halides can be converted to symmetrical ethers by treatment with oxide ion generated in situ by a reaction between an organotin oxide and fluoride ion in the presence of a quaternary ammonium iodide or a crown ether.⁷¹⁵



The procedure was used for R = primary alkyl and benzylic. Some unsymmetrical ethers ROR' were also made, by using R''OSnR'₃ instead of R'₃SnOSnR'₃.

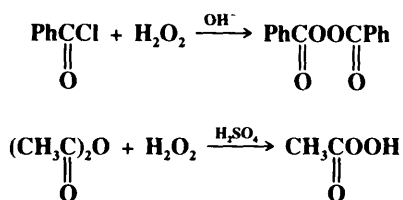
0-31 Preparation of Peroxides and Hydroperoxides

Hydroperoxy-de-halogenation

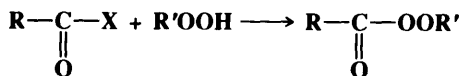


Hydroperoxides can be prepared by treatment of alkyl halides, esters of sulfuric or sulfonic acids, or alcohols with hydrogen peroxide in basic solution, where it is actually HO₂⁻.⁷¹⁶ Sodium peroxide is similarly used to prepare dialkyl peroxides (2RX + Na₂O₂ → ROOR). Another method, which gives primary, secondary, or tertiary hydroperoxides and peroxides, involves treatment of the halide with H₂O₂ or a peroxide in the presence of silver trifluoroacetate.⁷¹⁷ Peroxides can also be prepared⁷¹⁸ by treatment of alkyl bromides or tosylates with potassium superoxide KO₂ in the presence of crown ethers (though alcohols may be side products⁷¹⁹) and by the reaction between alkyl triflates and germanium or tin peroxide.⁷²⁰

Diacyl peroxides and acyl hydroperoxides can similarly be prepared⁷²¹ from acyl halides or anhydrides



and from carboxylic acids.⁷²² Diacyl peroxides can also be prepared by the treatment of carboxylic acids with hydrogen peroxide in the presence of dicyclohexylcarbodiimide,⁷²³ H₂SO₄, methanesulfonic acid, or some other dehydrating agent. Mixed alkyl-acyl peroxides (peresters) can be made from acyl halides and hydroperoxides.



OS III, 619, 649; V, 805, 904; VI, 276.

⁷¹⁵Harpp; Gingras *J. Am. Chem. Soc.* **1988**, *110*, 7737.

⁷¹⁶For a review, see Hiatt, in *Swern Organic Peroxides*, vol. 2, Wiley: New York, 1971, pp. 1-151. For a review of hydrogen peroxide, see Pandiarajan, in Pizey, Ref. 593, vol. 6, 1985, pp. 60-155.

⁷¹⁷Cookson; Davies; Roberts *J. Chem. Soc., Chem. Commun.* **1976**, 1022. For another preparation of unsymmetrical peroxides, see Bourgeois; Montaudon; Maillard *Synthesis* **1989**, 700.

⁷¹⁸Johnson; Nidy; Merritt *J. Am. Chem. Soc.* **1978**, *100*, 7960.

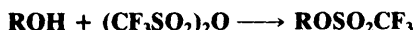
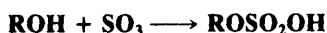
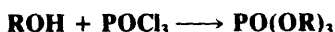
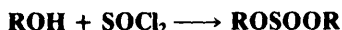
⁷¹⁹Alcohols have also been reported to be the main products: San Filippo; Chern; Valentine *J. Org. Chem.* **1975**, *40*, 1678; Corey; Nicolaou; Shibasaki; Machida; Shiner *Tetrahedron Lett.* **1975**, 3183.

⁷²⁰Salomon; Salomon *J. Am. Chem. Soc.* **1979**, *101*, 4290.

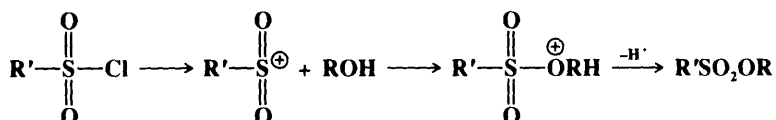
⁷²¹For a review of the synthesis and reactions of acyl peroxides and peresters, see Bouillon; Lick; Schank, in Patai, *The Chemistry of Peroxides*; Wiley: New York, 1983, pp. 279-309. For a review of the synthesis of acyl peroxides, see Hiatt, Ref. 716, vol. 2, pp. 799-929.

⁷²²See Silbert; Siegel; Swern *J. Org. Chem.* **1962**, *27*, 1336.

⁷²³Greene; Kazan *J. Org. Chem.* **1963**, *28*, 2168.

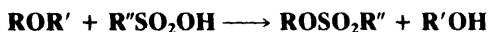
0-32 Preparation of Inorganic Esters**Nitrosooxy-de-hydroxylation**, etc.

The above transformations show a few of the many inorganic esters that can be prepared by attack of an inorganic acid or, better, its acid halide or anhydride, on an alcohol.⁷²⁴ Although for convenience all these similar reactions are grouped together, these are not all nucleophilic substitutions at R. The other possible pathway is nucleophilic substitution at the inorganic central atom:⁷²⁵



or a corresponding S_N2 type (see p. 496). In such cases there is no alkyl-O cleavage. Mono esters of sulfuric acid (alkylsulfuric acids), which are important industrially because their salts are used as detergents, can be prepared by treating alcohols with SO₃, H₂SO₄, Cl-SO₂OH, or SO₃ complexes.⁷²⁶ Alcohols are often converted to silyl ethers, for protection and other synthetic purposes: ROH + Me₃CSiCl → ROSiMe₃.⁷²⁷ Alkyl nitrites⁷²⁸ can be conveniently prepared by an exchange reaction ROH + R'ONO → RONO + R'OH, where R = *t*-Bu.⁷²⁹ Primary amines can be converted to alkyl nitrates (RNH₂ → RONO₂) by treatment with N₂O₄ at -78°C in the presence of an excess of amidine base.⁷³⁰

Alkyl halides are often used as substrates instead of alcohols. In such cases the *salt* of the inorganic acid is usually used and the mechanism is nucleophilic substitution at the carbon atom. An important example is the treatment of alkyl halides with silver nitrate to form alkyl nitrates. This is used as a test for alkyl halides. In some cases there is competition from the central atom. Thus nitrite ion is an ambident nucleophile that can give nitrites or nitro compounds (see 0-60).⁷³¹ Dialkyl or aryl alkyl ethers can be cleaved with anhydrous sulfonic acids.⁷³²



⁷²⁴For a review, see Ref. 575, pp. 481-497.

⁷²⁵For an example involving nitrite formation, see Aldred; Williams; Garley *J. Chem. Soc., Perkin Trans. 2* **1982**, 777.

⁷²⁶For a review, see Sandler; Karo, *Organic Functional Group Preparations*, 2d ed., vol. 3; Academic Press: New York, 1989, pp. 129-151.

⁷²⁷For a review, see Lalonde; Chan *Synthesis* **1985**, 817-845.

⁷²⁸For a review of alkyl nitrites, see Williams *Nitrosation*; Cambridge University Press: Cambridge, 1988, pp. 150-172.

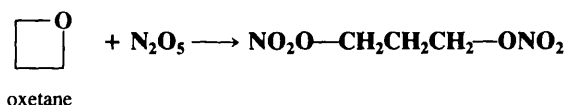
⁷²⁹Doyle; Terpstra; Pickering; LePoire *J. Org. Chem.* **1983**, 48, 3379. For a review of the nitrosation of alcohols, see Ref. 728, pp. 150-156.

⁷³⁰Barton; Narang *J. Chem. Soc., Perkin Trans. 1* **1977**, 1114.

⁷³¹For a review of formation of nitrates from alkyl halides, see Boguslavskaya; Chuvatkin; Kartashov *Russ. Chem. Rev.* **1988**, 57, 760-775.

⁷³²Klamann; Weyerstahl *Chem. Ber.* **1965**, 98, 2070.

R" may be alkyl or aryl. For dialkyl ethers, the reaction does not end as indicated above, since R'OH is rapidly converted to R'OR' by the sulfonic acid (reaction 0-16), which in turn is further cleaved to R'OSO₂R" so that the product is a mixture of the two sulfonates. For aryl alkyl ethers, cleavage always takes place to give the phenol, which is not converted to the aryl ether under these conditions. Ethers can also be cleaved in a similar manner by mixed anhydrides of sulfonic and carboxylic acids⁷³³ (prepared as in 0-33). β-Hydroxyalkyl perchlorates⁷³⁴ and sulfonates can be obtained from epoxides.⁷³⁵ Epoxides and oxetanes give dinitrates when treated with N₂O₅,⁷³⁶ e.g.,



Aziridines and azetidines react similarly, giving nitramine nitrates; e.g., N-butylazetidine gave NO₂OCH₂CH₂CH₂N(Bu)NO₂.⁷³⁶

OS II, 106, 108, 109, 112, 204, 412; III, 148, 471; IV, 955; V, 839; 66, 211; 67, 1, 13. Also see OS II, 111.

0-33 Preparation of Mixed Organic-Inorganic Anhydrides

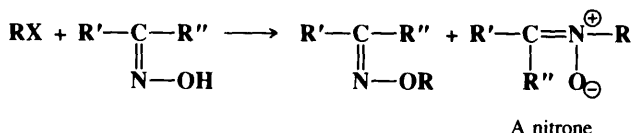
Nitrooxy-de-acyloxy-substitution



Mixed organic-inorganic anhydrides are seldom isolated, though they are often intermediates when acylation is carried out with acid derivatives catalyzed by inorganic acids. Sulfuric, perchloric, phosphoric, and other acids form similar anhydrides, most of which are unstable or not easily obtained because the equilibrium lies in the wrong direction. These intermediates are formed from amides, carboxylic acids, and esters, as well as anhydrides. Organic anhydrides of phosphoric acid are more stable than most others and, for example, RCOOPO(OH)₂ can be prepared in the form of its salts.⁷³⁷ Mixed anhydrides of carboxylic and sulfonic acids (RCOOSO₂R') are obtained in high yields by treatment of sulfonic acids with acyl halides or (less preferred) anhydrides.⁷³⁸

OS I, 495; VI, 207; VII, 81.

0-34 Alkylation of Oximes



Oximes can be alkylated by alkyl halides or sulfates. N-Alkylation is a side reaction, yielding a nitron.⁷³⁹ The relative yield of oxime ether and nitron depends on the nature of the

⁷³³Karger; Mazur *J. Org. Chem.* **1971**, 36, 532, 540.

⁷³⁴For a review of the synthesis and reactions of organic perchlorates, see Zefirov; Zhdankin; Koz'min *Russ. Chem. Rev.* **1988**, 57, 1041-1053.

⁷³⁵Zefirov; Kirin; Yur'eva; Zhdankin; Kozmin *J. Org. Chem. USSR* **1987**, 23, 1264.

⁷³⁶Golding; Millar; Paul; Richards *Tetrahedron Lett.* **1988**, 29, 2731, 2735.

⁷³⁷Avison *J. Chem. Soc.* **1955**, 732.

⁷³⁸Karger; Mazur *J. Org. Chem.* **1971**, 36, 528.

⁷³⁹For a review of nitrones, see Torssell *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*; VCH: New York, 1988, pp. 75-93.

reagents, including the configuration of the oxime, and on the reaction conditions.⁷⁴⁰ For example, *anti*-benzaldoximes give nitrones, while the *syn* isomers give oxime ethers.⁷⁴¹

OS III, 172; V, 1031. Also see OS V, 269; VI, 199.

Sulfur Nucleophiles

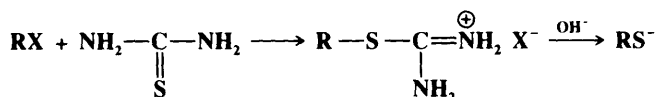
Sulfur compounds⁷⁴² are better nucleophiles than their oxygen analogs (p. 349), so in most cases these reactions take place faster and more smoothly than the corresponding reactions with oxygen nucleophiles. There is evidence that some of these reactions take place by SET mechanisms.⁷⁴³

0-35 Attack by SH at an Alkyl Carbon. Formation of Thiols⁷⁴⁴

Mercapto-de-halogenation



Sodium sulfhydryde (NaSH) is a much better reagent for the formation of thiols (mercaptans) from alkyl halides than H₂S and is used much more often. It is easily prepared by bubbling H₂S into an alkaline solution. The reaction is most useful for primary halides. Secondary substrates give much lower yields, and the reaction fails completely for tertiary halides because elimination predominates. Sulfuric and sulfonic esters can be used instead of halides. Thioethers (RSR) are often side products.⁷⁴⁵ The conversion can also be accomplished under neutral conditions by treatment of a primary halide with F⁻ and a tin sulfide such as Ph₃SnSSnPh₃.⁷⁴⁶ An indirect method for the conversion of an alkyl halide to a thiol consists of treatment with thiourea to give an isothiuronium salt, which with alkali or a high-molecular-weight amine is cleaved to the thiol:



Another indirect method is hydrolysis of Bunte salts (see 0-39).

Thiols have also been prepared from alcohols. One method involves treatment with H₂S and a catalyst such as Al₂O₃,⁷⁴⁷ but this is limited to primary alcohols. Another method involves treatment with Lawesson's reagent (see 6-11).⁷⁴⁸ Still another method, involving the use of a fluoropyridinium salt and sodium N,N-dimethylthiocarbamate, can be applied

⁷⁴⁰For a review, see Reutov; Beletskaya; Kurts, Ref. 422, pp. 262-272.

⁷⁴¹Buehler *J. Org. Chem.* **1967**, 32, 261.

⁷⁴²For monographs on sulfur compounds, see Bernardi; Csizmadia; Mangini *Organic Sulfur Chemistry*; Elsevier: New York, 1985; Oae *Organic Chemistry of Sulfur*; Plenum: New York, 1977. For monographs on selenium compounds, see Krief; Hevesi *Organoselenium Chemistry I*; Springer: New York, 1988; Liotta *Organoselenium Chemistry*; Wiley: New York, 1987.

⁷⁴³See Ashby; Park; Goel; Su *J. Org. Chem.* **1985**, 50, 5184.

⁷⁴⁴For a review, see Wardell, in Patai *The Chemistry of the Thiol Group*, pt. 1; Wiley: New York, 1974, pp. 179-211.

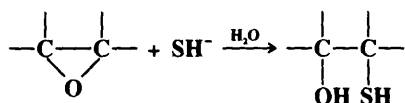
⁷⁴⁵For a method of avoiding thioether formation, see Vasil'tsov; Trofimov; Amosova *J. Org. Chem. USSR* **1983**, 19, 1197.

⁷⁴⁶Gingras; Harpp *Tetrahedron Lett.* **1990**, 31, 1397.

⁷⁴⁷Lucien; Barrault; Guisnet; Maurel *Nouv. J. Chim.* **1979**, 3, 15.

⁷⁴⁸Nishio *J. Chem. Soc., Chem. Commun.* **1989**, 205.

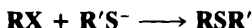
to primary, secondary, allylic, and benzylic alcohols.⁷⁴⁹ When epoxides are substrates, the products are β -hydroxy thiols:⁷⁵⁰



Tertiary nitro compounds give thiols ($\text{RNO}_2 \rightarrow \text{RSH}$) when treated with sulfur and sodium sulfide, followed by amalgamated aluminum.⁷⁵¹

OS III, 363, 440; IV, 401, 491; V, 1046; 65, 50. Also see OS II, 345, 411, 573; IV, 232; V, 223; VI, 620.

0-36 Attack by S at an Alkyl Carbon. Formation of Thioethers Alkylthio-de-halogenation



Thioethers (sulfides) can be prepared by treatment of alkyl halides with salts of thiols (thiolate ions).⁷⁵² R' may be alkyl or aryl. As in 0-35, RX cannot be a tertiary halide, and sulfuric and sulfonic esters can be used instead of halides. As in the Williamson reaction (0-12), yields are improved by phase-transfer catalysis.⁷⁵³ Instead of RS^- ions, thiols themselves can be used, if the reaction is run in benzene in the presence of DBU (p. 1023).⁷⁵⁴ Neopentyl bromide was converted to $\text{Me}_3\text{CCH}_2\text{SPh}$ in good yield by treatment with PhS^- in liquid NH_3 at -33°C under the influence of light.⁷⁵⁵ This probably takes place by an $\text{S}_{\text{RN}}1$ mechanism (see p. 648). Vinylic sulfides can be prepared by treating vinylic bromides with PhS^- in the presence of a nickel complex,⁷⁵⁶ and with R_3SnPh in the presence of $\text{Pd}(\text{PPh}_3)_4$.⁷⁵⁷

R can be tertiary if an alcohol is the substrate, e.g.,⁷⁵⁸



This reaction is analogous to 0-16. Primary and secondary alcohols can be converted to alkyl aryl sulfides ($\text{ROH} \rightarrow \text{RSAr}$) in high yields by treatment with Bu_3P and an N -(arylthio)succinimide in benzene.⁷⁵⁹ Thioethers RSR' can be prepared from an alcohol ROH and a halide $\text{R}'\text{Cl}$ by treatment with tetramethylthiourea $\text{Me}_2\text{NC}(=\text{S})\text{NMe}_2$ followed by NaH .⁷⁶⁰

Thiolate ions are also useful for the demethylation of certain ethers,⁷⁶¹ esters, amines, and quaternary ammonium salts. Aryl methyl ethers⁷⁶² can be cleaved by heating with EtS^-

⁷⁴⁹Hojo; Yoshino; Mukaiyama *Chem. Lett.* **1977**, 133, 437. For another method, see Alper; Sibtain *J. Org. Chem.* **1988**, 53, 3306.

⁷⁵⁰For a review, see Ref. 744, pp. 246-251.

⁷⁵¹Kornblum; Widmer *J. Am. Chem. Soc.* **1978**, 100, 7086.

⁷⁵²For a review, see Peach, in Patai, Ref. 744, pt. 2, pp. 721-735.

⁷⁵³For a review of the use of phase transfer catalysis to prepare sulfur-containing compounds, see Weber; Gokel *Phase Transfer Catalysis in Organic Synthesis*, Ref. 404, pp. 221-233.

⁷⁵⁴Ono; Miyake; Saito; Kaji *Synthesis* **1980**, 952. See also Ferreira; Comassetto; Braga *Synth. Commun.* **1982**, 12, 595; Ando; Furuhashi; Tsumaki; Sekiguchi *Synth. Commun.* **1982**, 12, 627.

⁷⁵⁵Pierini; Peñeñory; Rossi *J. Org. Chem.* **1985**, 50, 2739.

⁷⁵⁶Cristau; Chabaud; Labaudiniere; Christol *J. Org. Chem.* **1986**, 51, 875.

⁷⁵⁷Carpita; Rossi; Scamuzzi *Tetrahedron Lett.* **1989**, 30, 2699. For another method, see Ogawa; Hayami; Suzuki *Chem. Lett.* **1989**, 769.

⁷⁵⁸Fehnel; Carmack *J. Am. Chem. Soc.* **1949**, 71, 84; Cain; Evans; Lee *J. Chem. Soc.* **1962**, 1694.

⁷⁵⁹Walker *Tetrahedron Lett.* **1977**, 4475. See the references in this paper for other methods of converting alcohols to sulfides. See also Cleary *Synth. Commun.* **1989**, 19, 737.

⁷⁶⁰Fujisaki; Fujiwara; Norisue; Kajigaeshi *Bull. Chem. Soc. Jpn.* **1985**, 58, 2429.

⁷⁶¹For a review, see Evers *Chem. Scr.* **1986**, 26, 585-597.

⁷⁶²Certain other sulfur-containing reagents also cleave methyl and other ethers: see Hanessian; Guindon *Tetrahedron Lett.* **1980**, 21, 2305; Williard; Fryhle *Tetrahedron Lett.* **1980**, 21, 3731; Node; Nishide; Fuji; Fujita *J. Org. Chem.* **1980**, 45, 4275. For cleavage with selenium-containing reagents, see Evers; Christiaens *Tetrahedron Lett.* **1983**, 24, 377. For a review of the cleavage of aryl alkyl ethers, see Tiecco *Synthesis* **1988**, 749-759.

in the dipolar aprotic solvent DMF: $\text{ROAr} + \text{EtS}^- \rightarrow \text{ArO}^- + \text{EtSR}$.⁷⁶³ Carboxylic esters and lactones are cleaved (the lactones give ω -alkylthio carboxylic acids) with a thiol and AlCl_3 or AlBr_3 .⁷⁶⁴ Esters and lactones are similarly cleaved in high yield by phenyl selenide ion PhSe^- .⁷⁶⁵ Allylic sulfides have been prepared by treating allylic carbonates ROCOOMe (R = an allylic group) with a thiol and a $\text{Pd}(0)$ catalyst.⁷⁶⁶ A good method for the demethylation of quaternary ammonium salts consists of refluxing them with PhS^- in butanone.⁷⁶⁷

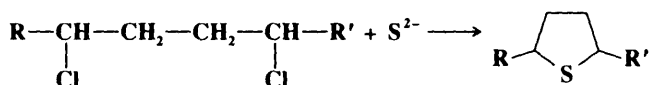


A methyl group is cleaved more readily than other simple alkyl groups (such as ethyl), though loss of these groups competes, but benzylic and allylic groups cleave even more easily, and this is a useful procedure for the cleavage of benzylic and allylic groups from quaternary ammonium salts, even if methyl groups are also present.⁷⁶⁸

Symmetrical thioethers can also be prepared by treatment of an alkyl halide with sodium sulfide,⁷⁶⁹ in a reaction similar to 0-30.



This reaction can be carried out internally, by treatment of sulfide ions with 1,4- or 1,5-dihalides, to prepare five- and six-membered sulfur-containing heterocyclic rings.



Certain larger rings have also been closed in this way.⁷⁷⁰

gem-Dihalides can be converted to thioacetals $\text{RCH}(\text{SR}')_2$,⁷⁷¹ and acetals have been converted to monothioacetals $\text{R}_2\text{C}(\text{OR}')(\text{SR}')$,⁷⁷² and to thioacetals.⁷⁷³

Selenides and tellurides can be prepared similarly.⁷⁷⁴ When epoxides are substrates, β -hydroxy sulfides are obtained in a manner analogous to that mentioned in 0-35. Epoxides can also be directly converted to episulfides,⁷⁷⁵ by treatment with a phosphine sulfide such as Ph_3PS ⁷⁷⁶ or with thiourea and titanium tetrakisopropoxide.⁷⁷⁷

⁷⁶³Feutrell; Mirrington *Tetrahedron Lett.* **1970**, 1327; *Aust. J. Chem.* **1972**, 25, 1719, 1731.

⁷⁶⁴Node; Nishide; Ochiai; Fuji; Fujita *J. Org. Chem.* **1981**, 46, 5163.

⁷⁶⁵Scarborough; Smith *Tetrahedron Lett.* **1977**, 4361; Liotta; Santiesteban *Tetrahedron Lett.* **1977**, 4369; Liotta; Sunay; Santiesteban; Markiewicz *J. Org. Chem.* **1981**, 46, 2605; Kong; Chen; Zhou *Synth. Commun.* **1988**, 18, 801.

⁷⁶⁶Trost; Scanlan *Tetrahedron Lett.* **1986**, 27, 4141.

⁷⁶⁷Shamma; Deno; Remar *Tetrahedron Lett.* **1966**, 1375. For alternative procedures, see Hutchins; Dux *J. Org. Chem.* **1973**, 38, 1961; Posner; Ting *Synth. Commun.* **1974**, 4, 355.

⁷⁶⁸Kametani; Kigasawa; Hiiragi; Wagatsuma; Wakisaka *Tetrahedron Lett.* **1969**, 635.

⁷⁶⁹For another reagent, see Harpp; Gingras; Aida; Chan *Synthesis* **1987**, 1122.

⁷⁷⁰See Hammerschmidt; Bieber; Vögtle *Chem. Ber.* **1978**, 111, 2445; Singh; Mehrotra; Regen *Synth. Commun.* **1981**, 11, 409.

⁷⁷¹See, for example Wähälä; Ojanperä; Häyri; Hase *Synth. Commun.* **1987**, 17, 137.

⁷⁷²Masaki; Serizawa; Kaji *Chem. Lett.* **1985**, 1933; Sato; Kobayashi; Gojo; Yoshida; Otera; Nozaki *Chem. Lett.* **1987**, 1661.

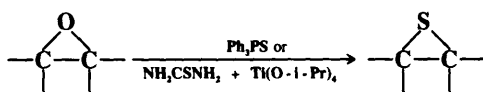
⁷⁷³Park; Kim *Chem. Lett.* **1989**, 629.

⁷⁷⁴Brandsma; Wijers *Recl. Trav. Chim. Pays-Bas* **1963**, 82, 68; Clarembau; Krief *Tetrahedron Lett.* **1984**, 25, 3625. For a review of nucleophilic selenium, see Monahan; Brown; Waykole; Liotta, in Liotta, Ref. 742, pp. 207-241.

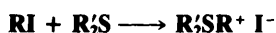
⁷⁷⁵For a review of episulfide information, see Fokin; Kolomiets *Russ. Chem. Rev.* **1975**, 44, 138-153.

⁷⁷⁶Chan; Finkenbine *J. Am. Chem. Soc.* **1972**, 94, 2880.

⁷⁷⁷Gao; Sharpless *J. Org. Chem.* **1988**, 53, 4114. For other methods, see Calō; Lopez; Marchese; Pesce *J. Chem. Soc., Chem. Commun.* **1975**, 621; Takido; Kobayashi; Itabashi *Synthesis* **1986**, 779; Bouda; Borredon; Delmas; Gaset *Synth. Commun.* **1987**, 17, 943, **1989**, 19, 491.

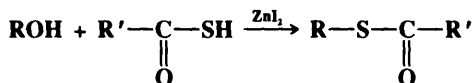


Alkyl halides, treated with thioethers, give sulfonium salts.⁷⁷⁸



Other leaving groups have also been used for this purpose.⁷⁷⁹

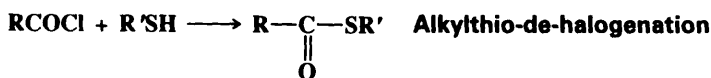
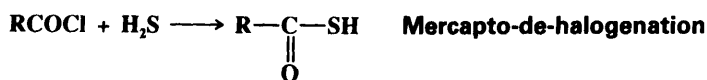
Alcohols, when treated with a thiol acid and zinc iodide, give thiol esters:⁷⁸⁰



This method is an alternative to 0-37 as a way to prepare thiol esters.

OS **II**, 31, 345, 547, 576; **III**, 332, 751, 763; **IV**, 396, 667, 892, 967; **V**, 562, 780, 1046; **VI**, 5, 31, 268, 364, 403, 482, 556, 601, 683, 704, 737, 833, 859; **VII**, 453; **65**, 150. See also OS **VI**, 776.

0-37 Attack by SH or SR at an Acyl Carbon⁷⁸¹



Thiol acids and thiol esters⁷⁸² can be prepared in this manner, which is analogous to 0-8 and 0-23. Anhydrides⁷⁸³ and aryl esters (RCOOAr)⁷⁸⁴ are also used as substrates, but the reagents in these cases are usually SH^- and SR^- . Thiol esters can also be prepared by treatment of carboxylic acids with trisalkylthioboranes $\text{B}(\text{SR})_3$,⁷⁸⁵ with P_4S_{10} - Ph_3SbO ,⁷⁸⁶ or with a thiol RSH and either polyphosphate ester or phenyl dichlorophosphate PhOPOCl_2 .⁷⁸⁷ Esters RCOOR' can be converted to thiol esters RCOSR'' by treatment with trimethylsilyl sulfides $\text{Me}_3\text{SiSR}''$ and AlCl_3 .⁷⁸⁸

OS **III**, 116, 599; **IV**, 924, 928; **VII**, 81; **66**, 108.

⁷⁷⁸For a review of the synthesis of sulfonium salts, see Lowe, in Stirling, Ref. 363, pp. 267-312.

⁷⁷⁹See Badet; Jacob; Julia *Tetrahedron* **1981**, 37, 887; Badet; Julia *Tetrahedron Lett.* **1979**, 1101, and references cited in the latter paper.

⁷⁸⁰Gauthier; Bourdon; Young *Tetrahedron Lett.* **1986**, 27, 15.

⁷⁸¹For a review, see Satchell *Q. Rev., Chem. Soc.* **1963**, 17, 160-203, pp. 182-184.

⁷⁸²For a review of these compounds, see Scheithauer; Mayer *Top. Sulfur Chem.* **1979**, 4, 1-373.

⁷⁸³Ahmad; Iqbal *Tetrahedron Lett.* **1986**, 27, 3791.

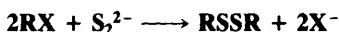
⁷⁸⁴Hirabayashi; Mizuta; Mazume *Bull. Chem. Soc. Jpn.* **1965**, 38, 320.

⁷⁸⁵Pelter; Levitt; Smith; Jones *J. Chem. Soc., Perkin Trans. 1* **1977**, 1672.

⁷⁸⁶Nomura; Miyazaki; Nakano; Matsuda *Chem. Ber.* **1990**, 123, 2081.

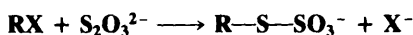
⁷⁸⁷Imamoto; Koda; Yokoyama *Synthesis* **1982**, 134; Liu; Sabesan *Can. J. Chem.* **1980**, 58, 2645. For other methods of converting carboxylic acids to thiol esters, see the references given in these papers. See also Dellaria; Nordeen; Swett *Synth. Commun.* **1986**, 16, 1043.

⁷⁸⁸Mukaiyama; Takeda; Atsumi *Chem. Lett.* **1974**, 187. See also Hatch; Weinreb *J. Org. Chem.* **1977**, 42, 3960; Cohen; Gapinski *Tetrahedron* **1978**, 4319.

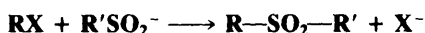
0-38 Formation of Disulfides**Dithio-de-dihalo-aggre-substitution**

Disulfides can be prepared by treatment of alkyl halides with disulfide ions and also indirectly by the reaction of Bunte salts (see **0-39**) with acid solutions of iodide, thiocyanate ion, or thiourea,⁷⁸⁹ or by pyrolysis or treatment with hydrogen peroxide. Alkyl halides also give disulfides when refluxed with sulfur and NaOH,⁷⁹⁰ and with piperidinium tetrathiotungstate or piperidinium tetrathiomolybdate.⁷⁹¹

There are no OS references, but a similar preparation of a polysulfide may be found in OS **IV**, 295.

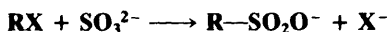
0-39 Formation of Bunte Salts**Sulfonatothio-de-halogenation**

Primary and secondary but not tertiary alkyl halides are easily converted to Bunte salts (RSSO_3^-) by treatment with thiosulfate ion.⁷⁹² Bunte salts can be hydrolyzed with acids to give the corresponding thiols⁷⁹³ or converted to disulfides, tetrasulfides, or pentasulfides.⁷⁹⁴ OS **VI**, 235.

0-40 Alkylation of Sulfinic Acid Salts**Alkylsulfonyl-de-halogenation**

Alkyl halides or alkyl sulfates, treated with the salts of sulfinic acids, give sulfones.⁷⁹⁵ Alkyl sulfonates $\text{R}'\text{SO-OR}$ may be side products.⁷⁹⁶ Sulfonic acids themselves can be used, if DBU (p. 1023) is present.⁷⁹⁷ Sulfones have also been prepared by treatment of alkyl halides with tosylhydrazide.⁷⁹⁸

OS **IV**, 674. See also OS **VI**, 1016.

0-41 Attack by Sulfite Ion**Sulfonato-de-halogenation**

Salts of sulfonic acids can be prepared by treatment of primary or secondary alkyl halides with sulfite ion.⁷⁹⁹ Even tertiary halides have been used, though the yields are low. Epoxides treated with bisulfite give β -hydroxy sulfonic acids.⁸⁰⁰

⁷⁸⁹Milligan; Swan *J. Chem. Soc.* **1962**, 2712.

⁷⁹⁰Chorbadjiev; Roumian; Markov *J. Prakt. Chem.* **1977**, 319, 1036.

⁷⁹¹Dhar; Chandrasekaran *J. Org. Chem.* **1989**, 54, 2998.

⁷⁹²For a review of Bunte salts, see Distler *Angew. Chem. Int. Ed. Engl.* **1967**, 6, 544-553 [*Angew. Chem.* 79, 520-529].

⁷⁹³Kice *J. Org. Chem.* **1963**, 28, 957.

⁷⁹⁴Milligan; Saville; Swan *J. Chem. Soc.* **1963**, 3608.

⁷⁹⁵For a review, see Schank, in Patai; Rappoport; Stirling *The Chemistry of Sulphones and Sulphoxides*; Wiley: New York, 1988, pp. 165-231, pp. 177-188.

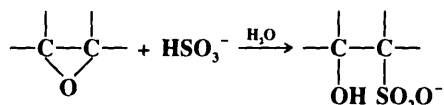
⁷⁹⁶See, for example Meek; Fowler *J. Org. Chem.* **1968**, 33, 3422; Kieľbasiński; Żurawiński; Drabowicz; Mikołajczyk *Tetrahedron* **1988**, 44, 6687.

⁷⁹⁷Biswas; Mal *J. Chem. Res. (S)* **1988**, 308.

⁷⁹⁸Ballini; Marcantoni; Petrini *Tetrahedron* **1989**, 45, 6791.

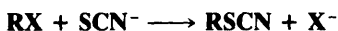
⁷⁹⁹For a review, see Gilbert *Sulfonation and Related Reactions*; Wiley: New York, 1965, pp. 136-148, 161-163.

⁸⁰⁰For a discussion, see Yoneda; Griffin; Carlyle *J. Org. Chem.* **1975**, 40, 375.



OS II, 558, 564; IV, 529.

0-42 Formation of Alkyl Thiocyanates
Thiocyanato-de-halogenation



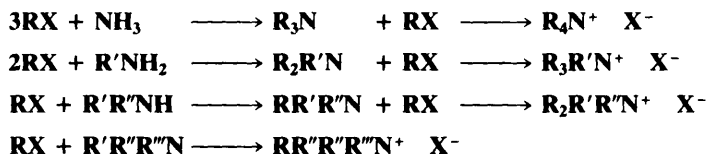
Alkyl halides or sulfuric or sulfonic esters can be heated with sodium or potassium thiocyanate to give alkyl thiocyanates,⁸⁰¹ though the attack by the analogous cyanate ion (**0-62**) gives exclusive N-alkylation. Primary amines can be converted to thiocyanates by the Katrietzky pyrylium-pyridinium method (p. 354).⁸⁰²

OS II, 366.

Nitrogen Nucleophiles

A. Attack by NH₂, NHR, or NR₂ at an Alkyl Carbon

0-43 Alkylation of Amines
Amino-de-halogenation



The reaction between alkyl halides and ammonia or primary amines is not usually a feasible method for the preparation of primary or secondary amines, since they are stronger bases than ammonia and preferentially attack the substrate. However, the reaction is very useful for the preparation of tertiary amines⁸⁰³ and quaternary ammonium salts. If ammonia is the nucleophile,⁸⁰⁴ the three or four alkyl groups on the nitrogen of the product must be identical. If a primary, secondary, or tertiary amine is used, then different alkyl groups can be placed on the same nitrogen atom. The conversion of tertiary amines to quaternary salts is called the *Menshutkin reaction*.⁸⁰⁵ It is sometimes possible to use this method for the preparation of a primary amine by the use of a large excess of ammonia or a secondary amine by the use of a large excess of primary amine. However, the limitations of this approach can be seen in the reaction of a saturated solution of ammonia in 90% ethanol with ethyl bromide

⁸⁰¹For a review of thiocyanates, see Guy, in Patai *The Chemistry of Cyanates and Their Thio Derivatives*, pt. 2; pp. 819-886, Wiley: New York, 1977, pp. 819-886.

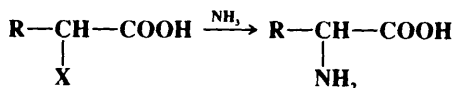
⁸⁰²Katritzky; Gruntz; Mongelli; Rezende *J. Chem. Soc., Perkin Trans. I* **1979**, 1953. For the conversion of primary alcohols to thiocyanates, see Tamura; Kawasaki; Adachi; Tanio; Kita *Tetrahedron Lett.* **1977**, 4417.

⁸⁰³For reviews of this reaction, see Gibson, in Patai, Ref. 355, pp. 45-55; Spialter; Pappalardo *The Acyclic Aliphatic Tertiary Amines*; Macmillan: New York, 1965, pp. 14-29.

⁸⁰⁴For a review of ammonia as a synthetic reagent, see Jeyaraman, in Pizey, Ref. 593, vol. 5, 1983, pp. 9-83.

⁸⁰⁵For a review of stereoselectivity in this reaction, especially where the tertiary nitrogen is included in a ring, see Bottini, *Sel. Org. Transform.* **1970**, 1, 89-142. For a review of quaternization of heteroaromatic rings, see Zoltewicz; Deady *Adv. Heterocycl. Chem.* **1978**, 22, 71-121.

in a 16:1 molar ratio, under which conditions the yield of primary amine was 34.2% (at a 1:1 ratio the yield was 11.3%).⁸⁰⁶ One type of substrate that does give reasonable yields of primary amine (provided a large excess of NH_3 is used) are α -halo acids, which are converted to amino acids.



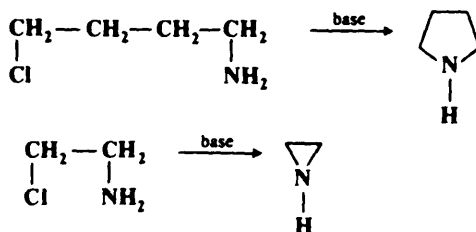
Primary amines can be prepared from alkyl halides by **0-44**, by **0-63**, by **0-61** followed by reduction of the azide (**9-53**), or by the Gabriel synthesis (**0-58**).

The immediate product in any particular step is the protonated amine, which, however, rapidly loses a proton to another molecule of ammonia or amine in an equilibrium process, e.g.,

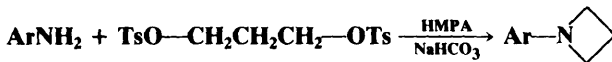


When it is desired to convert a primary or secondary amine directly to the quaternary salt (*exhaustive alkylation*), the rate can be increased by the addition of a nonnucleophilic strong base that serves to remove the proton from $\text{RR}'\text{NH}_2^+$ or $\text{RR}'\text{R}''\text{NH}^+$ and thus liberates the amine to attack another molecule of RX .⁸⁰⁷

The conjugate bases of ammonia and of primary and secondary amines (NH_2^- , RNH^- , R_2N^-) are sometimes used as nucleophiles,⁸⁰⁸ but in most cases offer no advantage over ammonia or amines, since the latter are basic enough. This is in contrast to the analogous methods **0-1**, **0-12**, **0-35**, and **0-36**. Primary arylamines are easily alkylated, but diaryl- and triarylamines are very poor nucleophiles. However, the reaction has been carried out with diarylamines.⁸⁰⁹ Sulfates or sulfonates can be used instead of halides. The reaction can be carried out intramolecularly to give cyclic amines, with three-, five-, and six-membered (but not four-membered) rings being easily prepared. Thus, 4-chloro-1-aminobutane treated with base gives pyrrolidine, and 2-chloroethylamine gives aziridine⁸¹⁰ (analogous to **0-13**):



Four-membered cyclic amines (azetidines) have been prepared in a different way:⁸¹¹



This reaction was also used to close five-, six-, and seven-membered rings.

⁸⁰⁶Werner *J. Chem. Soc.* **1918**, 113, 899.

⁸⁰⁷Sommer; Jackson *J. Org. Chem.* **1970**, 35, 1558; Sommer; Lipp; Jackson *J. Org. Chem.* **1971**, 36, 824.

⁸⁰⁸For a discussion of the mechanism of the reaction between a primary halide and $\text{Ph}_2\text{N}^-\text{Li}$, see DePue; Collum *J. Am. Chem. Soc.* **1988**, 110, 5524.

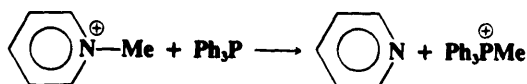
⁸⁰⁹Patai; Weiss *J. Chem. Soc.* **1959**, 1035.

⁸¹⁰For a review of aziridine formation by this method, see Dermer; Ham, Ref. 437, pp. 1-59.

⁸¹¹Juaristi; Madrigal *Tetrahedron* **1989**, 45, 629.

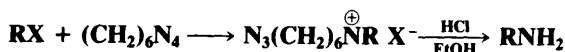
As usual, tertiary substrates do not give the reaction at all but undergo preferential elimination. However, tertiary (but not primary or secondary) halides R_3CCl can be converted to primary amines R_3CNH_2 by treatment with NCl_3 and $AlCl_3$ ⁸¹² in a reaction related to 0-50.

Phosphines behave similarly, and compounds of the type R_3P and $R_4P^+ X^-$ can be so prepared. The reaction between triphenylphosphine and quaternary salts of nitrogen heterocycles in an aprotic solvent is probably the best way of dealkylating the heterocycles, e.g.,⁸¹³



OS I, 23, 48, 102, 300, 488; II, 85, 183, 290, 328, 374, 397, 419, 563; III, 50, 148, 254, 256, 495, 504, 523, 705, 753, 774, 813, 848; IV, 84, 98, 383, 433, 466, 582, 585, 980; V, 88, 124, 306, 361, 434, 499, 541, 555, 608, 736, 751, 758, 769, 825, 883, 985, 989, 1018, 1085, 1145; VI, 56, 75, 104, 106, 175, 552, 652, 704, 818, 967; 67, 105, 133; 68, 188, 227. Also see OS II, 395; IV, 950.

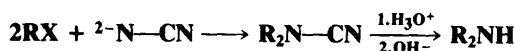
0-44 Conversion of Alkyl Halides to Primary Amines with Hexamethylenetetramine
Amino-de-halogenation (overall transformation)



Primary amines can be prepared from alkyl halides by the use of hexamethylenetetramine⁸¹⁴ followed by cleavage of the resulting salt with ethanolic HCl. The method, called the *Delépine reaction*, is most successful for active halides such as allylic and benzylic halides and α -halo ketones, and for primary iodides.

OS V, 121.

0-45 Conversion of Alkyl Halides to Secondary Amines with Cyanamide
Imino-de-dihalo-aggre-substitution (overall transformation)



A convenient way of obtaining secondary amines without contamination by primary or tertiary amines involves treatment of alkyl halides with the sodium or calcium salt of cyanamide NH_2-CN to give disubstituted cyanamides, which are then hydrolyzed and decarboxylated to secondary amines. Good yields are obtained when the reaction is carried out under phase-transfer conditions.⁸¹⁵ R may be primary, secondary, allylic, or benzylic. 1, ω -Dihalides give cyclic secondary amines.

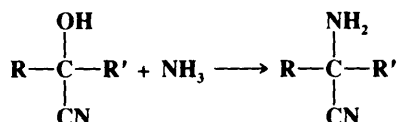
OS I, 203.

⁸¹²Kovacic; Lowery *J. Org. Chem.* **1969**, 34, 911; Strand; Kovacic *J. Am. Chem. Soc.* **1973**, 95, 2977.

⁸¹³For example, see Deady; Finlayson; Korytsky *Aust. J. Chem.* **1979**, 32, 1735.

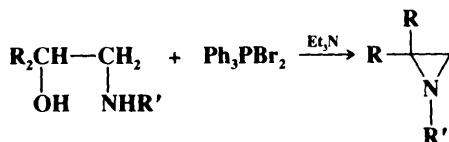
⁸¹⁴For a review of the reactions of this reagent, see Blažević; Kolbah; Belin; Šunjić; Kajfež *Synthesis* **1979**, 161-176.

⁸¹⁵Jończyk; Ochal; Mąkosza *Synthesis* **1978**, 882.

0-46 Replacement of a Hydroxy by an Amino Group**Amino-de-hydroxylation**

Cyanohydrins can be converted to amines by treatment with ammonia. The use of primary or secondary amines instead of ammonia leads to secondary and tertiary cyanoamines, respectively. It is more common to perform the conversion of an aldehyde or ketone directly to the cyanoamine without isolation of the cyanohydrin (see 6-50). α -Hydroxy ketones (acyloins and benzoin) behave similarly.⁸¹⁶ The conversion $\text{ROH} \rightarrow \text{RNH}_2$ can be accomplished for primary and secondary alcohols by treatment with hydrazoic acid (HN_3), diisopropyl azodicarboxylate ($i\text{-Pr}-\text{OOCN}=\text{NCOO}-i\text{-Pr}$), and excess Ph_3P in THF, followed by water or aqueous acid.⁸¹⁷ This is a type of Mitsunobu reaction (see 0-22). Other alcohol-to-amine Mitsunobu reactions have also been reported.⁸¹⁸ Primary and secondary alcohols ROH (but not methanol) can be converted to tertiary amines⁸¹⁹ $\text{R}_2'\text{NR}$ by treatment with the secondary amine $\text{R}_2'\text{NH}$ and $(t\text{-BuO})_3\text{Al}$ in the presence of Raney nickel.⁸²⁰ The use of aniline gives secondary amines PhNHR . Allylic alcohols ROH react with primary ($\text{R}'\text{NH}_2$) or secondary ($\text{R}_2'\text{NH}$) amines in the presence of platinum or palladium complexes, to give secondary (RNHR') or tertiary (RNR_2') allylic amines.⁸²¹

β -Amino alcohols give aziridines when treated with triphenylphosphine dibromide in the presence of triethylamine:⁸²²



The fact that inversion takes place at the OH carbon indicates that an $\text{S}_{\text{N}}2$ mechanism is involved, with OPPh_3 as the leaving group.

Alcohols can be converted to amines in an indirect manner.⁸²³ The alcohols are converted to alkyloxyphosphonium perchlorates which in DMF successfully *monoalkylate* not only secondary but also primary amines.⁸²⁴



⁸¹⁶For example, see Klemmensen; Schroll; Lawesson *Ark. Kemi* **1968**, 28, 405.

⁸¹⁷Fabiano; Golding; Sadeghi *Synthesis* **1987**, 190.

⁸¹⁸See, for example, Henry; Marcin; McIntosh; Scola; Harris; Weinreb *Tetrahedron Lett.* **1989**, 30, 5709; Edwards; Stemerick; McCarthy *Tetrahedron Lett.* **1990**, 31, 3417.

⁸¹⁹For other methods of converting certain alcohols to secondary and tertiary amines, see Murahashi; Kondo; Hakata *Tetrahedron Lett.* **1982**, 23, 229; Baiker; Richarz *Tetrahedron Lett.* **1977**, 1937; *Helv. Chim. Acta* **1978**, 61, 1169; *Synth. Commun.* **1978**, 8, 27; Grigg; Mitchell; Sutthivaiyakit; Tongpenyai *J. Chem. Soc., Chem. Commun.* **1981**, 611; Arcelli; Bui-The-Khai; Porzi *J. Organomet. Chem.* **1982**, 235, 93; Kelly; Eskew; Evans *J. Org. Chem.* **1986**, 51, 95; Huh; Tsuji; Kobayashi; Okuda; Watanabe *Chem. Lett.* **1988**, 449.

⁸²⁰Botta; De Angelis; Nicoletti *Synthesis* **1977**, 722.

⁸²¹Atkins; Walker; Manyik *Tetrahedron Lett.* **1970**, 3821; Tsuji; Takeuchi; Ogawa; Watanabe *Chem. Lett.* **1986**, 293.

⁸²²Okada; Ichimura; Sudo *Bull. Chem. Soc. Jpn.* **1970**, 43, 1185. See also Pfister *Synthesis* **1984**, 969; Suzuki; Tani *Chem. Lett.* **1984**, 2129; Marsella *J. Org. Chem.* **1987**, 52, 467.

⁸²³For some other indirect methods, see White; Ellinger *J. Am. Chem. Soc.* **1965**, 87, 5261; Burgess; Penton; Taylor *J. Am. Chem. Soc.* **1970**, 92, 5224; Hendrickson; Joffe *J. Am. Chem. Soc.* **1973**, 95, 4083; Trost; Keinan *J. Org. Chem.* **1979**, 44, 3451; Ref 619 in Chapter 19.

⁸²⁴Castro; Selve *Bull. Soc. Chim. Fr.* **1971**, 4368. For a similar method, see Tanigawa; Murahashi; Moritani *Tetrahedron Lett.* **1975**, 471.

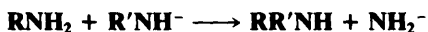
Thus by this means secondary as well as tertiary amines can be prepared in good yields.

A solution of the sodium salt of N-methylaniline in HMPA can be used to cleave the methyl group from aryl methyl ethers:⁸²⁵ $\text{ArOMe} + \text{PhNMe}^- \rightarrow \text{ArO}^- + \text{PhNMe}_2$. This reagent also cleaves benzylic groups. In a similar reaction, methyl groups of aryl methyl ethers can be cleaved with lithium diphenylphosphide Ph_2PLi .⁸²⁶ This reaction is specific for methyl ethers and can be carried out in the presence of ethyl ethers with high selectivity.

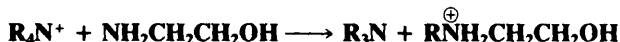
OS II, 29, 231; IV, 91, 283; VI, 567, 788; VII, 501. Also see OS I, 473; III, 272, 471.

0-47 Transamination

Alkylamino-de-amination



Where the nucleophile is the conjugate base of a primary amine, NH_2 can be a leaving group. The method has been used to prepare secondary amines.⁸²⁷ In another process, primary amines are converted to secondary amines in which both R groups are the same ($2\text{RNH}_2 \rightarrow \text{R}_2\text{NH} + \text{NH}_3$)⁸²⁸ by refluxing in xylene in the presence of Raney nickel.⁸²⁹ Quaternary salts can be dealkylated with ethanolamine.⁸³⁰



In this reaction, methyl groups are cleaved in preference to other saturated alkyl groups. A similar reaction takes place between a Mannich base (see 6-16) and a secondary amine, where the mechanism is elimination-addition (see p. 338). See also 9-5.

OS V, 1018.

0-48 Alkylation of Amines with Diazo Compounds

Hydro,dialkylamino-de-diazo-bisubstitution



The reaction of diazo compounds with amines is similar to 0-15.⁸³¹ The acidity of amines is not great enough for the reaction to proceed without a catalyst, but BF_3 , which converts the amine to the $\text{F}_3\text{B-NHR}'_2$ complex, enables the reaction to take place. Cuprous cyanide can also be used as a catalyst.⁸³² The most common substrate is diazomethane,⁵⁹³ in which case this is a method for the methylation of amines. Ammonia has been used as the amine but, as in the case of 0-43, mixtures of primary, secondary, and tertiary amines are obtained. Primary aliphatic amines give mixtures of secondary and tertiary amines. Secondary amines give successful alkylation. Primary aromatic amines also give the reaction, but diaryl or arylalkylamines react very poorly.

⁸²⁵Loubinoux; Coudert; Guillaumet *Synthesis* **1980**, 638.

⁸²⁶Ireland; Walba *Org. Synth.* VI, 567.

⁸²⁷Baltzly; Blackman *J. Org. Chem.* **1963**, 28, 1158.

⁸²⁸In a similar manner, a mixture of primary amines can be converted to a mixed secondary amine. For a review of the mechanism, see Geller *Russ. Chem. Rev.* **1978**, 47, 297-306.

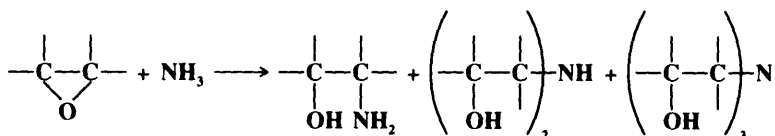
⁸²⁹De Angelis; Grgurina; Nicoletti *Synthesis* **1979**, 70; See also Ballantine; Purnell; Rayanakorn; Thomas; Williams *J. Chem. Soc., Chem. Commun.* **1981**, 9; Arcelli; Bui-The-Khai; Porzi *J. Organomet. Chem.* **1982**, 231, C31; Jung; Fellmann; Garrou *Organometallics* **1983**, 2, 1042; Tsuji; Shida; Takeuchi; Watanabe *Chem. Lett.* **1984**, 889; Bank; Jewett *Tetrahedron Lett.* **1991**, 32, 303.

⁸³⁰Hünig; Baron *Chem. Ber.* **1957**, 90, 395, 403.

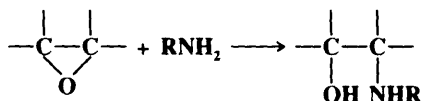
⁸³¹Müller; Huber-Emden; Rundel *Liebigs. Ann. Chem.* **1959**, 623, 34.

⁸³²Saegusa; Ito; Kobayashi; Hirota; Shimizu *Tetrahedron Lett.* **1966**, 6131.

0-49 Amination of Epoxides

(3) OC-*seco*-Amino-de-alkoxylation

The reaction between epoxides and ammonia is a general and useful method for the preparation of β -hydroxyamines.⁸³³ Ammonia gives largely the primary amine, but also some secondary and tertiary amines. The useful solvents, the ethanolamines, are prepared by this reaction. For another way of accomplishing this conversion, see 0-51. Primary and secondary amines give, respectively, secondary and tertiary amines,⁸³⁴ e.g.,

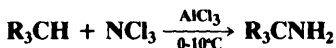


Episulfides, which can be generated in situ in various ways, react similarly to give β -amino thiols,⁸³⁵ and aziridines give 1,2-diamines.⁸³⁶ Triphenylphosphine similarly reacts with epoxides to give an intermediate that undergoes elimination to give olefins (see the Wittig reaction, 6-47).

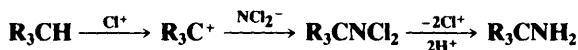
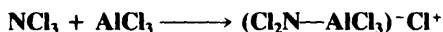
There are no OS references, but see OS VI, 652 for a related reaction.

0-50 Amination of Alkanes

Amino-de-hydrogenation or Amination



Alkanes, arylalkanes, and cycloalkanes can be aminated, at tertiary positions only, by treatment with trichloroamine and aluminum chloride at 0 to 10°C.⁸³⁷ For example, *p*-MeC₆H₄CHMe₂ gives *p*-MeC₆H₄CMe₂NH₂, methylcyclopentane gives 1-amino-1-methylcyclopentane, and adamantane gives 1-aminoadamantane, all in good yields. This is a useful reaction, since there are not many other methods for the preparation of *t*-alkyl amines. The mechanism has been rationalized as an S_N1 process with H⁻ as the leaving group:⁸³⁷



See also 2-11.

OS V, 35.

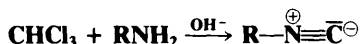
⁸³³For an example, see McManus; Larson; Hearn *Synth. Commun.* **1973**, 3, 177.

⁸³⁴For improved methods, see Carre; Houmounou; Caubere *Tetrahedron Lett.* **1985**, 26, 3107; Fujiwara; Imada; Baba; Matsuda *Tetrahedron Lett.* **1989**, 30, 739; Yamada; Yumoto; Yamamoto *Tetrahedron Lett.* **1989**, 30, 4255; Chini; Crotti; Macchia *Tetrahedron Lett.* **1990**, 31, 4661.

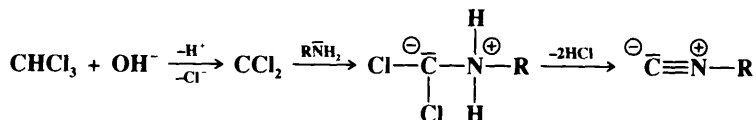
⁸³⁵Reynolds; Massad; Fields; Johnson *J. Org. Chem.* **1961**, 26, 5109; Reynolds; Fields; Johnson *J. Org. Chem.* **1961**, 26, 5111, 5116, 5119, 5125; Wineman; Gollis; James; Pomponi *J. Org. Chem.* **1962**, 27, 4222.

⁸³⁶For a review, see Dermer; Ham, Ref. 437, pp. 262-268.

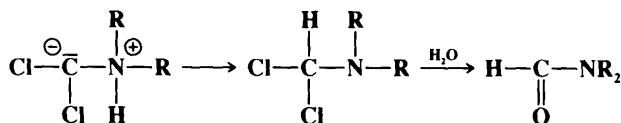
⁸³⁷Kovacic; Chaudhary *Tetrahedron* **1967**, 23, 3563; Strand; Kovacic, Ref. 812; Wnuk; Chaudhary; Kovacic *J. Am. Chem. Soc.* **1976**, 98, 5678, and references cited in these papers.

0-51 Formation of Isocyanides**Haloform–isocyanide transformation**

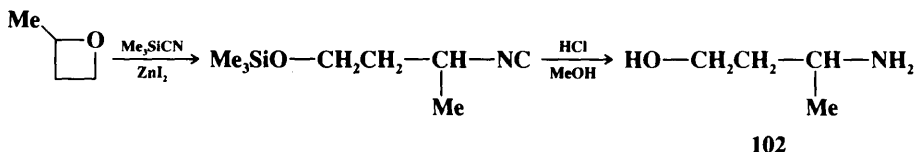
Reaction with chloroform under basic conditions is a common test for primary amines, both aliphatic and aromatic, since isocyanides have very strong bad odors. The reaction probably proceeds by an $\text{S}_{\text{N}}1\text{cB}$ mechanism with dichlorocarbene as an intermediate:



The reaction can also be used synthetically for the preparation of isocyanides, though yields are generally not high.⁸³⁸ An improved procedure has been reported.⁸³⁹ When secondary amines are involved, the adduct cannot lose two moles of HCl. Instead it is hydrolyzed to an N,N-disubstituted formamide:⁸⁴⁰



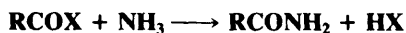
A completely different way of preparing isocyanides involves the reaction of epoxides or oxetanes with trimethylsilyl cyanide and zinc iodide, e.g.,⁸⁴¹



102

The products can be hydrolyzed to hydroxyamines, e.g., **102**.

OS VI, 232.

B. Attack by NH_2 , NHR , or NR_2 at an Acyl Carbon⁸⁴²**0-52 Acylation of Amines by Acyl Halides****Amino-de-halogenation**

The treatment of acyl halides with ammonia or amines is a very general reaction for the preparation of amides.⁸⁴³ The reaction is highly exothermic and must be carefully controlled,

⁸³⁸For a review of isocyanides, see Periasamy; Walborsky *Org. Prep. Proced. Int.* **1979**, 11, 293-311.

⁸³⁹Weber; Gokel *Tetrahedron Lett.* **1972**, 1637; Weber; Gokel; Ugi *Angew. Chem. Int. Ed. Engl.* **1972**, 11, 530 [*Angew. Chem.* **84**, 587].

⁸⁴⁰Saunders; Murray *Tetrahedron* **1959**, 6, 88; Frankel; Feuer; Bank *Tetrahedron Lett.* **1959**, no. 7, 5.

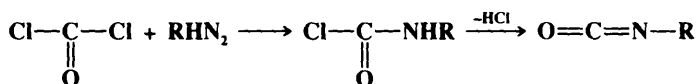
⁸⁴¹Gassman; Haberman *Tetrahedron Lett.* **1985**, 26, 4971, and references cited therein.

⁸⁴²For a review, see Challis; Butler, in Patai, Ref. 355, pp. 279-290.

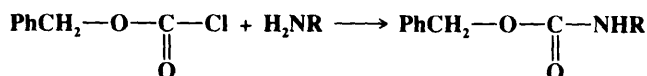
⁸⁴³For a review, see Beckwith, in Zabicky, Ref. 555, pp. 73-185.

usually by cooling or dilution. Ammonia gives unsubstituted amides, primary amines give N-substituted amides, and secondary amines give N,N-disubstituted amides. Arylamines can be similarly acylated. In some cases aqueous alkali is added to combine with the liberated HCl. This is called the *Schotten-Baumann procedure*, as in 0-20.

Hydrazine and hydroxylamine also react with acyl halides to give, respectively, hydrazides RCONHNH_2 ⁸⁴⁴ and hydroxamic acids RCONHOH ,⁸⁴⁵ and these compounds are often made in this way. When phosgene is the acyl halide, both aliphatic and aromatic primary amines give chloroformamides ClCONHR that lose HCl to give isocyanates RNCO .⁸⁴⁶ This is one of the most common methods for the preparation of isocyanates.⁸⁴⁷ Thiophosgene,^{847a} sim-



ilarly treated, gives isothiocyanates. A safer substitute for phosgene in this reaction is trichloromethyl chloroformate CCl_3OCOCl .⁸⁴⁸ When chloroformates ROCOCl are treated with primary amines, carbamates ROCONHR' are obtained.⁸⁴⁹ An example of this reaction is the use of benzyl chloroformate to protect the amino group of amino acids and peptides:



The PhCH_2OCO group is called the carbobenzoxy group, and is often abbreviated Cbz or Z. Another important group similarly used is the *t*-butoxycarbonyl group Me_3COCO , abbreviated as Boc. In this case, the chloride Me_3COCOCl is unstable, so the anhydride $(\text{Me}_3\text{COCO})_2\text{O}$ is used instead, in an example of 0-53. Amino groups in general are often protected by conversion to amides. The treatment of acyl halides with lithium nitride gives N,N-diacyl amides (triacylamines):⁸⁵⁰

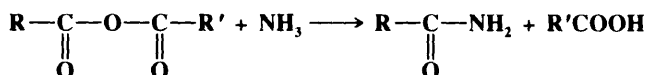


The reactions proceed by the tetrahedral mechanism.⁸⁵¹

OS I, 99, 165; II, 76, 208, 278, 328, 453; III, 167, 375, 415, 488, 490, 613; IV, 339, 411, 521, 620, 780; V, 201, 336; VI, 382, 715; VII, 56, 287, 307; 67, 187; 68, 83. See also OS VII, 302.

0-53 Acylation of Amines by Anhydrides

Amino-de-acyloxy-substitution



⁸⁴⁴For a review of hydrazides, see Paulsen; Stoye, in Zabicky, Ref. 555, pp. 515-600.

⁸⁴⁵For an improved method, see Ando; Tsumaki *Synth. Commun.* **1983**, 13, 1053.

⁸⁴⁶For reviews of the preparation and reactions of isocyanates and isothiocyanates, see, respectively, the articles by Richter; Ulrich, pp. 619-818, and Drobnica; Kristián; Augustin pp. 1003-1221, in Patai *The Chemistry of Cyanates and Their Thio Derivatives*, pt. 2; Wiley: New York, 1977.

⁸⁴⁷For examples, see Ozaki *Chem. Rev.* **1972**, 72, 457-496, pp. 457-460. For a review of the industrial preparation of isocyanates by this reaction, see Twitchett *Chem. Soc. Rev.* **1974**, 3, 209-230.

^{847a}For a review of thiophosgene, see Sharma *Sulfur Rep.* **1986**, 5, 1-100.

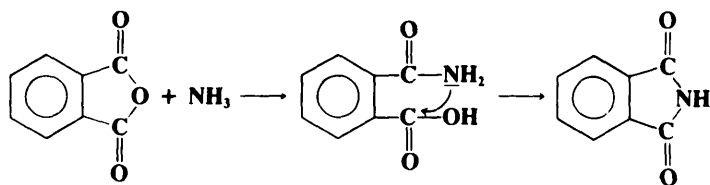
⁸⁴⁸Kurita; Iwakura *Org. Synth.* VI, 715.

⁸⁴⁹For an improved procedure, see Raucher; Jones *Synth. Commun.* **1985**, 15, 1025.

⁸⁵⁰Baldwin; Blanchard; Koenig *J. Org. Chem.* **1965**, 30, 671.

⁸⁵¹Kivinen, Ref. 502; Bender; Jones *J. Org. Chem.* **1962**, 27, 3771. See also Song; Jencks *J. Am. Chem. Soc.* **1989**, 111, 8479.

This reaction, similar in scope and mechanism⁸⁵² to **0-52**, can be carried out with ammonia or primary or secondary amines.⁸⁵³ However, ammonia and primary amines can also give imides, in which two acyl groups are attached to the nitrogen. This is especially easy with cyclic anhydrides, which produce cyclic imides.⁸⁵⁴



The second step in this case, which is much slower than the first, is the attack of the amide nitrogen on the carboxylic carbon. Unsubstituted and N-substituted amides have been used instead of ammonia. Since the other product of this reaction is RCOOH, this is a way of "hydrolyzing" such amides in the absence of water.⁸⁵⁵

Even though formic anhydride is not a stable compound (see p. 542), amines can be formylated with the mixed anhydride of acetic and formic acids HCOOCOMe⁸⁵⁶ or with a mixture of formic acid and acetic anhydride. Acetamides are not formed with these reagents. Secondary amines can be acylated in the presence of a primary amine by conversion to their salts and addition of 18-crown-6.⁸⁵⁷ The crown ether complexes the primary ammonium salt, preventing its acylation, while the secondary ammonium salts, which do not fit easily into the cavity, are free to be acylated.

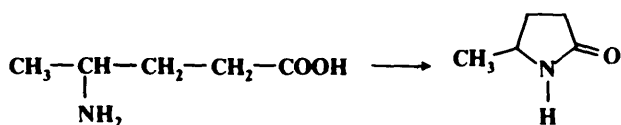
OS **I**, 457; **II**, 11; **III**, 151, 456, 661, 813; **IV**, 5, 42, 106, 657; **V**, 27, 373, 650, 944, 973; **VI**, 1; **VII**, 4, 70; **66**, 132.

0-54 Acylation of Amines by Carboxylic Acids

Amino-dehydroxylation



When carboxylic acids are treated with ammonia or amines, salts are obtained. The salts of ammonia or primary or secondary amines can be pyrolyzed to give amides,⁸⁵⁸ but the method is less convenient than **0-52**, **0-53**, and **0-55** and is seldom of preparative value.⁸⁵⁹ Lactams are produced fairly easily from γ - or δ -amino acids,⁸⁶⁰ e.g.,



Although treatment of carboxylic acids with amines does not directly give amides, the reaction can be made to proceed in good yield at room temperature or slightly above by

⁸⁵²For a discussion of the mechanism, see Kluger; Hunt *J. Am. Chem. Soc.* **1989**, *111*, 3325.

⁸⁵³For a review, see Beckwith, in Zabicky, Ref. 555, pp. 86-96.

⁸⁵⁴For reviews of imides, see Wheeler; Rosado, in Zabicky, Ref. 555, pp. 335-381; Hargreaves; Pritchard; Dave *Chem. Rev.* **1970**, *70*, 439-469 (cyclic imides).

⁸⁵⁵Eaton; Rounds; Urbanowicz; Gribble *Tetrahedron Lett.* **1988**, *29*, 6553.

⁸⁵⁶For the formylation of amines with the mixed anhydride of formic and trimethylacetic acid, see Vlietstra; Zwikker; Nolte; Drenth *Recl. Trav. Chim. Pays-Bas* **1982**, *101*, 460.

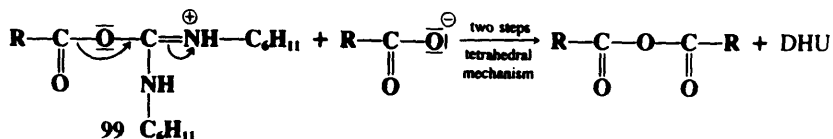
⁸⁵⁷Barrett; Lana *J. Chem. Soc., Chem. Commun.* **1978**, 471.

⁸⁵⁸For example, see Mitchell; Reid *J. Am. Chem. Soc.* **1931**, *53*, 1879.

⁸⁵⁹For a review of amide formation from carboxylic acids, see Beckwith, in Zabicky, Ref. 555, pp. 105-109.

⁸⁶⁰See, for example, Bladé-Font *Tetrahedron Lett.* **1980**, *21*, 2443.

the use of coupling agents,⁸⁶¹ the most important of which is dicyclohexylcarbodiimide. This is very convenient and is used⁸⁶² a great deal in peptide synthesis.⁸⁶³ The mechanism is probably the same as in **0-22** up to the formation of **99**. This intermediate is then attacked by another molecule of RCOO^- to give the anhydride $(\text{RCO})_2\text{O}$, which is the actual species that reacts with the amine:



The anhydride has been isolated from the reaction mixture and then used to acylate an amine.⁸⁶⁴ Other promoting agents⁸⁶⁵ are $\text{N,N}'$ -carbonyldiimidazole (**100**, p. 396),⁶⁶⁴ which behaves as in reaction **0-22**, POCl_3 ,⁸⁶⁶ TiCl_4 ,⁸⁶⁷ sulfonyl chloride fluoride SO_2ClF ,⁸⁶⁸ benzotriazol-1-yl diethyl phosphate,⁸⁶⁹ $\text{Ti}(\text{O}i\text{Bu})_4$,⁸⁷⁰ molecular sieves,⁸⁷¹ $\text{N,N,N}',\text{N}'$ -tetramethyl(succinimido)uronium tetrafluoroborate,⁸⁷² CBMIT⁶⁵⁶ (p. 396), Lawesson's reagent (p. 893),⁸⁷³ chlorosulfonyl isocyanate,⁶⁶⁰ P_2I_4 ,⁸⁷⁴ pyridinium salts- Bu_3N ,⁸⁷⁵ and a mixture of Bu_3P and PhCNO .⁸⁷⁶ Certain dicarboxylic acids form amides simply on treatment with primary aromatic amines. In these cases the cyclic anhydride is an intermediate and is the species actually attacked by the amine.⁸⁷⁷ Carboxylic acids can also be converted to amides by heating with amides of carboxylic acids (exchange),⁸⁷⁸ sulfonic acids, or phosphoric acids, e.g.,⁸⁷⁹



or by treatment with trisalkylaminoboranes $[\text{B}(\text{NHR}')_3]$, with trisdialkylaminoboranes $[\text{B}(\text{NR}'_2)_3]$,⁸⁸⁰



or with bis(diorganoamino)magnesium reagents $(\text{R}_2\text{N})_2\text{Mg}$.⁸⁸¹

⁸⁶¹For a review of peptide synthesis with dicyclohexylcarbodiimide and other coupling agents, see Klausner; Bodansky *Synthesis* **1972**, 453-463.

⁸⁶²It was first used this way by Sheehan; Hess *J. Am. Chem. Soc.* **1955**, 77, 1067.

⁸⁶³For a treatise on peptide synthesis, see Gross; Meienhofer *The Peptides*, 3 vols.; Academic Press: New York, 1979-1981. For a monograph, see Bodanszky; Bodanszky *The Practice of Peptide Synthesis*; Springer: New York, 1984.

⁸⁶⁴Schüssler; Zahn *Chem. Ber.* **1962**, 95, 1076; Rebek; Feitler *J. Am. Chem. Soc.* **1974**, 96, 1606. There is evidence that some of the **99** is converted to products by another mechanism. See Rebek; Feitler *J. Am. Chem. Soc.* **1973**, 95, 4052.

⁸⁶⁵For a list of reagents, with references, see Ref. 508, pp. 972-976.

⁸⁶⁶Klosa *J. Prakt. Chem.* **1963**, [4] 19, 45.

⁸⁶⁷Wilson; Weingarten *Can. J. Chem.* **1970**, 48, 983.

⁸⁶⁸Olah; Narang; Garcia-Luna *Synthesis* **1980**, 661.

⁸⁶⁹Kim; Chang; Ko *Tetrahedron Lett.* **1985**, 26, 1341.

⁸⁷⁰Shteinberg; Kondratov; Shein *J. Org. Chem. USSR* **1988**, 24, 1774.

⁸⁷¹Cossy; Pale-Grosdemange *Tetrahedron Lett.* **1989**, 30, 2771.

⁸⁷²Bannwarth; Knorr *Tetrahedron Lett.* **1991**, 32, 1157.

⁸⁷³Thorsen; Andersen; Pedersen; Yde; Lawesson *Tetrahedron* **1985**, 41, 5633.

⁸⁷⁴Suzuki; Tsuji; Hiroi; Sato; Osuka *Chem. Lett.* **1983**, 449.

⁸⁷⁵Bald; Saigo; Mukaiyama *Chem. Lett.* **1975**, 1163. See also Mukaiyama; Aikawa; Kobayashi *Chem. Lett.* **1976**, 57.

⁸⁷⁶Grieco; Clark; Withers *J. Org. Chem.* **1979**, 44, 2945.

⁸⁷⁷Higuchi; Miki; Shah; Herd *J. Am. Chem. Soc.* **1963**, 85, 3655.

⁸⁷⁸For example, see Schindbauer *Monatsh. Chem.* **1968**, 99, 1799.

⁸⁷⁹Zhmurova; Voitsekhovskaya; Kirsanov *J. Gen. Chem. USSR* **1959**, 29, 2052. See also Kopecký; Šmejkal *Chem. Ind. (London)* **1966**, 1529; Liu; Chan; Lee *Synth. Commun.* **1979**, 9, 31.

⁸⁸⁰Pelter; Levitt; Nelson *Tetrahedron* **1970**, 26, 1539; Pelter; Levitt *Tetrahedron* **1970**, 26, 1545, 1899.

⁸⁸¹Sanchez; Vest; Despres *Synth. Commun.* **1989**, 19, 2909.

An important technique, discovered by R. B. Merrifield in 1963⁸⁸² and since used for the synthesis of many peptides,⁸⁸³ is called *solid phase synthesis* or *polymer-supported synthesis*.⁸⁸⁴ The reactions used are the same as in ordinary synthesis, but one of the reactants is anchored onto a solid polymer. For example, if it is desired to couple two amino acids (to form a dipeptide), the polymer selected might be polystyrene with CH_2Cl side chains (Fig. 10.2, 103). One of the amino acids, protected by a *t*-butoxycarbonyl group (Boc), would then be coupled to the side chains (step A). It is not necessary that all the side chains be converted, but a random selection will be. The Boc group is then removed by hydrolysis with trifluoroacetic acid in CH_2Cl_2 (step B) and the second amino acid is coupled to the first, using DCC or some other coupling agent (step C). The second Boc group is removed (step D), resulting in a dipeptide that is still anchored to the polymer. If this dipeptide is the desired product, it can be cleaved from the polymer by various methods,⁸⁸⁵ one of which is treatment with HF (step E). If a longer peptide is wanted, additional amino acids can be added by repeating steps C and D.

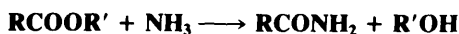
The basic advantage of the polymer support techniques is that the polymer (including all chains attached to it) is easily separated from all other reagents, because it is insoluble in the solvents used. Excess reagents, other reaction products (such as DHU), side products, and the solvents themselves are quickly washed away. Purification of the polymeric species (such as 104, 105, and 106) is rapid and complete. The process can even be automated,⁸⁸⁶ to the extent that six or more amino acids can be added to a peptide chain in one day. Commercial automated peptide synthesizers are now available.⁸⁸⁷

Although the solid phase technique was first developed for the synthesis of peptide chains and has seen considerable use for this purpose, it has also been used to synthesize chains of polysaccharides and polynucleotides; in the latter case, solid phase synthesis has almost completely replaced synthesis in solution.⁸⁸⁸ The technique has been applied less often to reactions in which only two molecules are brought together (nonrepetitive syntheses), but many examples have been reported.⁸⁸⁹

OS I, 3, 82, 111, 172, 327; II, 65, 562; III, 95, 328, 475, 590, 646, 656, 768; IV, 6, 62, 513; V, 670, 1070; 69, 55. Also see OS III, 360; VI, 263; 67, 69.

0-55 Acylation of Amines by Carboxylic Esters

Amino-de-alkoxylation



⁸⁸²Merrifield *J. Am. Chem. Soc.* **1963**, 85, 2149.

⁸⁸³For a monograph on solid state peptide synthesis, see Birt *Aspects of the Merrifield Peptide Synthesis*; Springer: New York, 1978. For reviews, see Bayer *Angew. Chem. Int. Ed. Engl.* **1991**, 30, 113-129 [*Angew. Chem.* 103, 117-133]; Kaiser *Acc. Chem. Res.* **1989**, 22, 47-54; Jacquier *Bull. Soc. Chim. Fr.* **1989**, 220-236; Barany; Kneib-Cordonier; Mullen *Int. J. Pept. Protein Res.* **1987**, 30, 705-739; Andreev; Samoilova; Davidovich; Rogozhin *Russ. Chem. Rev.* **1987**, 56, 366-381; in vol. 2 of Ref. 863, the articles by Barany; Merrifield, pp. 1-184, Fridkin, pp. 333-363; Erickson; Merrifield, in Neurath; Hill; Boeder *The Proteins*, 3rd ed., vol. 2; Academic Press: New York, 1976, pp. 255-527. For R. B. Merrifield's Nobel Prize lecture, see Merrifield *Angew. Chem. Int. Ed. Engl.* **1985**, 24, 799-810 [*Angew. Chem.* 97, 801-812]; *Chem. Scr.* **1985**, 25, 121-131.

⁸⁸⁴For monographs on solid phase synthesis in general, see Laszlo *Preparative Organic Chemistry Using Supported Reagents*; Academic Press: New York, 1987; Mathur; Narang; Williams *Polymers as Aids in Organic Chemistry*; Academic Press: New York 1980; Hodge; Sherrington *Polymer-supported Reactions in Organic Synthesis*; Wiley: New York, 1980. For reviews, see Sheppard, *Chem. Br.* **1983**, 402-414; Pillai; Mutter *Top. Curr. Chem.* **1982**, 106, 119-175; Akelah; Sherrington *Chem. Rev.* **1981**, 81, 557-587; Akelah *Synthesis* **1981**, 413-438; Rebek *Tetrahedron* **1979**, 35, 723-731; McKillop; Young *Synthesis* **1979**, 401-422, 481-500; Neckers, *CHEMTECH* **1978** (Feb.), 108-116; Crowley; Rapoport *Acc. Chem. Res.* **1976**, 9, 135-144; Patchornik; Kraus *Pure Appl. Chem.* **1975**, 43, 503-526.

⁸⁸⁵For some of these methods, see Whitney; Tam; Merrifield *Tetrahedron* **1984**, 40, 4237.

⁸⁸⁶This was first reported by Merrifield; Stewart; Jernberg *Anal. Chem.* **1966**, 38, 1905.

⁸⁸⁷For a discussion of automated organic synthesis, see Frisbee; Nantz; Kramer; Fuchs *J. Am. Chem. Soc.* **1984**, 106, 7143. For an improved method, see Schnorrenberg; Gerhardt *Tetrahedron* **1989**, 45, 7759.

⁸⁸⁸For a review, see Bannwarth *Chimia* **1987**, 41, 302-317.

⁸⁸⁹For reviews, see Fréchet *Tetrahedron* **1981**, 37, 663-683; Fréchet, in Hodge; Sherrington, Ref. 884, pp. 293-342. Leznoff, *Acc. Chem. Res.* **1978**, 11, 327-333; *Chem. Soc. Rev.* **1974**, 3, 64-85.

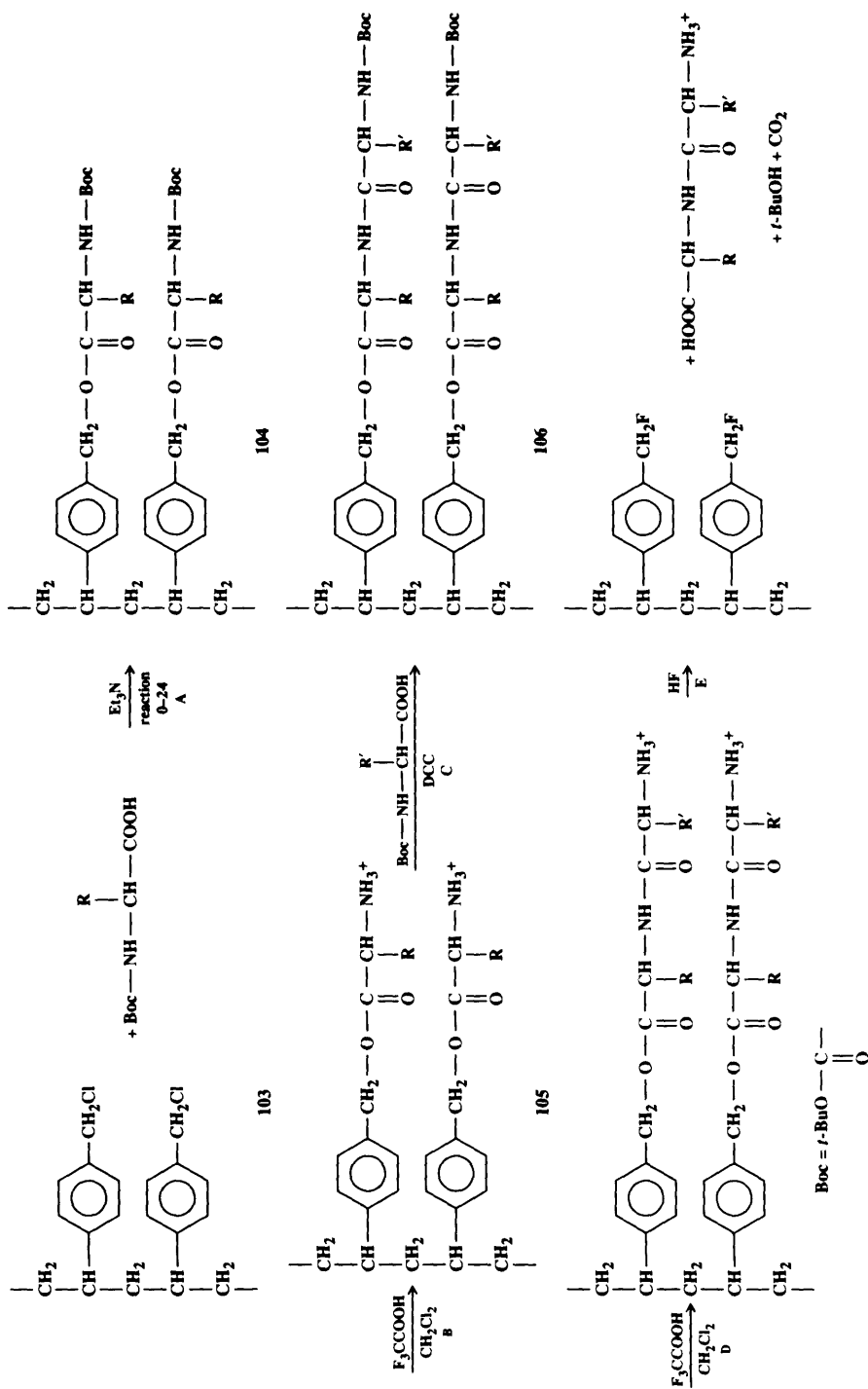


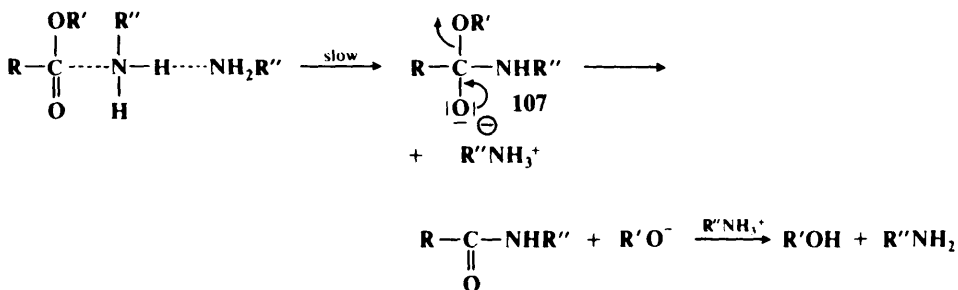
FIGURE 10.2 An outline of dipeptide synthesis by the solid phase technique.

The conversion of carboxylic esters to amides is a useful reaction, and unsubstituted, N-substituted, and N,N-disubstituted amides can be prepared this way from the appropriate amine.⁸⁹⁰ Both R and R' can be alkyl or aryl. An especially good leaving group is *p*-nitrophenyl. Many simple esters (R = Me, Et, etc.) are not very reactive, and strongly basic catalysis has been used,⁸⁹¹ as well as catalysis by cyanide ion,⁸⁹² and high pressure.⁸⁹³ β -Keto esters undergo the reaction especially easily.⁸⁹⁴ In another procedure, esters are treated with dimethylaluminum amides $\text{Me}_2\text{AlNRR}'$ to give good yields of amides under mild conditions.⁸⁹⁵ The reagents are easily prepared from Me_3Al and NH_3 or a primary or secondary amine or their salts. The ester-to-amide conversion has also been accomplished electrochemically, by passing electric current in the cathodic compartment.⁸⁹⁶

As in 0-52 hydrazides and hydroxamic acids can be prepared from carboxylic esters, with hydrazine and hydroxylamine, respectively. Both hydrazine and hydroxylamine react more rapidly than ammonia or primary amines (the alpha effect, p. 351). Imidates $\text{RC}(=\text{NH})\text{OR}'$ give amidines $\text{RC}(=\text{NH})\text{NH}_2$. Lactones, when treated with ammonia or primary amines, give lactams. Lactams are also produced from γ - and δ -amino esters in an internal example of this reaction. Isopropenyl formate is a useful compound for the formylation of primary and secondary amines.⁸⁹⁷



Although more studies have been devoted to the mechanism of the acylation of amines with carboxylic esters than with other reagents, the mechanistic details are not yet entirely clear.⁸⁹⁸ In its broad outlines, the mechanism appears to be essentially BAC_2 .⁸⁹⁹ Under the normal basic conditions, the reaction is general base-catalyzed,⁹⁰⁰ indicating that a proton is being transferred in the rate-determining step and that two molecules of amine are involved.⁹⁰¹



⁸⁹⁰For a review, see Ref. 843, pp. 96-105. For a list of reagents, with references, see Ref. 508, pp. 987-988.

⁸⁹¹For references, see Ref. 893.

⁸⁹²Högberg; Ström; Ebner; Råmsby *J. Org. Chem.* **1987**, 52, 2033.

⁸⁹³Matsumoto; Hashimoto; Uchida; Okamoto; Otani *Chem. Ber.* **1989**, 122, 1357.

⁸⁹⁴Labelle; Gravel *J. Chem. Soc., Chem. Commun.* **1985**, 105.

⁸⁹⁵Basha; Lipton; Weinreb *Tetrahedron Lett.* **1977**, 4171, *Org. Synth.* VI, 492; Levin; Turos; Weinreb *Synth. Commun.* **1982**, 12, 989; Barrett; Dhanak *Tetrahedron Lett.* **1987**, 28, 3327. For the extension of this method to the formation of hydrazides, see Benderly; Stavchansky *Tetrahedron Lett.* **1988**, 29, 739.

⁸⁹⁶Arai; Shaw; Nozawa; Kawai; Nakajima *Tetrahedron Lett.* **1987**, 28, 441.

⁸⁹⁷van Melick; Wolters *Synth. Commun.* **1972**, 2, 83.

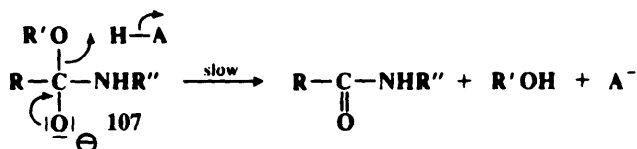
⁸⁹⁸For a discussion of the mechanism, see Satchell; Satchell, Ref. 197, pp. 410-431.

⁸⁹⁹Bunnett; Davis *J. Am. Chem. Soc.* **1960**, 82, 665; Bruice; Donzel; Huffman; Butler *J. Am. Chem. Soc.* **1967**, 89, 2106.

⁹⁰⁰Bunnett; Davis, Ref. 899; Jencks; Carriuolo *J. Am. Chem. Soc.* **1960**, 82, 675; Bruice; Mayahi *J. Am. Chem. Soc.* **1960**, 82, 3067.

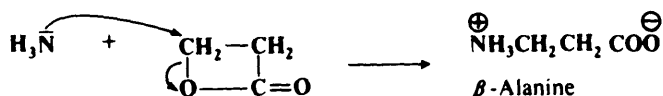
⁹⁰¹Blackburn; Jencks *J. Am. Chem. Soc.* **1968**, 90, 2638; Bruice; Felton *J. Am. Chem. Soc.* **1969**, 91, 2799; Felton; Bruice *J. Am. Chem. Soc.* **1969**, 91, 6721; Nagy; Reuliaux; Bertrand; Van Der Mensbrugghe; Lescut; Nagy *Bull. Soc. Chim. Belg.* **1985**, 94, 1055.

Alternatively, another base, such as H_2O or OH^- , can substitute for the second molecule of amine. With some substrates and under some conditions, especially at low pH, the breakdown of **107** can become rate-determining.⁹⁰² The reaction also takes place under acidic conditions and is general acid-catalyzed, so that breakdown of **107** is rate-determining and proceeds as follows:⁹⁰³



HA may be $\text{R}''\text{NH}_3^+$ or another acid. **107** may or may not be further protonated on the nitrogen. Even under basic conditions, a proton donor may be necessary to assist leaving-group removal. Evidence for this is that the rate is lower with NR_2^- in liquid ammonia than with NHR_2 in water, apparently owing to the lack of acids to protonate the leaving oxygen.⁹⁰⁴

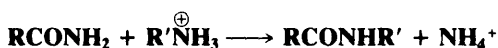
In the special case of β -lactones, where small-angle strain is an important factor, alkyl-oxygen cleavage is observed (BAL2 mechanism, as in the similar case of hydrolysis of β -lactones, **0-10**), and the product is not an amide but a β -amino acid:



A similar result has been found for certain sterically hindered esters.⁹⁰⁵ This reaction is similar to **0-43**, with OCOR as the leaving group.

OS **I**, 153, 179; **II**, 67, 85; **III**, 10, 96, 108, 404, 440, 516, 536, 751, 765; **IV**, 80, 357, 441, 486, 532, 566, 819; **V**, 168, 301, 645; **VI**, 203, 492, 620, 936; **VII**, 4, 30, 41, 411; **65**, 173; **67**, 52; **68**, 77. Also see OS **I**, 5; **V**, 582; **VII**, 75.

0-56 Acylation of Amines by Amides Alkylamino-de-amination



This is an exchange reaction and is usually carried out with the salt of the amine.⁹⁰⁶ The leaving group is usually NH_2 rather than NHR or NR_2 and primary amines (in the form of their salts) are the most common reagents. BF_3 can be added to complex with the leaving ammonia. The reaction is often used to convert urea to substituted ureas: $\text{NH}_2\text{CONH}_2 + \text{RNH}_3^+ \rightarrow \text{NH}_2\text{CONHR} + \text{NH}_4^+$.⁹⁰⁷ N-R-Substituted amides are converted to N-R'-substituted amides by treatment with N_2O_4 to give an N-nitroso compound, followed by treat-

⁹⁰²Hansen *Acta Chem. Scand.* **1963**, 17, 1307; Satterthwait; Jencks *J. Am. Chem. Soc.* **1974**, 96, 7018, 7031; Blackburn; Jencks, Ref. 901; Gresser; Jencks *J. Am. Chem. Soc.* **1977**, 99, 6963, 6970. See also Yang; Jencks *J. Am. Chem. Soc.* **1968**, 110, 2972.

⁹⁰³Blackburn; Jencks, Ref. 901.

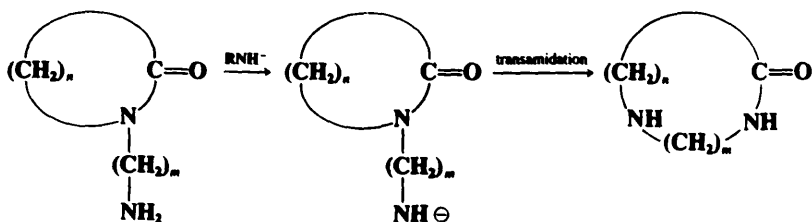
⁹⁰⁴Bunnett; Davis, Ref. 899.

⁹⁰⁵Zaugg; Helgren; Schaefer *J. Org. Chem.* **1963**, 28, 2617. See also Weintraub; Terrell *J. Org. Chem.* **1965**, 30, 2470; Harada; Kinoshita *Bull. Chem. Soc. Jpn.* **1967**, 40, 2706.

⁹⁰⁶For a list of procedures, with references, see Ref. 508, pp. 990-991.

⁹⁰⁷For a discussion of the mechanism, see Chimishkyan; Snagovskii; Gulyaev; Leonova; Kusakin *J. Org. Chem. USSR* **1985**, 21, 1955.

ment of this with a primary amine $R'NH_2$.⁹⁰⁸ Lactams can be converted to ring-expanded lactams if a side chain containing an amino group is present on the nitrogen. A strong base



is used to convert the NH_2 to NH^- , which then acts as a nucleophile, expanding the ring by means of a transamidation.⁹⁰⁹ The discoverers call it the Zip reaction, by analogy with the action of zippers.⁹¹⁰

OS I, 302 (but see V, 589), 450, 453; II, 461; III, 151, 404; IV, 52, 361. See also OS 67, 60.

0-57 Acylation of Amines by Other Acid Derivatives

Acid derivatives that can be converted to amides include thiol acids $RCOSH$, thiol esters $RCOSR$,⁹¹¹ acyloxyboranes $RCOB(OR')_2$,⁹¹² silicic esters $(RCOO)_4Si$, 1,1,1-trihalo ketones $RCOCX_3$,⁹¹³ α -keto nitriles, acyl azides, and nonenolizable ketones (see the Haller-Bauer reaction 2-33).

OS III, 394; IV, 6, 569; V, 160, 166; VI, 1004.

C. Attack by $NHCOR$

0-58 N-Alkylation of Amides and Imides Acylamino-de-halogenation



Amides are very weak bases, far too weak to attack alkyl halides, so they must first be converted to their conjugate bases. By this method, unsubstituted amides can be converted to N-substituted, or N-substituted to N,N-disubstituted, amides.⁹¹⁴ Esters of sulfuric or sulfonic acids can also be substrates. Tertiary substrates give elimination. O-Alkylation is at times a side reaction.⁹¹⁵ Both amides and sulfonamides have been alkylated under phase transfer conditions.⁹¹⁶

⁹⁰⁸Garcia; Vilarrasa *Tetrahedron Lett.* **1982**, 23, 1127.

⁹⁰⁹Kramer; Guggisberg; Hesse; Schmid *Angew. Chem. Int. Ed. Engl.* **1977**, 16, 861 [*Angew. Chem.* 89, 899]. *Helv. Chim. Acta* **1978**, 61, 1342; Askitoglu; Guggisberg; Hesse *Helv. Chim. Acta* **1985**, 68, 750. For a carbon analog, see Nakashita; Hesse *Helv. Chim. Acta* **1983**, 66, 845; Süss; Hájíček; Hesse *Helv. Chim. Acta* **1985**, 68, 1986.

⁹¹⁰For a review of this reaction, and of other ring expansions to form macrocyclic rings, see Stach; Hesse *Tetrahedron* **1988**, 44, 1573-1590.

⁹¹¹For a discussion of the mechanism, see Douglas *Acc. Chem. Res.* **1986**, 19, 186-192.

⁹¹²The best results are obtained when the acyloxyboranes are made from a carboxylic acid and catecholborane (p. 615); Collum; Chen; Ganem *J. Org. Chem.* **1978**, 43, 4393.

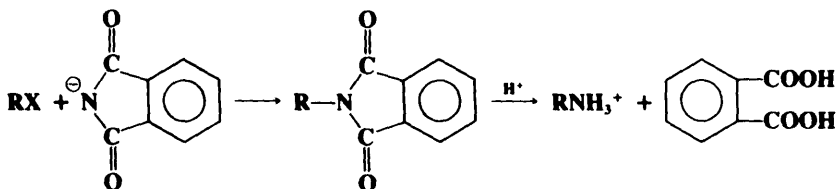
⁹¹³See, for example Sahim; Nome; Rezende *Synth. Commun.* **1989**, 19, 1181; Druzian; Zucco; Rezende; Nome *J. Org. Chem.* **1989**, 54, 4767.

⁹¹⁴For procedures, see Luh; Fung *Synth. Commun.* **1979**, 9, 757; Koziara; Zawadzki; Zwierzak *Synthesis* **1979**, 527; Gajda; Koziara; Zawadzki; Zwierzak *Synthesis* **1979**, 549; Yamawaki; Ando; Hanafusa *Chem. Lett.* **1981**, 1143; Sukata *Bull. Chem. Soc. Jpn.* **1985**, 58, 838.

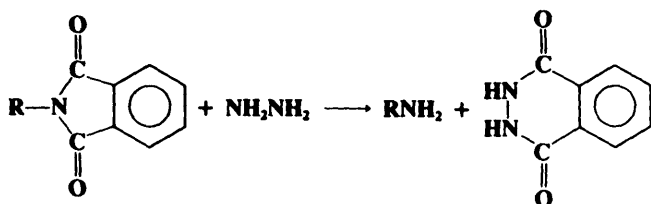
⁹¹⁵For a review of alkylation of amides, see Challis; Challis, Ref. 555, pp. 734-754.

⁹¹⁶Gajda; Zwierzak *Synthesis* **1981**, 1005; Burke; Spillane *Synthesis* **1985**, 935.

The *Gabriel synthesis*⁹¹⁷ for converting halides to primary amines is based on this reaction. The halide is treated with potassium phthalimide and the product hydrolyzed (**0-11**):



It is obvious that the primary amines formed in this reaction will be uncontaminated by secondary or tertiary amines (unlike **0-43**). The reaction is usually rather slow but can be conveniently speeded by the use of a dipolar aprotic solvent such as DMF⁹¹⁸ or with a crown ether.⁹¹⁹ Hydrolysis of the phthalimide, whether acid- or base-catalyzed (acid catalysis is used far more frequently), is also usually very slow, and better procedures are generally used. A common one is the Ing-Manske procedure,⁹²⁰ in which the phthalimide is heated



with hydrazine in an exchange reaction, but other methods have been introduced, using Na_2S in aqueous THF or acetone,⁹²¹ NaBH_4 -2-propanol followed by acetic acid;⁹²² 40% aqueous methylamine,⁹²³ and *n*-pentylamine.⁹²⁴

N-Alkyl amides or imides can also be prepared starting from alcohols by treatment of the latter with equimolar amounts of the amide or imide, Ph_3P , and diethyl azodicarboxylate ($\text{EtOOCN}=\text{NCOOEt}$) at room temperature (the Mitsunobu reaction, see p. 396).⁹²⁵

An alternative to the Gabriel synthesis, in which alkyl halides can be converted to primary amines in good yields, involves treatment of the halide with the strong base guanidine followed by alkaline hydrolysis.⁹²⁶ In another alternative,⁹²⁷ the sodium salt of diphenyl-

⁹¹⁷For a review, see Gibson; Bradshaw *Angew. Chem. Int. Ed. Engl.* **1968**, 7, 919-930 [*Angew. Chem.* 80, 986-996].

⁹¹⁸For example, see Sheehan; Bolhofer *J. Am. Chem. Soc.* **1950**, 72, 2786. See also Landini; Rolla *Synthesis* **1976**, 389.

⁹¹⁹Soai; Ookawa; Kato *Bull. Chem. Soc. Jpn.* **1982**, 55, 1671.

⁹²⁰Ing; Manske *J. Chem. Soc.* **1926**, 2348.

⁹²¹Kukulja; Lammert *J. Am. Chem. Soc.* **1975**, 97, 5582.

⁹²²Osby; Martin; Ganem *Tetrahedron Lett.* **1984**, 25, 2093.

⁹²³Wolfe; Hasan *Can. J. Chem.* **1970**, 48, 3572.

⁹²⁴Kasztreiner; Szilágyi; Kószáry; Huszti *Acta. Chim. Acad. Sci. Hung.* **1975**, 84, 167 [*Chem. Abstr.* 83, 113084].

⁹²⁵Mitsunobu; Wada; Sano *J. Am. Chem. Soc.* **1972**, 94, 679; Grunewald; Paradkar; Pazhenchevsky; Pleiss; Sall; Seibel; Reitz *J. Org. Chem.* **1983**, 48, 2321; Ślusarska; Zwierzak *Liebigs Ann. Chem.* **1986**, 402; Kolasa; Miller *J. Org. Chem.* **1987**, 52, 4978; Sammes; Thetford *J. Chem. Soc., Perkin Trans. 1* **1989**, 655.

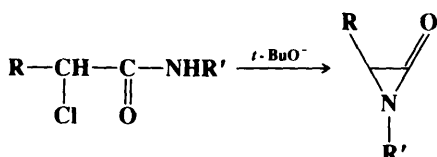
⁹²⁶Hebrard; Olomucki *Bull. Soc. Chim. Fr.* **1970**, 1938.

⁹²⁷For other methods, see Mukaiyama; Taguchi; Nishi *Bull. Chem. Soc. Jpn.* **1971**, 44, 2797; Hendrickson; Bergeron; Sternbach *Tetrahedron* **1975**, 31, 2517; Hendrickson; Bergeron; Giga; Sternbach *J. Am. Chem. Soc.* **1973**, 95, 3412; Clarke; Elliott; Jones *J. Chem. Soc., Perkin Trans. 1* **1978**, 1088; Mukaiyama; Tsuji; Watanabe *Chem. Lett.* **1978**, 1057; Zwierzak; Pilichowska *Synthesis* **1982**, 922; Calverley *Synth. Commun.* **1983**, 13, 601; Harland; Hodge; Maughan; Wildsmith *Synthesis* **1984**, 941; Grehn; Ragnarsson *Synthesis* **1987**, 275; Dalla Croce; La Rosa; Ritieni *J. Chem. Res. (S)* **1988**, 346; Yinglin; Hongwen *Synthesis* **1990**, 122.

phosphinamide Ph_2PONH_2 is alkylated with primary⁹²⁸ or secondary⁹²⁹ alkyl halides or with alcohols in the presence of MeSO_2Cl ,⁹³⁰ which converts ROH to ROSO_2Me . Hydrolysis of Ph_2PONHR with HCl gives the amine.

Amides can also be alkylated with diazo compounds, as in **0-48**. Salts of sulfonamides (ArSO_2NH^-) can be used to attack alkyl halides to prepare N-alkyl sulfonamides (ArSO_2NHR) that can be further alkylated to $\text{ArSO}_2\text{NRR}'$. Hydrolysis of the latter is a good method for the preparation of secondary amines. Secondary amines can also be made by crown-ether assisted alkylation of F_3CCONHR (R = alkyl or aryl) and hydrolysis of the resulting $\text{F}_3\text{CCONRR}'$.⁹³¹

Internal N-alkylation has been used to prepare the highly strained compounds α -lactams.⁹³²



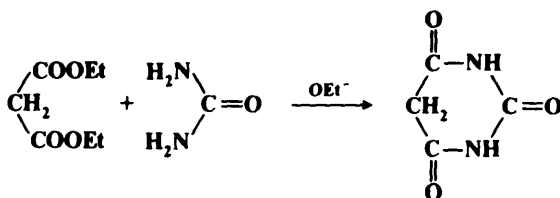
OS **I**, 119, 203, 271; **II**, 25, 83, 208; **III**, 151; **IV**, 810; **V**, 1064; **VI**, 951; **VII**, 501.

0-59 N-Acylation of Amides and Imides Acylamino-de-halogenation



Imides can be prepared by the attack of amides or their salts on acyl halides, anhydrides, and carboxylic acids or esters.⁹³³ The best synthetic method for the preparation of acyclic imides is the reaction between an amide and an anhydride at 100°C catalyzed by H_2SO_4 .⁹³⁴ When acyl chlorides are treated with amides in a 2:1 molar ratio at low temperatures in the presence of pyridine, the products are N,N-diacylamides $(\text{RCO})_2\text{N}$.⁹³⁵

This reaction is often used to prepare urea derivatives, an important example being the preparation of barbituric acid:⁹³⁶



⁹²⁸Zwierzak; Podstawczyńska *Angew. Chem. Int. Ed. Engl.* **1977**, 16, 702 [*Angew. Chem.* 89, 737].

⁹²⁹Ślusarska; Zwierzak *Synthesis* **1980**, 717.

⁹³⁰Ślusarska; Zwierzak *Synthesis* **1981**, 155.

⁹³¹Nordlander; Catalane; Eberlein; Farkas; Howe; Stevens; Tripoulas *Tetrahedron Lett.* **1978**, 4987. For other methods, see Zwierzak; Brylikowska-Piotrowicz *Angew. Chem. Int. Ed. Engl.* **1977**, 16, 107 [*Angew. Chem.* 89, 109]; Briggs; Brown; Jiricny; Meidine *Synthesis* **1980**, 295; Ref. 928.

⁹³²Baumgarten; Fuerholzer; Clark; Thompson *J. Am. Chem. Soc.* **1963**, 85, 3303; Quast; Leybach *Chem. Ber.* **1991**, 124, 849. For a review of α -lactams, see Lengyel; Sheehan *Angew. Chem. Int. Ed. Engl.* **1968**, 7, 25-36 [*Angew. Chem.* 80, 27-37].

⁹³³For a review, see Challis; Challis, Ref. 555, pp. 759-773.

⁹³⁴Baburao; Costello; Petterson; Sander *J. Chem. Soc. C* **1968**, 2779; Davidson; Skovronek *J. Am. Chem. Soc.* **1958**, 80, 376.

⁹³⁵For example, see LaLonde; Davis *J. Org. Chem.* **1970**, 35, 771.

⁹³⁶For a review of barbituric acid, see Bojarski; Mokrosz; Bartoń; Paluchowska *Adv. Heterocycl. Chem.* **1985**, 38, 229-297.

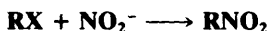
When the substrate is oxalyl chloride (ClCOCOCl) and the reagent an unsubstituted amide, an acyl isocyanate (RCONCO) is formed. The "normal" product (RCONHCOCOCl) does not form, or if it does, it rapidly loses CO and HCl.⁹³⁷

OS II, 60, 79, 422; III, 763; IV, 245, 247, 496, 566, 638, 662, 744; V, 204, 944.

D. Other Nitrogen Nucleophiles

0-60 Formation of Nitro Compounds⁹³⁸

Nitro-de-halogenation

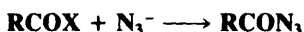
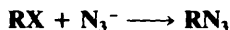


Sodium nitrite can be used to form nitro compounds with primary or secondary alkyl bromides or iodides, though the method is of limited scope. Silver nitrite gives nitro compounds only when RX is a primary bromide or iodide. Nitrite esters are an important side product in all these cases (0-32) and become the major product (by an S_N1 mechanism) when secondary or tertiary halides are treated with silver nitrite.

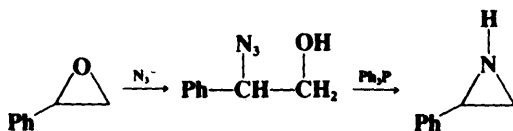
OS I, 410; IV, 368, 454, 724.

0-61 Formation of Azides

Azido-de-halogenation



Alkyl azides can be prepared by treatment of the appropriate halide with azide ion.⁹³⁹ Phase transfer catalysis⁹⁴⁰ and ultrasound⁹⁴¹ have been used. Other leaving groups have also been used,⁹⁴² for example, OH,⁹⁴³ OMs, OTs,⁹⁴⁴ and OAc.⁹⁴⁵ Epoxides react with NaN₃, with HN₃ in DMF,⁹⁴⁶ or with HN₃-Et₃Al⁹⁴⁷ to give β-azido alcohols; these are easily converted to aziridines,⁹⁴⁸ e.g.,



⁹³⁷Speziale; Smith *J. Org. Chem.* **1962**, 27, 3742; Speziale; Smith; Fedder *J. Org. Chem.* **1965**, 30, 4306.

⁹³⁸For reviews, see Larson, in Feuer *The Chemistry of the Nitro and Nitroso Groups*, pt. 1; Wiley: New York, 1969, pp. 325-339; Kornblum *Org. React.* **1962**, 12, 101-156.

⁹³⁹For reviews, see Scriven; Turnbull *Chem. Rev.* **1988**, 88, 297-368; Biffin; Miller; Paul, in Patai *The Chemistry of the Azido Group*; Wiley: New York, 1971, pp. 57-119.

⁹⁴⁰See Reeves; Bahr *Synthesis* **1979**, 823; Nakajima; Oda; Inouye *Tetrahedron Lett.* **1978**, 3107; Marti; Rico; Ader; de Savignac; Lattes *Tetrahedron Lett.* **1989**, 30, 1245.

⁹⁴¹Priebe *Acta Chem. Scand., Ser. B* **1984**, 38, 895.

⁹⁴²See, for example, Svetlakov; Mikheev; Fedotov *J. Org. Chem. USSR* **1971**, 7, 2304; Hojo; Kobayashi; Soai; Ikeda; Mukaiyama *Chem. Lett.* **1977**, 635; Murahashi; Tanigawa; Imada; Taniguchi *Tetrahedron Lett.* **1986**, 27, 227.

⁹⁴³See, for example, Viaud; Rollin *Synthesis* **1990**, 130.

⁹⁴⁴Scriven; Turnbull, Ref. 939, p. 306.

⁹⁴⁵Murahashi; Taniguchi; Imada; Tanigawa *J. Org. Chem.* **1989**, 54, 3292.

⁹⁴⁶Saito; Bunya; Inaba; Moriwake; Torii *Tetrahedron Lett.* **1985**, 26, 5309.

⁹⁴⁷Mereyala; Frei *Helv. Chim. Acta* **1986**, 69, 415.

⁹⁴⁸See, for example, Ittah; Sasson; Shahak; Tsaroom; Blum *J. Org. Chem.* **1978**, 43, 4271. For the mechanism of the conversion to aziridines, see Pöchlauer; Müller; Peringer *Helv. Chim. Acta* **1984**, 67, 1238.

This conversion has been used as a key step in the preparation of optically active aziridines from optically active 1,2-diols (prepared by **5-35**).⁹⁴⁹ Even hydrogen can be the leaving group: Benzylic hydrogens have been replaced by N₃ by treatment with HN₃ in CHCl₃ in the presence of DDQ (p. 1163).⁹⁵⁰

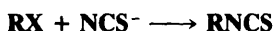
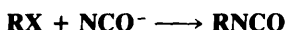
Tertiary alkyl azides can be prepared by stirring tertiary alkyl chlorides with NaN₃ and ZnCl₂ in CS₂⁹⁵¹ or by treating tertiary alcohols with NaN₃ and CF₃COOH⁹⁵² or with HN₃ and TiCl₄⁹⁵³ or BF₃.⁹⁵⁴ Acyl azides, which can be used in the Curtius reaction (**8-15**), can be similarly prepared from acyl halides or anhydrides.⁹⁵⁵

OS **III**, 846; **IV**, 715; **V**, 273, 586; **VI**, 95, 207, 210, 910; **VII**, 433; **69**, 205. See also OS **VII**, 206.

0-62 Formation of Isocyanates and Isothiocyanates

Isocyanato-de-halogenation

Isothiocyanato-de-halogenation



When the reagent is the thiocyanate ion, S-alkylation is an important side reaction (**0-42**), but the cyanate ion practically always gives exclusive N-alkylation.⁴²² Primary alkyl halides have been converted to isocyanates by treatment with sodium nitrocyanamide NaNCNNO₂ and *m*-chloroperbenzoic acid, followed by heating of the initially produced RN(NO₂)CN.⁹⁵⁶ When alkyl halides are treated with NCO⁻ in the presence of ethanol, carbamates can be prepared directly (see **6-8**).⁹⁵⁷ Acyl halides give the corresponding acyl isocyanates and isothiocyanates.⁹⁵⁸ For the formation of isocyanides, see **0-101**.

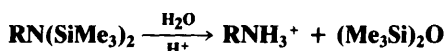
OS **III**, 735.

0-63 Formation of Bis(trimethylsilyl)amines

Bis(trimethylsilyl)amino-de-halogenation



Primary alkyl, allylic, and benzylic bromides, iodides, and tosylates react with sodium bis(trimethylsilyl)amide to give derivatives that are easily hydrolyzed to produce amine salts in high overall yields.⁹⁵⁹



This is therefore an indirect way of converting halides to primary amines.

⁹⁴⁹Lohray; Gao; Sharpless *Tetrahedron Lett.* **1989**, 30, 2623.

⁹⁵⁰Guy; Lemor; Doussot; Lemaire *Synthesis* **1988**, 900.

⁹⁵¹Miller *Tetrahedron Lett.* **1975**, 2959. See also Koziara; Zwierzak *Tetrahedron Lett.* **1987**, 28, 6513.

⁹⁵²Balderman; Kalir *Synthesis* **1978**, 24.

⁹⁵³Hassner; Fibiger; Andisik *J. Org. Chem.* **1984**, 49, 4237.

⁹⁵⁴See, for example, Adam; Andrieux; Plat *Tetrahedron* **1985**, 41, 399.

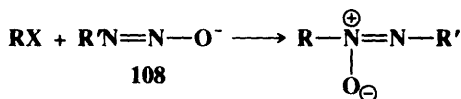
⁹⁵⁵For a review of acyl azides, see Lwowski, in Patai, Ref. 939, pp. 503-554.

⁹⁵⁶Manimaran; Wolford; Boyer *J. Chem. Res. (S)* **1989**, 331.

⁹⁵⁷Argabright; Rider; Sieck *J. Org. Chem.* **1965**, 30, 3317; Effenberger; Drauz; Förster; Müller *Chem. Ber.* **1981**, 114, 173.

⁹⁵⁸For reviews of acyl isocyanates, see Tsuge, in Patai, Ref. 585, pt. 1, pp. 445-506; Nuridzhanyan *Russ. Chem. Rev.* **1970**, 39, 130-139; Lozinskii; Pel'kis *Russ. Chem. Rev.* **1968**, 37, 363-375.

⁹⁵⁹Bestmann; Wölfel *Chem. Ber.* **1984**, 117, 1250.

0-64 Formation of Azoxy Compounds**Alkyl-*NNO*-azoxy-de-halogenation**

The reaction between alkyl halides and alkanediazotates (**108**) gives azoxyalkanes.⁹⁶⁰ R and R' may be the same or different, but neither may be aryl or tertiary alkyl. The reaction is regioselective; only the isomer shown is obtained.

Halogen Nucleophiles⁹⁶¹**A. Attack at an Alkyl Carbon****0-65** Halide Exchange**Halo-de-halogenation**

Halide exchange, sometimes call the *Finkelstein reaction*, is an equilibrium process, but it is often possible to shift the equilibrium.⁹⁶² The reaction is most often applied to the preparation of iodides and fluorides. Iodides can be prepared from chlorides or bromides by taking advantage of the fact that sodium iodide, but not the bromide or chloride, is soluble in acetone. When an alkyl chloride or bromide is treated with a solution of sodium iodide in acetone, the equilibrium is shifted by the precipitation of sodium chloride or bromide. Since the mechanism is S_N2, the reaction is much more successful for primary halides than for secondary or tertiary halides; sodium iodide in acetone can be used as a test for primary bromides or chlorides. Tertiary chlorides can be converted to iodides by treatment with excess NaI in CS₂, with ZnCl₂ as catalyst.⁹⁶³ Vinylic bromides give vinylic iodides with retention of configuration when treated with KI and a nickel bromide-zinc catalyst,⁹⁶⁴ or with KI and CuI in hot HMPA.⁹⁶⁵

Fluorides⁹⁶⁶ are prepared by treatment of other alkyl halides with any of a number of fluorinating agents, among them anhydrous HF (which is useful only for reactive substrates such as benzylic or allylic), AgF, KF, HgF₂, Bu₄N⁺ HF₂⁻,⁹⁶⁷ BrF₃,⁹⁶⁸ Et₃N·2HF,⁹⁶⁹ and, for polyhalo compounds (such as chloroform), HF plus SbF₃.⁹⁷⁰ The equilibria in these cases

⁹⁶⁰For reviews, see Yandovskii; Gidaspov; Tselinskii *Russ. Chem. Rev.* **1980**, *49*, 237-248; Moss *Acc. Chem. Res.* **1974**, *7*, 421-427.

⁹⁶¹For a review of the formation of carbon-halogen bonds, see Hudlicky; Hudlicky, in Patai; Rappoport, Ref. 88, pt. 2, pp. 1021-1172.

⁹⁶²For a list of reagents for alkyl halide interconversion, see Ref. 508, pp. 337-339.

⁹⁶³Miller; Nunn *J. Chem. Soc., Perkin Trans I* **1976**, 416.

⁹⁶⁴Takagi; Hayama; Inokawa *Chem. Lett.* **1978**, 1435.

⁹⁶⁵Suzuki; Aihara; Yamamoto; Takamoto; Ogawa *Synthesis* **1988**, 236.

⁹⁶⁶For reviews of the introduction of fluorine into organic compounds, see Mann *Chem. Soc. Rev.* **1987**, *16*, 381-436; Rozen; Filler *Tetrahedron* **1985**, *41*, 1111-1153; Hudlický, Ref. 448, pp. 24-169; Sheppard; Sharts, Ref. 448, pp. 52-184, 409-430.

⁹⁶⁷Bosch; Camps; Chamorro; Gasol; Guerrero *Tetrahedron Lett.* **1987**, *28*, 4733. See also Cox; Terpinski; Lawrynowicz *J. Org. Chem.* **1984**, *49*, 3216.

⁹⁶⁸Kartashov; Chuvatkin; Kurskii; Boguslavskaya *J. Org. Chem. USSR* **1988**, *24*, 2279.

⁹⁶⁹Giudicelli; Picq; Veyron *Tetrahedron Lett.* **1990**, *31*, 6527.

⁹⁷⁰For reviews of the use of halogen exchange to prepare alkyl fluorides, see Sharts; Sheppard *Org. React.* **1974**, *21*, 125-406; Hudlický, Ref. 448, pp. 91-136.

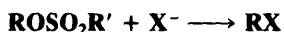
are shifted because the alkyl fluoride once formed has little tendency to react, owing to the extremely poor leaving-group ability of fluorine. Phase transfer catalysis of the exchange reaction is a particularly effective way of preparing both fluorides and iodides.⁹⁷¹

Primary alkyl chlorides can be converted to bromides with ethyl bromide, N-methyl-2-pyrrolidinone and a catalytic amount of NaBr,⁹⁷² with LiBr under phase-transfer conditions,⁹⁷³ and with Bu₄N⁺ Br⁻.⁹⁷⁴ For secondary and tertiary alkyl chlorides, treatment in CH₂Cl₂ with excess gaseous HBr and an anhydrous FeBr₃ catalyst has given high yields⁹⁷⁵ (this procedure is also successful for chloride-to-iodide conversions). Alkyl chlorides or bromides can be prepared from iodides by treatment with HCl or HBr in the presence of HNO₃, making use of the fact that the leaving I⁻ is oxidized to I₂ by the HNO₃.⁹⁷⁶ Primary iodides give the chlorides when treated with PCl₅ in POCl₃.⁹⁷⁷ Alkyl fluorides and chlorides are converted to the bromides and iodides (and alkyl fluorides to the chlorides) by heating with the corresponding HX in excess amounts.⁹⁷⁸

OS II, 476; IV, 84, 525; 66, 87.

0-66 Formation of Alkyl Halides from Esters of Sulfuric and Sulfonic Acids

Halo-de-sulfonyloxy-substitution, etc.



Alkyl sulfates, tosylates, and other esters of sulfuric and sulfonic acids can be converted to alkyl halides with any of the four halide ions.⁹⁷⁹ Neopentyl tosylate reacts with Cl⁻, Br⁻, or I⁻ without rearrangement in HMPA.⁹⁸⁰ Similarly, allylic tosylates can be converted to chlorides without allylic rearrangement by reaction with LiCl in the same solvent.⁹⁸¹ Inorganic esters are intermediates in the conversion of alcohols to alkyl halides with SOCl₂, PCl₅, PCl₃, etc. (0-67), but are seldom isolated.

OS I, 25; II, 111, 404; IV, 597, 753; V, 545.

0-67 Formation of Alkyl Halides from Alcohols

Halo-de-hydroxylation



Alcohols can be converted to alkyl halides with several reagents,⁹⁸² the most common of which are halogen acids HX and inorganic acid halides such as SOCl₂,⁹⁸³ PCl₅, PCl₃, POCl₃, etc.⁹⁸⁴ HBr is usually used for alkyl bromides and HI for alkyl iodides. These reagents are

⁹⁷¹For reviews, see Starks; Liotta, Ref. 404, pp. 112-125; Weber; Gokel *Phase Transfer Catalysis in Organic Synthesis*. Ref. 404, pp. 117-124. See also Clark; Macquarrie *Tetrahedron Lett.* **1987**, 28, 111; Bram; Loupy; Pigeon *Synth. Commun.* **1988**, 18, 1661.

⁹⁷²Willy; McKean; Garcia *Bull. Chem. Soc. Jpn.* **1976**, 49, 1989. See also Babler; Spina *Synth. Commun.* **1984**, 14, 1313.

⁹⁷³Sasson; Weiss; Loupy; Bram; Pardo *J. Chem. Soc., Chem. Commun.* **1986**, 1250; Loupy; Pardo *Synth. Commun.* **1988**, 18, 1275.

⁹⁷⁴Bidd; Whiting *Tetrahedron Lett.* **1984**, 25, 5949.

⁹⁷⁵Yoon; Kochi *J. Org. Chem.* **1989**, 54, 3028.

⁹⁷⁶Svetlakov; Moisak; Averko-Antonovich *J. Org. Chem. USSR* **1969**, 5, 971.

⁹⁷⁷Bartley; Carman; Russell-Maynard *Aust. J. Chem.* **1985**, 38, 1879.

⁹⁷⁸Namavari; Satyamurthy; Phelps; Barrio *Tetrahedron Lett.* **1990**, 31, 4973.

⁹⁷⁹For a list of reagents, with references, see Ref. 508, pp. 360-362.

⁹⁸⁰Stephenson; Solladié; Mosher, Ref. 248.

⁹⁸¹Stork; Grieco; Gregson *Tetrahedron Lett.* **1969**, 1393.

⁹⁸²For a list of reagents, with references, see Ref. 508, pp. 353-360.

⁹⁸³For a review of thionyl chloride SOCl₂, see Pizey, Ref. 593, vol. 1, 1974, pp. 321-357.

⁹⁸⁴For a review, see Brown, in Patai, Ref. 575, pt. 1, pp.595-622.

often generated in situ from the halide ion and an acid such as phosphoric or sulfuric. The use of HI sometimes results in reduction of the alkyl iodide to the alkane (**0-76**) and, if the substrate is unsaturated, can also reduce the double bond.⁹⁸⁵ The reaction can be used to prepare primary, secondary, or tertiary halides, but alcohols of the isobutyl or neopentyl type often give large amounts of rearrangement products. Tertiary chlorides are easily made with concentrated HCl, but primary and secondary alcohols react with HCl so slowly that a catalyst, usually zinc chloride, is required.⁹⁸⁶ Primary alcohols give good yields of chlorides upon treatment with HCl in HMPA.⁹⁸⁷ The inorganic acid chlorides SOCl_2 , PCl_3 , etc., give primary, secondary, or tertiary alkyl chlorides with much less rearrangement than is observed with HCl.

Analogous bromides and iodides, especially PBr_3 , have also been used, but they are more expensive and used less often than HBr or HI, though some of them may also be generated in situ (e.g., PBr_3 from phosphorous and bromine). Secondary alcohols always gives *some* rearranged bromides if another secondary position is available, even with PBr_3 , PBr_5 , or SOBr_2 ; thus 3-pentanol gives both 2- and 3-bromopentane. Such rearrangement can be avoided by converting the alcohol to a sulfonate and then using **0-66**,⁹⁸⁸ or by the use of phase transfer catalysis.⁹⁸⁹ HF does not generally convert alcohols to alkyl fluorides.⁹⁹⁰ The most important reagent for this purpose is the commercially available diethylaminosulfur trifluoride Et_2NSF_3 (DAST),⁹⁹¹ which converts primary, secondary, tertiary, allylic, and benzylic alcohols to fluorides in high yields under mild conditions.⁹⁹² Fluorides have also been prepared from alcohols by treatment with SF_4 ,⁹⁹³ SeF_4 ,⁹⁹⁴ TsF ,⁹⁹⁵ and indirectly, by conversion to a sulfate or tosylate, etc. (**0-66**).

Primary, secondary, and tertiary alcohols can be converted to any of the four halides by treatment with the appropriate NaX , KX , or NH_4X in polyhydrogen fluoride-pyridine solution.⁹⁹⁶ This method is even successful for neopentyl halides. Another reagent that converts neopentyl alcohol to neopentyl chloride, in 95% yield, is $\text{PPh}_3\text{-CCl}_3\text{CN}$.⁹⁹⁷

Other reagents⁹⁹⁸ have also been used, for example, $(\text{RO})_3\text{PRX}$ ⁹⁹⁹ and R_3PX_2 ¹⁰⁰⁰ (made from R_3P and X_2), which give good yields for primary (including neopentyl), secondary,

⁹⁸⁵Jones; Pattison *J. Chem. Soc. C* **1969**, 1046.

⁹⁸⁶Phase-transfer catalysts have been used instead of ZnCl_2 ; Landini; Montanari; Rolla *Synthesis* **1974**, 37.

⁹⁸⁷Fuchs; Cole *Can. J. Chem.* **1975**, 53, 3620.

⁹⁸⁸Cason; Correia *J. Org. Chem.* **1961**, 26, 3645.

⁹⁸⁹Dakka; Sasson *Tetrahedron Lett.* **1987**, 28, 1223.

⁹⁹⁰For an exception, see Hanack; Eggensperger; Hähnle *Liebigs Ann. Chem.* **1962**, 652, 96; See also Politanskii; Ivanyk; Sarancha; Shevchuk *J. Org. Chem. USSR* **1974**, 10, 697.

⁹⁹¹For a review of this reagent, see Hudlický *Org. React.* **1988**, 35, 513-637.

⁹⁹²Middleton *J. Org. Chem.* **1975**, 40, 574.

⁹⁹³For reviews, see Wang *Org. React.* **1985**, 34, 319-400; Kollonitsch *Isr. J. Chem.* **1978**, 17, 53-59; Boswell; Ripka; Scribner; Tullock *Org. React.* **1974**, 21, 1-124.

⁹⁹⁴Olah; Nojima; Kerekes *J. Am. Chem. Soc.* **1974**, 96, 925.

⁹⁹⁵Shimizu; Nakahara; Yoshioka *Tetrahedron Lett.* **1985**, 26, 4207. For another method, see Olah; Li *Synlett* **1990**, 267.

⁹⁹⁶Olah; Welch *Synthesis* **1974**, 653; Olah; Welch; Vankar; Nojima; Kerekes; Olah *J. Org. Chem.* **1979**, 44, 3872; Alverne; Lacombe; Laurent; Rousset *J. Chem. Res., (S)* **1983**, 246.

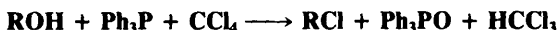
⁹⁹⁷Matveeva; Yalovskaya; Cherepanov; Kurts; Bundel' *J. Org. Chem. USSR* **1989**, 25, 587.

⁹⁹⁸For some other reagents, not listed here, see Echigo; Mukaiyama *Chem. Lett.* **1978**, 465; Barton; Stick; Subramanian *J. Chem. Soc., Perkin Trans. 1* **1976**, 2112; Savel'yanov; Nazarov; Savel'yanova; Suchkov *J. Org. Chem. USSR* **1977**, 13, 604; Jung; Hatfield *Tetrahedron Lett.* **1978**, 4483; Sevrin; Krief *J. Chem. Soc., Chem. Commun.* **1980**, 656; Olah; Gupta; Malhotra; Narang *J. Org. Chem.* **1980**, 45, 1638; Hanessian; Leblanc; Lavallée *Tetrahedron Lett.* **1982**, 23, 4411; Cristol; Seapy *J. Org. Chem.* **1982**, 47, 132; Richter; Tucker *J. Org. Chem.* **1983**, 48, 2625; Imamoto; Matsumoto; Kusumoto; Yokoyama *Synthesis* **1983**, 460; Ref. 515; Toto; Doi *J. Org. Chem.* **1987**, 52, 4999; Camps; Gasol; Guerrero *Synthesis* **1987**, 511; Schmidt; Brooks *Tetrahedron Lett.* **1987**, 28, 767; Collingwood; Davies; Golding *Tetrahedron Lett.* **1987**, 28, 4445; Kozikowski; Lee *Tetrahedron Lett.* **1988**, 29, 3053; Classon; Liu; Samuelsson *J. Org. Chem.* **1988**, 53, 6126; Munyemana; Frisque-Hesbain; Devos; Ghosez *Tetrahedron Lett.* **1989**, 30, 3077; Ernst; Winkler *Tetrahedron Lett.* **1989**, 30, 3081.

⁹⁹⁹Rydon *Org. Synth.* VI, 830.

¹⁰⁰⁰Wiley; Hershkowitz; Rein; Chung *J. Am. Chem. Soc.* **1964**, 86, 964; Wiley; Rein; Hershkowitz *Tetrahedron Lett.* **1964**, 2509; Schaefer; Weinberg *J. Org. Chem.* **1965**, 30, 2635; Kaplan *J. Org. Chem.* **1966**, 31, 3454; Weiss; Snyder *J. Org. Chem.* **1971**, 36, 403; Garegg; Johansson; Samuelsson *Synthesis* **1984**, 168.

and tertiary halides without rearrangements,¹⁰⁰¹ Me_2SBr_2 ¹⁰⁰² (prepared from Me_2S and Br_2), $\text{Me}_3\text{SiCl-SeO}_2$,¹⁰⁰³ and a mixture of PPh_3 and CCl_4 ¹⁰⁰⁴ (or CBr_4 ¹⁰⁰⁵).



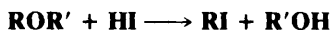
The last method converts allylic alcohols¹⁰⁰⁶ to the corresponding halides without allylic rearrangements.¹⁰⁰⁷ A simple method that is specific for benzylic and allylic alcohols (and does not give allylic rearrangement) involves reaction with N-chloro- or N-bromosuccinimide and methyl sulfide.¹⁰⁰⁸ The specificity of this method is illustrated by the conversion, in 87% yield, of (Z)- $\text{HOCH}_2\text{CH}_2\text{CMe}=\text{CHCH}_2\text{OH}$ to (Z)- $\text{HOCH}_2\text{CH}_2\text{CMe}=\text{CHCH}_2\text{Cl}$. Only the allylic OH group was affected. Allylic and benzylic alcohols can also be converted to bromides or iodides with NaX-BF_3 etherate,¹⁰⁰⁹ and to iodides with AlI_3 .¹⁰¹⁰

When the reagent is HX , the mechanism is $\text{S}_{\text{N}}1\text{cA}$ or $\text{S}_{\text{N}}2\text{cA}$; i.e., the leaving group is not OH^- , but OH_2 (p. 352). The leaving group is not OH^- with the other reagents either, since in these cases the alcohol is first converted to an inorganic ester, e.g., ROSOCl with SOCl_2 (0-32). The leaving group is therefore OSOCl^- or a similar group (0-66). These may react by the $\text{S}_{\text{N}}1$ or $\text{S}_{\text{N}}2$ mechanism and, in the case of ROSOCl , by the $\text{S}_{\text{N}}\text{i}$ mechanism (p. 326).

OS I, 25, 36, 131, 142, 144, 292, 294, 533; II, 91, 136, 159, 246, 308, 322, 358, 399, 476; III, 11, 227, 370, 446, 698, 793, 841; IV, 106, 169, 323, 333, 576, 681; V, 1, 249, 608; VI, 75, 628, 634, 638, 781, 830, 835; VII, 210, 319, 356; 65, 119, 211. Also see OS III, 818; IV, 278, 383, 597.

0-68 Formation of Alkyl Halides from Ethers

Halo-de-alkoxylation



Ethers can be cleaved by heating with concentrated HI or HBr .¹⁰¹¹ HCl is seldom successful.¹⁰¹² HBr reacts more slowly than HI , but it is often a superior reagent, since it causes fewer side reactions. Phase transfer catalysis has also been used.¹⁰¹³ Dialkyl ethers and alkyl aryl ethers can be cleaved. In the latter case the alkyl-oxygen bond is the one broken. As in 0-67 the actual leaving group is not OR'^- , but OHR' . Although alkyl aryl ethers always cleave so as to give an alkyl halide and a phenol, there is no general rule for dialkyl ethers. Often cleavage occurs from both sides, and a mixture of two alcohols and two alkyl halides is obtained. However, methyl ethers are usually cleaved so that methyl iodide or bromide is a product. An excess of HI or HBr converts the alcohol product into alkyl halide, so that dialkyl ethers (but not alkyl aryl ethers) are converted to 2 moles of alkyl halide. This

¹⁰⁰¹For reviews of reactions with these reagents, see Castro *Org. React.* **1983**, 29, 1-162; Mackie, in Cadogan *Organophosphorus Reagents in Organic Synthesis*; Academic Press: New York, 1979; pp. 433-466.

¹⁰⁰²Furukawa; Inoue; Aida; Oae *J. Chem. Soc., Chem. Commun.* **1973**, 212.

¹⁰⁰³Lee; Kang *J. Org. Chem.* **1988**, 53, 3634.

¹⁰⁰⁴For a review, see Appel, *Angew. Chem. Int. Ed. Engl.* **1975**, 14, 801-811 [*Angew. Chem.* 87, 863-874]. For a general review of this and related reagents, see Appel; Halstenberg, in Cadogan, Ref. 1001, pp. 387-431. For a discussion of the mechanism, see Slagle, Huang, Franzus *J. Org. Chem.* **1981**, 46, 3526.

¹⁰⁰⁵Katritzky; Nowak-Wydra; Marson *Chem. Scr.* **1987**, 27, 477; Wagner; Heitz; Mioskowski *Tetrahedron Lett.* **1989**, 30, 557.

¹⁰⁰⁶For a review of the conversion of allylic alcohols to allylic halides, see Magid *Tetrahedron* **1980**, 36, 1901-1930, pp. 1924-1926.

¹⁰⁰⁷Snyder *J. Org. Chem.* **1972**, 37, 1466; Axelrod; Milne; van Tamelen *J. Am. Chem. Soc.* **1973**, 92, 2139.

¹⁰⁰⁸Corey; Kim; Takeda *Tetrahedron Lett.* **1972**, 4339.

¹⁰⁰⁹Vankar; Rao *Tetrahedron Lett.* **1985**, 26, 2717; Mandal; Mahajan *Tetrahedron Lett.* **1985**, 26, 3863.

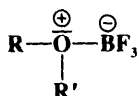
¹⁰¹⁰Sarmah; Barua *Tetrahedron* **1989**, 45, 3569.

¹⁰¹¹For reviews of ether cleavage in general, see Bhatt; Kulkarni *Synthesis* **1983**, 249-282; Ref. 333. For a review of cleavage of aryl alkyl ethers, see Tiecco, Ref. 762.

¹⁰¹²Cleavage with HCl has been accomplished in the presence of surfactants: Juršić *J. Chem. Res. (S)* **1989**, 284.

¹⁰¹³Landini; Montanari; Rolla *Synthesis* **1978**, 771.

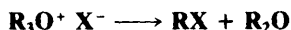
procedure is often carried out so that a mixture of only two products is obtained instead of four. Cyclic ethers (usually tetrahydrofuran derivatives) can be similarly cleaved (see 0-69 for epoxides). Ethers have also been cleaved with Lewis acids such as BF_3 , BCl_3 , Me_2BBr ,¹⁰¹⁴ BBr_3 ,¹⁰¹⁵ or AlCl_3 .¹⁰¹⁶ In such cases, the departure of the OR is assisted by complex formation with the Lewis acid:



Lewis acids are also used in conjunction with acyl halides. The reagent NaI-BF_3 etherate selectively cleaves ethers in the order benzylic ethers > alkyl methyl ethers > aryl methyl ethers.¹⁰¹⁷

Dialkyl and alkyl aryl ethers can be cleaved with iodotrimethylsilane:^{1017a} $\text{ROR}' + \text{Me}_3\text{SiI} \rightarrow \text{RI} + \text{Me}_3\text{SiOR}$.¹⁰¹⁸ A more convenient and less expensive alternative, which gives the same products, is a mixture of chlorotrimethylsilane and NaI .¹⁰¹⁹ A mixture of SiCl_4 and NaI has also been used,¹⁰²⁰ as has diiodosilane SiH_2I_2 .¹⁰²¹ Alkyl aryl ethers can also be cleaved with LiI to give alkyl iodides and salts of phenols¹⁰²² in a reaction similar to 0-70. Triphenyldibromophosphorane (Ph_3PBr_2) cleaves dialkyl ethers to give 2 moles of alkyl bromide.¹⁰²³

A closely related reaction is cleavage of oxonium salts.



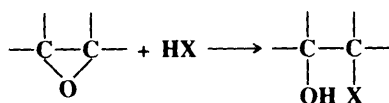
For these substrates, HX is not required, and X can be any of the four halide ions.

t-Butyldimethylsilyl ethers $\text{ROSiMe}_2\text{CMe}_3$ can be converted to bromides RBr by treatment with Ph_3PBr_2 ,¹⁰²⁴ $\text{Ph}_3\text{P-CBr}_4$,¹⁰²⁵ or BBr_3 .¹⁰²⁶ Alcohols are often protected by conversion to this kind of silyl ether.¹⁰²⁷

OS I, 150; II, 571; III, 187, 432, 586, 692, 753, 774, 813; IV, 266, 321; V, 412; VI, 353. See also OS 65, 68; 67, 210.

0-69 Formation of Halohydrins from Epoxides

(3) OC-seco-Halo-de-alkoxylation



¹⁰¹⁴Guindon; Yoakim; Morton *Tetrahedron Lett.* **1983**, 24, 2969; Guindon; Bernstein; Anderson *Tetrahedron Lett.* **1987**, 28, 2225; Guindon; Therien; Girard; Yoakim *J. Org. Chem.* **1987**, 52, 1680.

¹⁰¹⁵Manson; Musgrave *J. Chem. Soc.* **1963**, 1011; McOmie; Watts; West *Tetrahedron* **1968**, 24, 2289; Egly; Pousse; Brini *Bull. Soc. Chim. Fr.* **1972**, 1357; Press *Synth. Commun.* **1979**, 9, 407; Niwa; Hida; Yamada *Tetrahedron Lett.* **1981**, 22, 4239.

¹⁰¹⁶For a review, see Johnson, in Olah *Friedel-Crafts and Related Reactions*, vol. 4; Wiley: New York, 1965. pp. 1-109.

¹⁰¹⁷Vankar; Rao *J. Chem. Res. (S)* **1985**, 232. See also Mandal; Soni; Ratnam *Synthesis* **1985**, 274.

^{1017a}For a review of this reagent, see Olah; Prakash; Krishnamurti *Adv. Silicon Chem.* **1991**, 1, 1-64.

¹⁰¹⁸Jung; Lyster *J. Org. Chem.* **1977**, 42, 3761; *Org. Synth.* VI, 353.

¹⁰¹⁹Morita; Okamoto; Sakurai *J. Chem. Soc., Chem. Commun.* **1978**, 874; Olah; Narang; Gupta; Malhotra *J. Org. Chem.* **1979**, 44, 1247; Amouroux; Jatczak; Chastrette *Bull. Soc. Chim. Fr.* **1987**, 505.

¹⁰²⁰Bhatt; El-Morey *Synthesis* **1982**, 1048.

¹⁰²¹Keinan; Perez *J. Org. Chem.* **1987**, 52, 4846.

¹⁰²²Harrison *Chem. Commun.* **1969**, 616.

¹⁰²³Anderson; Freenor *J. Org. Chem.* **1972**, 37, 626.

¹⁰²⁴Aizpurua; Cossio; Palomo *J. Org. Chem.* **1986**, 51, 4941.

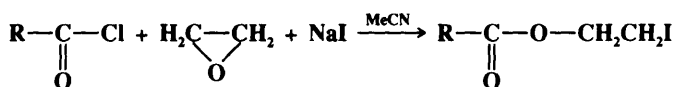
¹⁰²⁵Mattes; Benzra *Tetrahedron Lett.* **1987**, 28, 1697.

¹⁰²⁶Kim; Park *J. Org. Chem.* **1988**, 53, 3111.

¹⁰²⁷See Corey; Venkateswarlu *J. Am. Chem. Soc.* **1972**, 94, 6190.

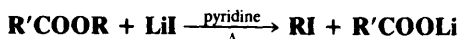
This is a special case of 0-68 and is frequently used for the preparation of halohydrins. In contrast to the situation with open-chain ethers and with larger rings, many epoxides react with all four hydrohalic acids, though with HF¹⁰²⁸ the reaction is unsuccessful with simple aliphatic and cycloalkyl epoxides.¹⁰²⁹ HF does react with more rigid epoxides, such as those in steroid systems. The reaction can be applied to simple epoxides¹⁰³⁰ if polyhydrogen fluoride-pyridine is the reagent. The epoxide-to-fluorohydrin conversion has also been carried out with SiF₄ and a tertiary amine.¹⁰³¹ Chloro-, bromo-, and iodohydrins can also be prepared¹⁰³² by treating epoxides with Ph₃P and X₂.¹⁰³³ Epoxides can be converted directly to 1,2-dichloro compounds by treatment with SOCl₂ and pyridine,¹⁰³⁴ with Ph₃P and CCl₄,¹⁰³⁵ or with Ph₃PCl₂.¹⁰³⁶ These are two-step reactions: a halohydrin is formed first and is then converted by the reagents to the dihalide (0-67). As expected, inversion is found at both carbons. Meso epoxides were cleaved enantioselectively with the chiral reagents B-halodiisopinocampheylboranes (see 5-12), where the halogen was Cl, Br, or I.¹⁰³⁷

Acyl chlorides react with ethylene oxide in the presence of NaI to give 2-iodoethyl esters.¹⁰³⁸

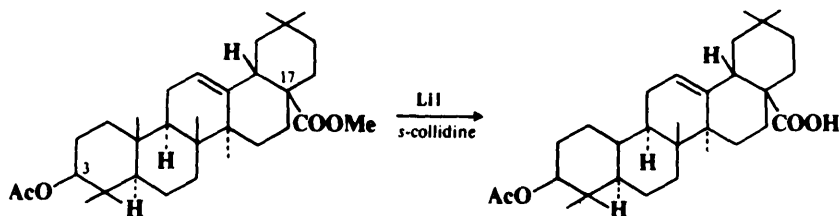


OS I, 117; VI, 424.

0-70 Cleavage of Carboxylic Esters with Lithium Iodide Iodo-de-acyloxy-substitution



Carboxylic esters where R is methyl or ethyl can be cleaved by heating with lithium iodide in refluxing pyridine or a higher-boiling amine.¹⁰³⁹ The reaction is useful where a molecule is sensitive to acid and base (so that 0-10 cannot be used) or where it is desired to cleave selectively only one ester group in a molecule containing two or more. For example, refluxing O-acetyloleanolic acid methyl ester with LiI in *s*-collidine cleaved only the 17-carbomethoxy



¹⁰²⁸For a review of reactions HF with epoxides, see Sharts; Sheppard, Ref. 966. For a related review, see Yoneda *Tetrahedron* **1991**, 47, 5329-5365.

¹⁰²⁹Shahak; Manor; Bergmann *J. Chem. Soc. C* **1968**, 2129.

¹⁰³⁰Olah; Meidar *Isr. J. Chem.* **1978**, 17, 148.

¹⁰³¹Shimizu; Yoshioka *Tetrahedron Lett.* **1988**, 29, 4101. For other methods, see Muehlbacher; Poulter *J. Org. Chem.* **1988**, 53, 1026; Ichihara; Hanafusa *J. Chem. Soc., Chem. Commun.* **1989**, 1848.

¹⁰³²Einhorn; Luche *J. Chem. Soc., Chem. Commun.* **1986**, 1368; Ciaccio; Address; Bell *Tetrahedron Lett.* **1986**, 27, 3697; Spawn; Drtina; Wiemer *Synthesis* **1986**, 315.

¹⁰³³Palumbo; Ferreri; Caputo *Tetrahedron Lett.* **1983**, 24, 1307.

¹⁰³⁴Campbell; Jones; Wolfe *Can. J. Chem.* **1966**, 44, 2339.

¹⁰³⁵Isacs; Kirkpatrick *Tetrahedron Lett.* **1972**, 3869.

¹⁰³⁶Sonnet; Oliver *J. Org. Chem.* **1976**, 41, 3279; *Org. Synth.* VI, 424. This method also applies to Ph₃PBr₂. For another method, see Echigo; Watanabe; Mukaiyama *Chem. Lett.* **1977**, 1013.

¹⁰³⁷Srebnik; Joshi; Brown *Isr. J. Chem.* **1989**, 29, 229.

¹⁰³⁸Belsner; Hoffmann *Synthesis* **1982**, 239. See also Roloff *Chimia* **1985**, 39, 392; Iqbal; Khan; Srivastava *Tetrahedron Lett.* **1988**, 29, 4985.

¹⁰³⁹Taschner; Liberek *Rocz. Chem.* **1956**, 30, 323 [*Chem. Abstr.* **1957**, 51, 1039]. For a review, see Ref. 364.

group, not the 3-acetyl group.¹⁰⁴⁰ Esters RCOOR' and lactones can also be cleaved with a mixture of Me_3SiCl and NaI to give $\text{R}'\text{I}$ and RCOOH .¹⁰⁴¹

0-71 Conversion of Diazo Ketones to α -Halo Ketones
Hydro,halo-de-diazo-bisubstitution



When diazo ketones are treated with HBr or HCl , they give the respective α -halo ketones. HI does not give the reaction, since it reduces the product to a methyl ketone (**0-82**). α -Fluoro ketones can be prepared by addition of the diazo ketone to polyhydrogen fluoride-pyridine.¹⁰⁴² This method is also successful for diazoalkanes.

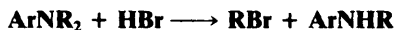
Diazotization of α -amino acids in the above solvent at room temperature gives α -fluoro carboxylic acids.¹⁰⁴³ If this reaction is run in the presence of excess KCl or KBr , the corresponding α -chloro or α -bromo acid is obtained instead.¹⁰⁴⁴

OS III, 119.

0-72 Conversion of Amines to Halides
Halo-de-amination



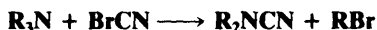
Primary alkyl amines RNH_2 can be converted¹⁰⁴⁵ to alkyl halides by (1) conversion to RNTs_2 (p. 354) and treatment of this with I^- or Br^- in DMF ,³⁴⁷ (2) diazotization with *t*-butyl nitrite and a metal halide such as TiCl_4 in DMF ,¹⁰⁴⁶ or (3) the Katritzky pyrylium-pyridinium method (p. 354).¹⁰⁴⁷ Alkyl groups can be cleaved from secondary and tertiary aromatic amines by concentrated HBr in a reaction similar to **0-68**, e.g.,¹⁰⁴⁸



Tertiary aliphatic amines are also cleaved by HI , but useful products are seldom obtained. Tertiary amines can be cleaved by reaction with phenyl chloroformate:¹⁰⁴⁹ $\text{R}_3\text{N} + \text{ClCOOPh} \rightarrow \text{RCl} + \text{R}_2\text{NCOOPh}$. α -Chloroethyl chloroformate behaves similarly.¹⁰⁵⁰ Alkyl halides may be formed when quaternary ammonium salts are heated: $\text{R}_4\text{N}^+ \text{X}^- \rightarrow \text{R}_3\text{N} + \text{RX}$.¹⁰⁵¹

OS 66, 151. See also OS I, 428.

0-73 Conversion of Tertiary Amines to Cyanamides. The von Braun Reaction
Bromo-de-dialkylamino-substitution



¹⁰⁴⁰Elsinger; Schreiber; Eschenmoser *Helv. Chim. Acta* **1960**, 43, 113.

¹⁰⁴¹Olah; Narang; Gupta; Malhotra, Ref. 1019. See also Kolb; Barth *Synth. Commun.* **1981**, 11, 763.

¹⁰⁴²Olah; Welch *Synthesis* **1974**, 896; Olah; Welch; Vankar; Nojima; Kerekes; Olah, Ref. 996.

¹⁰⁴³Olah; Prakash; Chao *Helv. Chim. Acta* **1981**, 64, 2528; Faustini; De Munary; Panzeri; Villa; Gandolfi *Tetrahedron Lett.* **1981**, 22, 4533; Barber; Keck; Rétey *Tetrahedron Lett.* **1982**, 23, 1549.

¹⁰⁴⁴Olah; Shih; Prakash *Helv. Chim. Acta* **1983**, 66, 1028.

¹⁰⁴⁵For another method, see Lorenzo; Molina; Vilaplana *Synthesis* **1980**, 853.

¹⁰⁴⁶Doyle; Bosch; Seites *J. Org. Chem.* **1978**, 43, 4120.

¹⁰⁴⁷Katritzky; Horvath; Plau *Synthesis* **1979**, 437; Katritzky; Chermprapai; Patel *J. Chem. Soc., Perkin Trans. 1* **1980**, 2901.

¹⁰⁴⁸Chambers; Pearson *J. Org. Chem.* **1963**, 28, 3144.

¹⁰⁴⁹Hobson; McCluskey *J. Chem. Soc. C* **1967**, 2015. For a review, see Cooley; Evain *Synthesis* **1989**, 1-7.

¹⁰⁵⁰Olofson; Martz; Senet; Piteau; Malfroot *J. Org. Chem.* **1984**, 49, 2081; Olofson; Abbott *J. Org. Chem.* **1984**, 49, 2795. See also Campbell; Pilipauskas; Khanna; Rhodes *Tetrahedron Lett.* **1987**, 28, 2331.

¹⁰⁵¹For examples, see Ko; Leffek *Can. J. Chem.* **1970**, 48, 1865, **1971**, 49, 129; Deady; Korytsky *Tetrahedron Lett.* **1979**, 451.

The *von Braun reaction*, which involves the cleavage of tertiary amines by cyanogen bromide to give an alkyl bromide and a disubstituted cyanamide, has been applied to many tertiary amines.¹⁰⁵² Usually, the R group that cleaves is the one that gives the most reactive halide (for example, benzyl or allyl). For simple alkyl groups, the smallest are the most readily cleaved. One or two of the groups on the amine may be aryl, but they do not cleave. Cyclic amines have been frequently cleaved by this reaction. Secondary amines also give the reaction, but the results are usually poor.¹⁰⁵³

The mechanism consists of two successive nucleophilic substitutions, with the tertiary amine as the first nucleophile and the liberated bromide ion as the second:



The intermediate N-cyanoammonium bromide has been trapped, and its structure confirmed by chemical, analytical, and spectral data.¹⁰⁵⁴ The BrCN in this reaction has been called a *counterattack reagent*; that is, a reagent that accomplishes, in one flask, two transformations designed to give the product.¹⁰⁵⁵

OS III, 608.

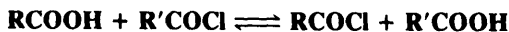
B. Attack at an Acyl Carbon

0-74 Formation of Acyl Halides from Carboxylic Acids

Halo-de-hydroxylation



The same inorganic acid halides that convert alcohols to alkyl halides (0-67) also convert carboxylic acids to acyl halides.¹⁰⁵⁶ The reaction is the best and the most common method for the preparation of acyl chlorides. Bromides and iodides¹⁰⁵⁷ are also made in this manner, but much less often. Thionyl chloride⁹⁸³ is the best reagent, since the by-products are gases and the acyl halide is easily isolated, but PX_3 and PX_5 ($\text{X} = \text{Cl}$ or Br) are also commonly used.¹⁰⁵⁸ Hydrogen halides do not give the reaction. A particularly mild procedure, similar to one mentioned in 0-67, involves reaction of the acid with Ph_3P in CCl_4 , whereupon acyl chlorides are produced without obtaining any acidic compound as a by-product.¹⁰⁵⁹ Acyl fluorides can be prepared by treatment of carboxylic acids with cyanuric fluoride.¹⁰⁶⁰ Acid salts are also sometimes used as substrates. Acyl halides are also used as reagents in an exchange reaction:



¹⁰⁵²For a review, see Cooley; Evain, Ref. 1049.

¹⁰⁵³For a detailed discussion of the scope of the reaction and of the ease of cleavage of different groups, see Hageman *Org. React.* **1953**, pp. 205-225.

¹⁰⁵⁴Fodor; Abidi *Tetrahedron Lett.* **1971**, 1369; Fodor; Abidi; Carpenter *J. Org. Chem.* **1974**, 39, 1507. See also Paukstelis; Kim *J. Org. Chem.* **1974**, 39, 1494.

¹⁰⁵⁵For a review of counterattack reagents, see Hwu; Gilbert *Tetrahedron* **1989**, 45, 1233-1261.

¹⁰⁵⁶For a review, see Ansell, in Patai, Ref. 502, pp. 35-68.

¹⁰⁵⁷Carboxylic acids and some of their derivatives react with diiodosilane SiH_2I_2 to give good yields of acyl iodides: Keinan; Sahai *J. Org. Chem.* **1990**, 55, 3922.

¹⁰⁵⁸For a list of reagents, with references, see Ref. 508, pp. 963-964.

¹⁰⁵⁹Lee *J. Am. Chem. Soc.* **1966**, 88, 3440. For other methods of preparing acyl chlorides, see Venkataraman; Wagle *Tetrahedron Lett.* **1979**, 3037; Devos; Remion; Frisque-Hesbain; Colens; Ghosez *J. Chem. Soc., Chem. Commun.* **1979**, 1180.

¹⁰⁶⁰Olah; Nojima; Kerekes *Synthesis* **1973**, 487. For other methods of preparing acyl fluorides, see Mukaiyama; Tanaka *Chem. Lett.* **1976**, 303; Ishikawa; Sasaki *Chem. Lett.* **1976**, 1407.

which probably involves an anhydride intermediate. This is an equilibrium reaction that must be driven to the desired side. Oxalyl chloride and bromide are frequently used as the acyl halide reagent, since oxalic acid decomposes to CO and CO₂, and the equilibrium is thus driven to the side of the other acyl halide.

OS I, 12, 147, 394; II, 74, 156, 169, 569; III, 169, 490, 547, 555, 613, 623, 712, 714; IV, 34, 88, 154, 263, 339, 348, 554, 608, 616, 620, 715, 739, 900; V, 171, 258, 887; VI, 95, 190, 549, 715; VII, 467; 66, 87, 116, 121.

0-75 Formation of Acyl Halides from Acid Derivatives

Halo-de-acyloxy-substitution

Halo-de-halogenation



These reactions are most important for the preparation of acyl fluorides.¹⁰⁶¹ Acyl chlorides and anhydrides can be converted to acyl fluorides by treatment with polyhydrogen fluoride–pyridine solution⁹⁹⁶ or with liquid HF at –10°C.¹⁰⁶² Formyl fluoride, which is a stable compound, was prepared by the latter procedure from the mixed anhydride of formic and acetic acids.¹⁰⁶³ Acyl fluorides can also be obtained by reaction of acyl chlorides with KF in acetic acid¹⁰⁶⁴ or with diethylaminosulfur trifluoride (DAST).¹⁰⁶⁵ Carboxylic esters and anhydrides can be converted to acyl halides other than fluorides by the inorganic acid halides mentioned in 074, as well as with Ph₃PX₂ (X = Cl or Br),¹⁰⁶⁶ but this is seldom done. Halide exchange can be carried out in a similar manner. When halide exchange is done, it is always acyl bromides and iodides that are made from chlorides, since chlorides are by far the most readily available.¹⁰⁶⁷

OS II, 528; III, 422; V, 66, 1103. See also OS IV, 307.

Hydrogen as Nucleophile

The reactions in this section (0-76 to 0-85) are reductions and could have been considered in Chapter 19. They are treated here because they involve replacement of a leaving group by hydrogen, which frequently attacks as the nucleophile hydride ion. However, not all the reactions in this section are true nucleophilic substitutions and for some of them more than one kind of mechanism may be involved, depending on the reagents and on the conditions. When cleavage of a carbon-hetero atom bond is accomplished by catalytic hydrogenation, the reaction is called *hydrogenolysis*.

A. Attack at an Alkyl Carbon

0-76 Reduction of Alkyl Halides

Hydro-de-halogenation or Dehalogenation



¹⁰⁶¹For lists of reagents converting acid derivatives to acyl halides, see Ref. 508, pp. 977, 980, 985.

¹⁰⁶²Olah; Kuhn *J. Org. Chem.* **1961**, 26, 237.

¹⁰⁶³Olah; Kuhn *J. Am. Chem. Soc.* **1960**, 82, 2380.

¹⁰⁶⁴Emsley; Gold; Hibbert; Szeto *J. Chem. Soc., Perkin Trans. 2* **1968**, 923.

¹⁰⁶⁵Markovski; Pashinnik *Synthesis* **1975**, 801.

¹⁰⁶⁶Burton; Koppes *J. Chem. Soc., Chem. Commun.* **1973**, 425, *J. Org. Chem.* **1975**, 40, 3026; Anderson; Kono *Tetrahedron Lett.* **1973**, 5121.

¹⁰⁶⁷For methods of converting acyl chlorides to bromides or iodides, see Schmidt; Russ; Grosse *Synthesis* **1981**, 216; Hoffmann; Haase *Synthesis* **1981**, 715.

This type of reduction can be accomplished with many reducing agents,¹⁰⁶⁸ the most common being lithium aluminum hydride.¹⁰⁶⁹ This reagent reduces almost all types of alkyl halide, including vinylic, bridgehead, and cyclopropyl halides.¹⁰⁷⁰ Reduction with lithium aluminum deuteride serves to introduce deuterium into organic compounds. An even more powerful reducing agent, reportedly the strongest S_N2 nucleophile known, is lithium triethylborohydride LiEt₃BH. This reagent rapidly reduces primary, secondary, allylic, benzylic, and neopentyl halides, but not tertiary (these give elimination) or aryl halides.¹⁰⁷¹ Another powerful reagent, which reduces primary, secondary, tertiary, allylic, vinylic, aryl, and neopentyl halides, is a complex formed from lithium trimethoxyaluminum hydride LiAlH(OMe)₃ and CuI.¹⁰⁷² A milder reducing agent is NaBH₄ in a dipolar aprotic solvent such as Me₂SO, DMF, or sulfolane,¹⁰⁷³ which at room temperature or above reduces primary, secondary, and some tertiary¹⁰⁷⁴ halides in good yield without affecting other functional groups that would be reduced by LiAlH₄, for example, COOH, COOR, CN.¹⁰⁷⁵ Other reducing agents¹⁰⁷⁶ are zinc (with acid or base), SnCl₂, chromium(II) ion,¹⁰⁷⁷ either in the form of simple chromous salts (for active substrates or *gem*-dihalides¹⁰⁷⁸) or complexed with ethylenediamine or ethanolamine (for ordinary alkyl halides¹⁰⁷⁹), tris(trimethylsilyl)silane (Me₃Si)₃SiH–NaBH₄,¹⁰⁸⁰ SmI₂–THF–HMPA,¹⁰⁸¹ and Et₃SiH in the presence of AlCl₃.¹⁰⁸² The last two methods are good for primary, secondary, and tertiary halides. Sodium arsenite and base, diethyl phosphonate–Et₃N,¹⁰⁸³ phosphorus tris(dimethylamide) (Me₂N)₃P,¹⁰⁸⁴ a metal carbonyl such as Fe(CO)₅ and a hydrogen donor,¹⁰⁸⁵ or organotin hydrides R_nSnH_{4–n}¹⁰⁸⁶ (chiefly Bu₃SnH).¹⁰⁸⁷ can be used to reduce just one halogen of a *gem*-dihalide or a 1,1,1-trihalide.¹⁰⁸⁸ The organotin hydride (MeOCH₂CH₂OCH₂CH₂CH₂)₃SnH reduces

¹⁰⁶⁸For reviews, see Hudlický *Reductions in Organic Chemistry*; Ellis Horwood: Chichester, 1984, pp. 62-67, 181; Pinder *Synthesis* **1980**, 425-452. For a list of reagents, see Ref. 508, pp. 18-24.

¹⁰⁶⁹For a review of LiAlH₄, see Pizey, Ref. 593, vol. 1, 1974, pp. 101-294. For monographs on complex metal hydrides, see Seyden-Penne *Reductions by the Almino- and Borohydrides*; VCH: New York, 1991; Hajós *Complex Hydrides*; Elsevier: New York, 1979.

¹⁰⁷⁰Jefford; Kirkpatrick; Delay *J. Am. Chem. Soc.* **1972**, *94*, 8905; Krishnamurthy; Brown *J. Org. Chem.* **1982**, *47*, 276.

¹⁰⁷¹Brown; Kim; Krishnamurthy *J. Org. Chem.* **1980**, *45*, 1; Krishnamurthy; Brown *J. Org. Chem.* **1980**, *45*, 849, **1983**, *48*, 3085.

¹⁰⁷²Masamune; Rossy; Bates *J. Am. Chem. Soc.* **1973**, *95*, 6452; Masamune; Bates; Georgiou *J. Am. Chem. Soc.* **1974**, *96*, 3686.

¹⁰⁷³Bell; Vanderslice; Spehar *J. Org. Chem.* **1969**, *34*, 3923; Hutchins; Hoke; Keogh; Koharski *Tetrahedron Lett.* **1969**, 3495; Vol'pin; Dvolaitzky; Levitin *Bull. Soc. Chim. Fr.* **1970**, 1526; Hutchins; Kandasamy; Dux; Maryanoff; Rotstein; Goldsmith; Burgoyne; Cistone; Dalessandro; Puglis *J. Org. Chem.* **1978**, *43*, 2259.

¹⁰⁷⁴Hutchins; Bertsch; Hoke *J. Org. Chem.* **1971**, *36*, 1568.

¹⁰⁷⁵For the use of NaBH₄ under phase transfer conditions, see Bergbreiter; Blanton *J. Org. Chem.* **1987**, *52*, 472.

¹⁰⁷⁶For some other reducing agents, not mentioned here, see Akiba; Shimizu; Ohnari; and Ohkata *Tetrahedron Lett.* **1985**, *26*, 3211; Kim; Yi *Bull. Chem. Soc. Jpn.* **1985**, *58*, 789; Cole; Kirwan; Roberts; Willis *J. Chem. Soc., Perkin Trans. 1* **1991**, 103; and Ref. 1068.

¹⁰⁷⁷For reviews, see Hanson *Synthesis* **1974**, 1-8, pp. 2-5; Hanson; Premuzic *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 247-252 [*Angew. Chem.* **80**, 271-276]. For a review of the mechanisms of reduction of alkyl halides by metal complexes, see Kochi *Organometallic Mechanisms and Catalysis*; Academic Press: New York, 1978, pp. 138-177.

¹⁰⁷⁸Castro; Kray *J. Am. Chem. Soc.* **1966**, *88*, 4447.

¹⁰⁷⁹Kochi; Mocadlo *J. Am. Chem. Soc.* **1966**, *88*, 4094; Kochi; Powers *J. Am. Chem. Soc.* **1970**, *92*, 137.

¹⁰⁸⁰Lesage; Chatgililoglu; Griller *Tetrahedron Lett.* **1989**, *30*, 2733. See also Ballestri; Chatgililoglu; Clark; Griller; Giese; Kopping *J. Org. Chem.* **1991**, *56*, 678.

¹⁰⁸¹Inanaga; Ishikawa; Yamaguchi *Chem. Lett.* **1987**, 1485. See also Molander; Hahn *J. Org. Chem.* **1986**, *51*, 1135. For reviews of SmI₂, see Soderquist *Aldrichimica Acta* **1991**, *24*, 15-23; Kagan *New J. Chem.* **1990**, *14*, 453-460.

¹⁰⁸²Doyle; McOsker; West *J. Org. Chem.* **1976**, *41*, 1393; Parnes; Romanova; Vol'pin *J. Org. Chem. USSR* **1988**, *24*, 254.

¹⁰⁸³Hirao; Kohno; Ohshiro; Agawa *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1881.

¹⁰⁸⁴Downie; Lee *Tetrahedron Lett.* **1968**, 4951.

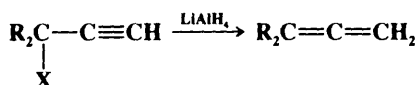
¹⁰⁸⁵For reviews, see Freidlina; Gasanov; Kuz'mina; Chukovskaya *Russ. Chem. Rev.* **1985**, *54*, 662-675; Chukovskaya; Freidlina; Kuz'mina *Synthesis* **1983**, 773-784.

¹⁰⁸⁶Seyferth; Yamazaki; Alleston *J. Org. Chem.* **1963**, *28*, 703.

¹⁰⁸⁷For reviews of organotin hydrides, see Neumann *Synthesis* **1987**, 665-683; Kuivila *Synthesis* **1970**, 499-509. *Acc. Chem. Res.* **1968**, *1*, 299-305.

¹⁰⁸⁸See, for example Chukovskaya; Freidlina; Kuz'mina, Ref. 1085.

alkyl halides and is water soluble, unlike Bu_3SnH .¹⁰⁸⁹ Reduction, especially of bromides and iodides, can also be effected by catalytic hydrogenation,¹⁰⁹⁰ and electrochemically.¹⁰⁹¹ A good reducing agent for the removal of all halogen atoms in a polyhalo compound (including vinylic, allylic, geminal, and even bridgehead halogens) is lithium¹⁰⁹² or sodium¹⁰⁹³ and *t*-BuOH in THF. Propargylic halides can often be reduced with allylic rearrangement to give allenes.¹⁰⁹⁴



The choice of a reducing agent usually depends on what other functional groups are present. Each reducing agent reduces certain groups and not others. This type of selectivity is called *chemoselectivity*. A chemoselective reagent is one that reacts with one functional group (e.g., halide) but not another (e.g., $\text{C}=\text{O}$). For example, there are several reagents that reduce only the halogen of α -halo ketones, leaving the carbonyl group intact.¹⁰⁹⁵ Among them are *i*- Pr_2NLi ,¹⁰⁹⁶ CH_3SNa ,¹⁰⁹⁷ aqueous TiCl_3 ,¹⁰⁹⁸ NaI in aqueous acid-THF,¹⁰⁹⁹ PI_3 or P_2I_4 ,¹¹⁰⁰ nickel boride,¹¹⁰¹ sodium formaldehyde sulfoxylate,¹¹⁰² *i*- $\text{Bu}_2\text{AlH-SnCl}_2$,¹¹⁰³ NaHS-SnCl_2 ,¹¹⁰⁴ $\text{AlCl}_3\text{-EtSH}$,¹¹⁰⁵ $\text{MeSiCl}_3\text{-NaI}$,⁵¹⁵ and sodium hydrosulfite $\text{Na}_2\text{S}_2\text{O}_4$.¹¹⁰⁶ Both $\text{NaBH}_3\text{CN-SnCl}_2$ ¹¹⁰⁷ and the *n*-butyllithium ate complex (p. 260) of *B-n*-butyl-9-BBN¹¹⁰⁸ (see p. 785) reduce tertiary alkyl, benzylic, and allylic halides, but do not react with primary or secondary alkyl or aryl halides. Another highly selective reagent, in this case for primary and secondary iodo and bromo groups, is sodium cyanoborohydride NaBH_3CN in HMPA.¹¹⁰⁹ Most of the reducing agents mentioned reduce chlorides, bromides, and iodides, but organotin hydrides also reduce fluorides.¹¹¹⁰ See page 1206 for a discussion of selectivity in reduction reactions.

¹⁰⁸⁹Light; Breslow *Tetrahedron Lett.* **1990**, 31, 2957.

¹⁰⁹⁰For a discussion, see Rylander *Hydrogenation Methods*; Academic Press: New York, 1985.

¹⁰⁹¹For reviews, see Fry *Synthetic Organic Electrochemistry*, 2nd ed.; Wiley: New York, 1989, pp. 136-151; Feoktistov, in Baizer; Lund *Organic Electrochemistry*; Marcel Dekker: New York, 1983, pp. 259-284.

¹⁰⁹²For example, see Bruck; Thompson; Winstein *Chem. Ind. (London)* **1960**, 405; Gassman; Pape *J. Org. Chem.* **1964**, 29, 160; Fieser; Sachs *J. Org. Chem.* **1964**, 29, 1113; Nazer *J. Org. Chem.* **1965**, 30, 1737; Berkowitz *Synthesis* **1990**, 649.

¹⁰⁹³For example, see Gassman; Aue; Patton *J. Am. Chem. Soc.* **1968**, 90, 7271; Gassman; Marshall *Org. Synth.* **V**, 424.

¹⁰⁹⁴For examples, see Crandall; Keyton; Kohn *J. Org. Chem.* **1968**, 33, 3655; Claesson; Olsson *J. Am. Chem. Soc.*, **1979**, 101, 7302.

¹⁰⁹⁵For a review of reductive dehalogenation of polyhalo ketones, see Noyori; Hayakawa *Org. React.* **1983**, 29, 163-344.

¹⁰⁹⁶Dubois; Lion; Dugast *Tetrahedron Lett.* **1983**, 24, 4207.

¹⁰⁹⁷Ōki; Funakoshi; Nakamura *Bull. Chem. Soc. Jpn.* **1971**, 44, 828. See also Inoue; Hata; Imoto *Chem. Lett.* **1975**, 1241.

¹⁰⁹⁸Ho; Wong *Synth. Commun.* **1973**, 3, 237; McMurry *Acc. Chem. Res.* **1974**, 7, 281-286, pp. 284-285; Pradhan; Patil *Tetrahedron Lett.* **1989**, 30, 2999. See also Clerici; Porta *Tetrahedron Lett.* **1987**, 28, 1541.

¹⁰⁹⁹Gemal; Luche *Tetrahedron Lett.* **1980**, 21, 3195. See also Olah; Arvanaghi; Vankar *J. Org. Chem.* **1980**, 45, 3531; Ho *Synth. Commun.* **1981**, 11, 101; Ono; Kamimura; Suzuki *Synthesis* **1987**, 406.

¹¹⁰⁰Denis; Krief *Tetrahedron Lett.* **1981**, 22, 1431.

¹¹⁰¹Sarma; Borbaruah; Sharma *Tetrahedron Lett.* **1985**, 26, 4657.

¹¹⁰²Harris *Synth. Commun.* **1987**, 17, 1587.

¹¹⁰³Oriyama; Mukaiyama *Chem. Lett.* **1984**, 2069.

¹¹⁰⁴Ono; Maruyama; Kamimura *Synthesis* **1987**, 1093.

¹¹⁰⁵Fuji; Node; Kawabata; Fujimoto *J. Chem. Soc., Perkin Trans. 1* **1987**, 1043.

¹¹⁰⁶Chung; Hu *Synth. Commun.* **1982**, 12, 261.

¹¹⁰⁷Kim; Ko *Synth. Commun.* **1985**, 15, 603.

¹¹⁰⁸Toi; Yamamoto; Sonoda; Murahashi *Tetrahedron* **1981**, 37, 2261.

¹¹⁰⁹Hutchins; Kandasamy; Maryanoff; Masilamani; Maryanoff *J. Org. Chem.* **1977**, 42, 82.

¹¹¹⁰Fluorides can also be reduced by a solution of K and dicyclohexano-18-crown-6 in toluene or diglyme: Ohsawa; Takagaki; Haneda; Oishi *Tetrahedron Lett.* **1981**, 22, 2583. See also Brandänge; Dahlman; Olund *Acta Chem. Scand., Ser. B* **1983**, 37, 141.

With lithium aluminum hydride and most other metallic hydrides, the mechanism usually consists of simple nucleophilic substitution with attack by hydride ion that may or may not be completely free. The mechanism is S_N2 rather than S_N1 , since primary halides react better than secondary or tertiary (tertiary generally give alkenes or do not react at all) and since Walden inversion has been demonstrated. However, rearrangements found in the reduction of bicyclic tosylates with $LiAlH_4$ indicate that the S_N1 mechanism can take place.¹¹¹¹ There is evidence that $LiAlH_4$ and other metal hydrides can also reduce halides by an SET mechanism,¹¹¹² especially those, such as vinylic,¹¹¹³ cyclopropyl,¹¹¹⁴ or bridgehead halides, that are resistant to nucleophilic substitution. Reduction of halides by $NaBH_4$ in 80% aqueous diglyme¹¹¹⁵ and by BH_3 in nitromethane¹¹¹⁶ takes place by an S_N1 mechanism. $NaBH_4$ in sulfolane reduces tertiary halides possessing a β hydrogen by an elimination-addition mechanism.¹¹¹⁷

With other reducing agents the mechanism is not always nucleophilic substitution. For example, reductions with organotin hydrides generally¹¹¹⁸ take place by free-radical mechanisms,¹¹¹⁹ as do those with $Fe(CO)_5$ ¹¹²⁰ and $(Me_3Si)_3SiH-NaBH_4$.¹⁰⁸⁰ Alkyl halides, including fluorides and polyhalides, can be reduced with magnesium and a secondary or tertiary alcohol (most often 2-propanol).¹¹²¹ This is actually an example of the occurrence in one step of the sequence:



More often the process is carried out in two separate steps (2-38 and 2-23).

OS I, 357, 358, 548; II, 320, 393; V, 424; VI, 142, 376, 731; 68, 32. See also OS 69, 66.

0-77 Reduction of Tosylates and Similar Compounds

Hydro-de-sulfonyloxy-substitution



Tosylates and other sulfonates can be reduced¹¹²² with $LiAlH_4$,¹¹²³ with $NaBH_4$ in a dipolar aprotic solvent,¹¹²⁴ with $LiEt_3BH$, with $i-Bu_2AlH$ (DIBALH),¹¹²⁵ or with $Bu_3SnH-NaI$.¹¹²⁶ The scope of the reaction seems to be similar to that of 0-76. When the reagent is $LiAlH_4$, alkyl tosylates are reduced more rapidly than iodides or bromides if the solvent is Et_2O ,

¹¹¹¹ Appleton; Fairlie; McCrindle *Chem. Commun.* **1967**, 690; Kraus; Chassin *Tetrahedron Lett.* **1970**, 1443.

¹¹¹² Ashby; DePriest; Goel *Tetrahedron Lett.* **1981**, 22, 1763, 3729; Singh; Khurana; Nigam *Tetrahedron Lett.* **1981**, 22, 2901; Srivastava; le Noble *Tetrahedron Lett.* **1984**, 25, 4871; Ashby; Pham *J. Org. Chem.* **1986**, 51, 3598; Hatem; Meslem; Waegell *Tetrahedron Lett.* **1986**, 27, 3723; Ashby; Pham; Amrollah-Majdjabadi *J. Org. Chem.* **1991**, 56, 1596. See however Hirabe; Takagi; Muraoka; Nojima; Kusabayashi *J. Org. Chem.* **1985**, 50, 1797; Park; Chung; Newcomb *J. Org. Chem.* **1987**, 52, 3275.

¹¹¹³ Chung *J. Org. Chem.* **1980**, 45, 3513.

¹¹¹⁴ McKinney; Anderson; Keyes; Schmidt *Tetrahedron Lett.* **1982**, 23, 3443; Hatem; Waegell *Tetrahedron* **1990**, 46, 2789.

¹¹¹⁵ Bell; Brown *J. Am. Chem. Soc.* **1966**, 88, 1473.

¹¹¹⁶ Matsumura; Tokura *Tetrahedron Lett.* **1969**, 363.

¹¹¹⁷ Jacobus *Chem. Commun.* **1970**, 338; Ref. 1074.

¹¹¹⁸ For an exception, see Carey; Tramper *Tetrahedron Lett.* **1969**, 1645.

¹¹¹⁹ Kuivila; Menapace *J. Org. Chem.* **1963**, 28, 2165; Menapace; Kuivila *J. Am. Chem. Soc.* **1964**, 86, 3047; Tanner; Singh *J. Org. Chem.* **1986**, 51, 5182.

¹¹²⁰ Nelson; Detre; Tanabe *Tetrahedron Lett.* **1973**, 447; Freidlina et al., Ref. 1085.

¹¹²¹ Bryce-Smith; Wakefield; Blues *Proc. Chem. Soc.* **1963**, 219.

¹¹²² For a list of substrate types and reagents, with references, see Ref. 508, pp. 28-31.

¹¹²³ For examples, see Rapoport; Bonner *J. Am. Chem. Soc.* **1951**, 73, 2872; Eschenmoser; Frey *Helv. Chim. Acta* **1952**, 35, 1660; Dimitriadis; Massy-Westropp *Aust. J. Chem.* **1982**, 35, 1895.

¹¹²⁴ Hutchins; Hoke; Keogh; Koharski, Ref. 1073.

¹¹²⁵ Janssen; Hendriks; Godefroi *Recl. Trav. Chim. Pays-Bas* **1984**, 103, 220.

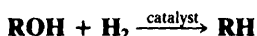
¹¹²⁶ Ueno; Tanaka; Okawara *Chem. Lett.* **1983**, 795.

but the order is reversed in diglyme.¹¹²⁷ The reactivity difference is great enough so that a tosylate function can be reduced in the presence of a halide and vice versa.

OS VI, 376, 762; 68, 138. See also OS VII, 66.

0-78 Hydrogenolysis of Alcohols¹¹²⁸

Hydro-de-hydroxylation or Dehydroxylation



The hydroxyl groups of most alcohols can seldom be cleaved by catalytic hydrogenation and alcohols are often used as solvents for hydrogenation of other compounds. However, benzyl-type alcohols undergo the reaction readily and have often been reduced.¹¹²⁹ Diaryl and triarylcarbinols are similarly easy to reduce and this has been accomplished with LiAlH_4 - AlCl_3 ,¹¹³⁰ with NaBH_4 in F_3CCOOH ,¹¹³¹ and with iodine, water, and red phosphorus (OS I, 224). Other reagents have been used,¹¹³² among them $\text{Fe}(\text{CO})_5$,¹¹³³ Me_3SiCl - MeI - MeCN ,¹¹³⁴ Et_3SiH - BF_3 ,¹¹³⁵ SmI_2 -THF-HMPA,¹¹³⁶ NaBH_4 - F_3CCOOH ,¹¹³⁷ P_2I_4 ,¹¹³⁸ Me_2SiI_2 ,¹¹³⁹ and tin and HCl . 1,3-Diols are especially susceptible to hydrogenolysis. Tertiary alcohols can be reduced by catalytic hydrogenolysis when the catalyst is Raney nickel.¹¹⁴⁰ Allylic alcohols (and ethers and acetates) can be reduced (often with accompanying allylic rearrangement) with Zn amalgam and HCl , as well as with certain other reagents.¹¹⁴¹ α -Acetylenic alcohols are converted to alkynes by reduction of their cobalt carbonyl complexes with NaBH_4 and CF_3COOH .¹¹⁴² Reagents that reduce the OH group of α -hydroxy ketones without affecting the $\text{C}=\text{O}$ group include lithium diphenylphosphide Ph_2PLi ,¹¹⁴³ red phosphorus-iodine,¹¹⁴⁴ and Me_3SiI .¹¹⁴⁵

Alcohols can also be reduced indirectly by conversion to a sulfonate and reduction of that compound (0-77). The two reactions can be carried out without isolation of the sulfonate if the alcohol is treated with pyridine- SO_3 in THF, and LiAlH_4 then added.¹¹⁴⁶ Another indirect reduction that can be done in one step involves treatment of the alcohol (primary, secondary, or benzylic) with NaI , Zn, and Me_3SiCl .¹¹⁴⁷ In this case the alcohol is first converted to the iodide, which is reduced. For other indirect reductions of OH, see 0-81.

¹¹²⁷Krishnamurthy J. *Org. Chem.* **1980**, 45, 2550.

¹¹²⁸For a review, see Müller, in Patai *The Chemistry of Functional Groups, Supplement E*, pt. 1; Wiley: New York, 1980, pp. 515-522.

¹¹²⁹For reviews, see Rylander, Ref. 1090, pp. 157-163, *Catalytic Hydrogenation over Platinum Metals*; Academic Press: New York, 1967, pp. 449-468. For a review of the stereochemistry of hydrogenolysis, see Klabunovskii *Russ. Chem. Rev.* **1966**, 35, 546-558.

¹¹³⁰Blackwell; Hickinbottom J. *Chem. Soc.* **1961**, 1405; Avendaño; de Diego; Elguero *Monatsh. Chem.* **1990**, 121, 649.

¹¹³¹For a review, see Gribble; Nutaitis *Org. Prep. Proced. Int.* **1985**, 17, 317-384.

¹¹³²For a list of reagents, with references, see Ref. 508, pp. 27-28.

¹¹³³Alper; Sališová *Tetrahedron Lett.* **1980**, 21, 801.

¹¹³⁴Sakai; Miyata; Utaka; Takeda *Tetrahedron Lett.* **1987**, 28, 3817.

¹¹³⁵Orfanopoulos; Smonou *Synth. Commun.* **1988**, 18, 833; Smonou; Orfanopoulos *Tetrahedron Lett.* **1988**, 29, 5793.

¹¹³⁶Kusuda; Inanaga; Yamaguchi *Tetrahedron Lett.* **1989**, 30, 2945.

¹¹³⁷Nutaitis; Bernardo *Synth. Commun.* **1990**, 20, 487.

¹¹³⁸Suzuki; Tani; Kubota; Sato; Tsuji; Osuka *Chem. Lett.* **1983**, 247.

¹¹³⁹Ando; Ikeno *Tetrahedron Lett.* **1979**, 4941; Wiggins *Synth. Commun.* **1988**, 18, 741.

¹¹⁴⁰Kraft; Crooks J. *Org. Chem.* **1988**, 53, 432. For another catalyst, see Parnes; Shaapuni; Kalinkin; Kursanov *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1974**, 23, 1592.

¹¹⁴¹For discussion, see Elphimoff-Felkin; Sarda *Org. Synth.* VI, 769; *Tetrahedron* **1977**, 33, 511. For another reagent, see Lee; Alper *Tetrahedron Lett.* **1990**, 31, 4101.

¹¹⁴²Nicholas; Siegel J. *Am. Chem. Soc.* **1985**, 107, 4999.

¹¹⁴³Leone-Bay J. *Org. Chem.* **1986**, 51, 2378.

¹¹⁴⁴Ho; Wong *Synthesis* **1975**, 161.

¹¹⁴⁵Ho *Synth. Commun.* **1979**, 9, 665.

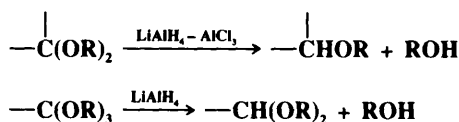
¹¹⁴⁶Corey; Achiwa J. *Org. Chem.* **1969**, 34, 3667.

¹¹⁴⁷Morita; Okamoto; Sakurai *Synthesis* **1981**, 32.

The mechanisms of most alcohol reductions are obscure.¹¹⁴⁸ Hydrogenolysis of benzyl alcohols can give inversion or retention of configuration, depending on the catalyst.¹¹⁴⁹

OS I, 224; IV, 25, 218, 482; V, 339; VI, 769.

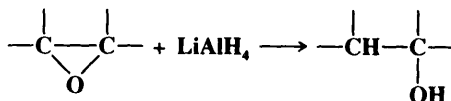
0-79 Replacement of Alkoxy by Hydrogen Hydro-de-alkoxylation or Dealkoxylation



Simple ethers are not normally cleaved by reducing agents, although such cleavage has sometimes been reported (for example, tetrahydrofuran treated with $\text{LiAlH}_4\text{--AlCl}_3$ ¹¹⁵⁰ or with a mixture of $\text{LiAlH}(\text{O-}t\text{-Bu})_3$ and Et_3B ¹¹⁵¹ gave 1-butanol; the latter reagent also cleaves methyl alkyl ethers).¹¹⁵² Certain types of ethers can be cleaved quite well by reducing agents.¹¹⁵³ Among these are allyl aryl,¹¹⁵⁴ vinyl aryl,¹¹⁵⁵ and benzylic ethers¹¹²⁹ (for epoxides, see 0-80). Acetals and ketals are resistant to LiAlH_4 and similar hydrides, and carbonyl groups are often converted to acetals or ketals for protection. However, a combination of LiAlH_4 and AlCl_3 ¹¹⁵⁶ does reduce acetals and ketals, removing one group, as shown above.¹¹⁵⁷ The actual reducing agents in this case are primarily chloroaluminum hydride AlH_2Cl and dichloroaluminum hydride AlHCl_2 , which are formed from the reagents.¹¹⁵⁸ This conversion can also be accomplished with DIBALH,¹¹⁵⁹ with Nafion-H,¹¹⁶⁰ with monochloroborane-etherate $\text{BH}_2\text{Cl--Et}_2\text{O}$,¹¹⁶¹ as well as with other reagents.¹¹⁶² Ortho esters are easily reduced to acetals by LiAlH_4 alone, offering a route to aldehydes, which are easily prepared by hydrolysis of the acetals (0-6).

OS III, 693; IV, 798; V, 303. Also see OS III, 742; VII, 386.

0-80 Reduction of Epoxides (3)OC-seco-Hydro-de-alkoxylation



¹¹⁴⁸For discussions of the mechanisms of the hydrogenolysis of benzyl alcohols, see Khan; McQuillin; Jardine *Tetrahedron Lett.* **1966**, 2649; *J. Chem. Soc. C* **1967**, 136; Garbisch; Schreuder; Frankel *J. Am. Chem. Soc.* **1967**, 89, 4233; Mitsui; Imaizumi; Esashi *Bull. Chem. Soc. Jpn.* **1970**, 43, 2143.

¹¹⁴⁹Mitsui; Kudo; Kobayashi *Tetrahedron* **1969**, 25, 1921; Mitsui; Imaizumi; Esashi, Ref. 1148.

¹¹⁵⁰Bailey; Marktscheffel *J. Org. Chem.* **1960**, 25, 1797.

¹¹⁵¹Krishnamurthy; Brown *J. Org. Chem.* **1979**, 44, 3678.

¹¹⁵²For a review of ether reduction, see Müller, Ref. 1128, pp. 522-528.

¹¹⁵³For a list of reagents, with references, see Ref. 508, pp. 501-504.

¹¹⁵⁴Tweedie; Cuscurida *J. Am. Chem. Soc.* **1957**, 79, 5463.

¹¹⁵⁵Tweedie; Barron *J. Org. Chem.* **1960**, 25, 2023. See also Hutchins; Learn *J. Org. Chem.* **1982**, 47, 4380.

¹¹⁵⁶For a review of reductions by metal hydride-Lewis acid combinations, see Rerick, in Augustinc *Reduction*; Marcel Dekker: New York, 1968, pp. 1-94.

¹¹⁵⁷Eliel; Badding; Rerick *J. Am. Chem. Soc.* **1962**, 84, 2371.

¹¹⁵⁸Ashby; Prather *J. Am. Chem. Soc.* **1966**, 88, 729; Diner; Davis; Brown *Can. J. Chem.* **1967**, 45, 207.

¹¹⁵⁹See, for example, Zakharkin; Khorlina *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1959**, 2156; Takano; Akiyama; Sato; Ogasawara *Chem. Lett.* **1983**, 1593.

¹¹⁶⁰Olah; Yamato; Iyer; Prakash *J. Org. Chem.* **1986**, 51, 2826.

¹¹⁶¹Borders; Bryson *Chem. Lett.* **1984**, 9.

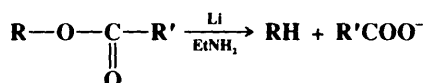
¹¹⁶²For lists of other reagents that accomplish this conversion, with references, see Tsunoda; Suzuki; Noyori *Tetrahedron Lett.* **1979**, 4679; Kotsuki; Ushio; Yoshimura; Ochi *J. Org. Chem.* **1987**, 52, 2594; Ref. 508, pp. 463-465.

Reduction of epoxides is a special case of 0-79 and is easily carried out.¹¹⁶³ The most common reagent is LiAlH_4 , which reacts by the $\text{S}_\text{N}2$ mechanism, giving inversion of configuration. An epoxide on a substituted cyclohexane ring cleaves in such a direction as to give an axial alcohol. As expected for an $\text{S}_\text{N}2$ mechanism, cleavage usually occurs so that a tertiary alcohol is formed if possible. If not, a secondary alcohol is preferred. However, for certain substrates, the epoxide ring can be opened the other way by reduction with $\text{NaBH}_3\text{CN}-\text{BF}_3$,¹¹⁶⁴ with $\text{Me}_3\text{SiCl}-\text{Zn}$,¹¹⁶⁵ with dicyclopentadienyltitanium chloride and 1,4-cyclohexadiene,¹¹⁶⁶ or with BH_3 in tetrahydrofuran.¹¹⁶⁷ The reaction has also been carried out with other reagents, for example, sodium amalgam in EtOH, Li in ethylenediamine,¹¹⁶⁸ $\text{Bu}_3\text{SnH}-\text{NaI}$,¹¹⁶⁹ and by catalytic hydrogenolysis.¹¹⁷⁰ Chemoselective and regioselective ring opening (e.g., of allylic epoxides and of epoxy ketones and esters) has been achieved with NaHTe ,¹¹⁷¹ SmI_2 ,¹¹⁷² sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al),¹¹⁷³ and H_2 and a Pd-phosphine catalyst.¹¹⁷⁴ Highly hindered epoxides can be conveniently reduced, without rearrangement, with lithium triethylborohydride.¹¹⁷⁵

Epoxides can be reductively halogenated (the product is the alkyl bromide or iodide rather than the alcohol) with $\text{Me}_3\text{SiCl}-\text{NaX}-(\text{Me}_2\text{SiH})_2\text{O}$ (1,1,3,3-tetramethyldisiloxane).¹¹⁷⁶

See 9-46 for another type of epoxide reduction.

0-81 Reductive Cleavage of Carboxylic Esters Hydro-de-acyloxylation or Deacyloxylation



The alkyl group R of certain carboxylic esters can be reduced to RH ¹¹⁷⁷ by treatment with lithium in ethylamine.¹¹⁷⁸ The reaction is successful when R is a tertiary or a sterically hindered secondary alkyl group. A free-radical mechanism is likely.¹¹⁷⁹ Similar reduction, also by a free-radical mechanism, has been reported with sodium in HMPA-*t*-BuOH.¹¹⁸⁰ In the latter case, tertiary R groups give high yields of RH, but primary and secondary R are converted to a mixture of RH and ROH. Both of these methods provide an indirect method

¹¹⁶³For a list of reagents, with references, see Ref. 508, pp. 505-508.

¹¹⁶⁴Hutchins; Taffer; Burgoyne *J. Org. Chem.* **1981**, *46*, 5214.

¹¹⁶⁵Vankar; Arya; Rao *Synth. Commun.* **1983**, *13*, 869. See also Vankar; Chaudhuri; Rao *Tetrahedron Lett.* **1987**, 28, 551.

¹¹⁶⁶RajanBabu; Nugent; Beattie *J. Am. Chem. Soc.* **1990**, *112*, 6408.

¹¹⁶⁷For a review of epoxide reduction with BH_3 , see Cragg, *Organoboranes in Organic Synthesis*; Marcel Dekker: New York, 1973, pp. 345-348. See also Yamamoto; Toi; Sonoda; Murahashi *J. Chem. Soc., Chem. Commun.* **1976**, 672.

¹¹⁶⁸Brown; Ikegami; Kawakami *J. Org. Chem.* **1970**, *35*, 3243.

¹¹⁶⁹Bonini; Di Fabio *Tetrahedron Lett.* **1988**, *29*, 819.

¹¹⁷⁰For a review, see Rylander, *Catalytic Hydrogenation over Platinum Metals*, Ref. 1129, pp. 478-485.

¹¹⁷¹Osuka; Taka-Oka; Suzuki *Chem. Lett.* **1984**, 271.

¹¹⁷²Molander; La Belle; Hahn *J. Org. Chem.* **1986**, *51*, 5259; Otsubo; Inanaga; Yamaguchi *Tetrahedron Lett.* **1987**, 28, 4437. See also Miyashita; Hoshino; Suzuki; Yoshikoshi *Chem. Lett.* **1988**, 507.

¹¹⁷³Gao; Sharpless *J. Org. Chem.* **1988**, *53*, 4081.

¹¹⁷⁴Oshima; Yamazaki; Shimizu; Nizar; Tsuji *J. Am. Chem. Soc.* **1989**, *111*, 6280.

¹¹⁷⁵Krishnamurthy; Schubert; Brown *J. Am. Chem. Soc.* **1973**, *95*, 8486.

¹¹⁷⁶Aizpurua; Palomo *Tetrahedron Lett.* **1984**, *25*, 3123.

¹¹⁷⁷For a review of some of the reactions in this section and some others, see Hartwig *Tetrahedron* **1983**, *39*, 2609-2645.

¹¹⁷⁸Barrett; Godfrey; Hollinshead; Prokopiou; Barton; Boar; Joukhadar; McGhie; Misra *J. Chem. Soc., Perkin Trans. 1* **1981**, 1501.

¹¹⁷⁹Barrett; Prokopiou; Barton; Boar; McGhie *J. Chem. Soc., Chem. Commun.* **1979**, 1173.

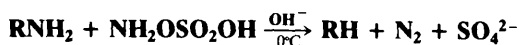
¹¹⁸⁰Deshayes; Pete *Can. J. Chem.* **1984**, *62*, 2063.

of accomplishing **0-78** for tertiary R.¹¹⁸¹ The same thing can be done for primary and secondary R by treating alkyl chloroformates ROCOCl with tri-*n*-propylsilane in the presence of *t*-butyl peroxide¹¹⁸² and by treating thiono ethers ROC(=S)W (where W can be OAr or other groups) with Ph₂SiH₂ and a free radical initiator.¹¹⁸³ Allylic acetates can be reduced with NaBH₄ and a palladium complex,¹¹⁸⁴ with *p*-bis(diphenylhydrosilyl)benzene,¹¹⁸⁵ and with SmI₂-Pd(0).¹¹⁸⁶ The last reagent converts propargylic acetates to allenes R¹C≡CR²R³OAc → R¹CH=C=CR²R³.¹¹⁸⁶ For other carboxylic ester reductions, see **9-40**, **9-42**, and **9-43**.

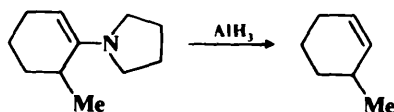
OS VII, 139.

0-82 Reduction of the C—N Bond

Hydro-de-amination or Deamination



Primary amines have been reduced to RH with hydroxylamine-O-sulfonic acid and aqueous NaOH.¹¹⁸⁷ It is postulated that R—N=N—H is an intermediate that decomposes to the carbocation. The reaction has also been accomplished with difluoroamine HNF₂,¹¹⁸⁸ the same intermediates are postulated in this case. An indirect means of achieving the same result is the conversion of the primary amine to the sulfonamide RNHSO₂R' (**0-116**) and treatment of this with NH₂OSO₂OH.¹¹⁸⁹ Other indirect methods involve reduction of N,N-ditosylates (p. 354) with NaBH₄ in HMPA¹¹⁹⁰ and modifications of the Katritzky pyrylium-pyridinium method.¹¹⁹¹ Allylic and benzylic amines¹¹²⁹ can be reduced by catalytic hydrogenolysis. Enamines are cleaved to olefins with alane AlH₃,¹¹⁹² e.g.,



and with 9-BBN (p. 785) or borane methyl sulfide (BMS).¹¹⁹³ Since enamines can be prepared from ketones (**6-14**), this is a way of converting ketones to alkenes. In the latter case BMS gives retention of configuration [an (*E*) isomer gives the (*E*) product] while 9-BBN gives the other isomer.¹¹⁹³ Diazo ketones are reduced to methyl ketones by HI: RCOCHN₂ + HI → RCOCH₃.¹¹⁹⁴

¹¹⁸¹For other methods, see Barton; Crich; Løbberding; Zard *J. Chem. Soc., Chem. Commun.* **1985**, 646; Barton; Crich *J. Chem. Soc., Perkin Trans. 1* **1986**, 1603.

¹¹⁸²Jackson; Malek *J. Chem. Soc., Perkin Trans. 1* **1980**, 1207.

¹¹⁸³See Barton; Jang; Jaszberenyi *Tetrahedron Lett.* **1990**, 31, 4681 and references cited therein. For similar methods, see Nozaki; Oshima; Utimoto *Bull. Chem. Soc. Jpn.* **1990**, 63, 2578; Kirwan; Roberts; Willis *Tetrahedron Lett.* **1990**, 31, 5093.

¹¹⁸⁴Hutchins; Learn; Fulton *Tetrahedron Lett.* **1980**, 21, 27. See also Ipaktschi *Chem. Ber.* **1984**, 117, 3320.

¹¹⁸⁵Sano; Takeda; Migita *Chem. Lett.* **1988**, 119. See also Keinan; Greenspoon *Isr. J. Chem.* **1984**, 24, 82.

¹¹⁸⁶Tabuchi; Inanaga; Yamaguchi *Tetrahedron Lett.* **1986**, 27, 601, 5237. See also Ref. 1136.

¹¹⁸⁷Doldouras; Kollonitsch *J. Am. Chem. Soc.* **1978**, 100, 341.

¹¹⁸⁸Bumgardner; Martin; Freeman *J. Am. Chem. Soc.* **1963**, 85, 97.

¹¹⁸⁹Nickon; Hill *J. Am. Chem. Soc.* **1964**, 86, 1152.

¹¹⁹⁰Hutchins; Cistone; Goldsmith; Heuman *J. Org. Chem.* **1975**, 40, 2018.

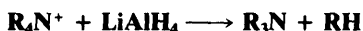
¹¹⁹¹See Katritzky; Bravo-Borja; El-Mowafy; Lopez-Rodriguez *J. Chem. Soc., Perkin Trans. 1* **1984**, 1671.

¹¹⁹²Coulter; Lewis; Lynch *Tetrahedron* **1968**, 24, 4489.

¹¹⁹³Singaram; Goralski; Rangaishenvi; Brown *J. Am. Chem. Soc.* **1989**, 111, 384.

¹¹⁹⁴For example, see Pojer; Ritchie; Taylor *Aust. J. Chem.* **1968**, 21, 1375.

Quaternary ammonium salts can be cleaved with LiAlH_4



as can quaternary phosphonium salts R_4P^+ . Other reducing agents have also been used, for example, lithium triethylborohydride (which preferentially cleaves methyl groups)¹¹⁹⁵ and sodium in liquid ammonia. When quaternary salts are reduced with sodium amalgam in water, the reaction is known as the *Emde reduction*. However, this reagent is not applicable to the cleavage of ammonium salts with four *saturated* alkyl groups. Of course, aziridines¹¹⁷⁰ can be reduced in the same way as epoxides (0-80).

Nitro compounds RNO_2 can be reduced to RH ¹¹⁹⁶ by sodium methylmercaptide CH_3SNa in an aprotic solvent¹¹⁹⁷ or by Bu_3SnH .¹¹⁹⁸ Both reactions have free-radical mechanisms.¹¹⁹⁹ Tertiary nitro compounds can be reduced to RH by NaHTe .¹²⁰⁰ Bu_3SnH also reduces isocyanides RNC (prepared from RNH_2 by formylation followed by 7-41) to RH .¹²⁰¹ a reaction that can also be accomplished with Li or Na in liquid NH_3 ,¹²⁰² or with K and a crown ether in toluene.¹²⁰³ α -Nitro ketones can be reduced to ketones with $\text{Na}_2\text{S}_2\text{O}_4$ - Et_3SiH in HMPA - H_2O .¹²⁰⁴

Hydrogenolysis with a Pt catalyst in the gas phase has been reported to reduce nitro compounds, as well as primary and secondary amines.¹²⁰⁵

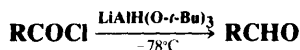
OS III, 148; IV, 508; 68, 227.

For reduction of the $\text{C}-\text{S}$ bond, see 4-36.

B. Attack at an Acyl Carbon

0-83 Reduction of Acyl Halides

Hydro-de-halogenation or Dehalogenation



Acyl halides can be reduced to aldehydes¹²⁰⁶ by treatment with lithium tri-*t*-butoxyaluminum hydride in diglyme at -78°C .¹²⁰⁷ R may be alkyl or aryl and may contain many types of substituents, including NO_2 , CN , and EtOOC groups. The reaction stops at the aldehyde stage because steric hindrance prevents further reduction under these conditions. Acyl halides can also be reduced to aldehydes by hydrogenolysis with palladium-on-barium sulfate

¹¹⁹⁵Cooke; Parlman *J. Org. Chem.* **1975**, 40, 531.

¹¹⁹⁶For a method of reducing allylic nitro groups, see Ono; Hamamoto; Kamimura; Kaji *J. Org. Chem.* **1986**, 51, 3734.

¹¹⁹⁷Kornblum; Carlson; Smith *J. Am. Chem. Soc.* **1979**, 101, 647; Kornblum; Widmer; Carlson *J. Am. Chem. Soc.* **1979**, 101, 658.

¹¹⁹⁸For reviews, see Ono, in Feuer; Nielsen *Nitro Compounds; Recent Advances in Synthesis and Chemistry*; VCH: New York, 1990, pp. 1-135, pp. 1-45; Rosini; Ballini *Synthesis* **1988**, 833-847, pp. 835-837; Ono; Kaji *Synthesis* **1986**, 693-704. For discussions of the mechanism, see Korth; Sustmann; Dupuis; Geise *Chem. Ber.* **1987**, 120, 1197; Kamimura; Ono *Bull. Chem. Soc. Jpn.* **1988**, 61, 3629.

¹¹⁹⁹For a discussion of the mechanism with Bu_3SnH , see Tanner; Harrison; Chen; Kharrat; Wayner; Griller; McPhee *J. Org. Chem.* **1990**, 55, 3321. If an α substituent is present, it may be reduced instead of the NO_2 . For a mechanistic discussion, see Bowman; Crosby; Westlake *J. Chem. Soc., Perkin Trans. 2* **1991**, 73.

¹²⁰⁰Suzuki; Takaoka; Osuka *Bull. Chem. Soc. Jpn.* **1985**, 58, 1067.

¹²⁰¹Barton; Bringmann; Motherwell *Synthesis* **1980**, 68.

¹²⁰²See Niznik; Walborsky *J. Org. Chem.* **1978**, 43, 2396; Yadav; Reddy; Joshi *Tetrahedron Lett.* **1988**, 44, 7243.

¹²⁰³Ohsawa; Mitsuda; Nezu; Oishi *Tetrahedron Lett.* **1989**, 30, 845.

¹²⁰⁴Kamimura; Kurata; Ono *Tetrahedron Lett.* **1989**, 30, 4819.

¹²⁰⁵Guttieri; Maier *J. Org. Chem.* **1984**, 49, 2875.

¹²⁰⁶For a review of the formation of aldehydes from acid derivatives, see Fuson, in Patai, Ref. 446, pp. 211-232. For a review of the reduction of acyl halides, see Wheeler, in Patai, Ref. 502, pp. 231-251.

¹²⁰⁷Brown; McFarlin *J. Am. Chem. Soc.* **1958**, 80, 5372; Brown; Subba Rao *J. Am. Chem. Soc.* **1958**, 80, 5377.

as catalyst. This is called the *Rosenmund reduction*.¹²⁰⁸ A more convenient hydrogenolysis procedure involves palladium-on-charcoal as the catalyst, with ethyldiisopropylamine as acceptor of the liberated HCl and acetone as the solvent.¹²⁰⁹ The reduction of acyl halides to aldehydes has also been carried out¹²¹⁰ with Bu_3SnH ,¹²¹¹ with $\text{Bu}_3\text{GeH-Pd(PPh}_3)_4$,¹²¹² with NaBH_4 in a mixture of DMF and THF,¹²¹³ and with ions of the form HM(CO)_4^- ($\text{M} = \text{Fe, Cr, W}$).¹²¹⁴ In some of these cases, the mechanisms are free-radical. There are several indirect methods for the conversion of acyl halides to aldehydes, most of them involving prior conversion of the halides to certain types of amides (see 0-85). There is also a method in which the COOH group is replaced by a completely different CHO group (0-110). Also see 9-45.

OS III, 551, 627; VI, 529, 1007. Also see OS III, 818; VI, 312.

0-84 Reduction of Carboxylic Acids, Esters, and Anhydrides to Aldehydes¹²¹⁵

Hydro-de-hydroxylation or **Dehydroxylation** (overall transformation)



With most reducing agents, reduction of carboxylic acids generally gives the primary alcohol (9-38) and the isolation of aldehydes is not feasible. However, simple straight-chain carboxylic acids have been reduced to aldehydes¹²¹⁶ by treatment with Li in MeNH_2 or NH_3 followed by hydrolysis of the resulting imine,¹²¹⁷ with borane- Me_2S followed by pyridinium chlorochromate,¹²¹⁸ with isobutylmagnesium bromide and a titanium-complex catalyst followed by hydrolysis,¹²¹⁹ with hexylchloroborane- Me_2S ¹²²⁰ or hexylbromoborane- Me_2S ¹²²¹ (see 5-12 for the hexyl group), with $\text{LiAlH(O-}i\text{-Bu)}_3$ and chloromethylene dimethylammonium chloride¹²²² $\text{Me}_2\text{N=CHCl}^+ \text{Cl}^-$ in pyridine,¹²²³ and with diaminoaluminum hydrides.¹²²⁴ Caproic and isovaleric acids have been reduced to aldehydes in 50% yields or better with DIBALH ($i\text{-Bu}_2\text{AlH}$) at -75 to -70°C .¹²²⁵

¹²⁰⁸For a review, see Ref. 1170, pp. 398-404. For a discussion of the Pt catalyst, see Maier; Chettle; Rai; Thomas *J. Am. Chem. Soc.* **1986**, 108, 2608.

¹²⁰⁹Peters; van Bekkum *Recl. Trav. Chim. Pays-Bas* **1971**, 90, 1323, **1981**, 100, 21. See also Burgstahler; Weigel; Shaefer *Synthesis* **1976**, 767.

¹²¹⁰For some other methods, see Wagenknecht *J. Org. Chem.* **1972**, 37, 1513; Smith; Smith *J. Chem. Soc., Chem. Commun.* **1975**, 459; Leblanc; Moise; Tirouflet *J. Organomet. Chem.* **1985**, 292, 225; Corriu; Lanneau; Perrot *Tetrahedron Lett.* **1988**, 29, 1271. For a list of reagents, with references, see Ref. 508, pp. 620-621.

¹²¹¹Kuivila *J. Org. Chem.* **1960**, 25, 284; Walsh; Stoneberg; Yorke; Kuivila *J. Org. Chem.* **1969**, 34, 1156; Four; Guibe *J. Org. Chem.* **1981**, 46, 4439; Luszytk; Luszytk; Maillard; Ingold *J. Am. Chem. Soc.* **1984**, 106, 2923.

¹²¹²Geng; Lu *J. Organomet. Chem.* **1989**, 376, 41.

¹²¹³Babler; Invergo *Tetrahedron Lett.* **1981**, 22, 11; Babler *Synth. Commun.* **1982**, 12, 839. For the use of NaBH_4 and metal ions, see Entwistle; Boehm; Johnstone; Telford *J. Chem. Soc., Perkin Trans. 1* **1980**, 27.

¹²¹⁴Cainelli; Manescalchi; Umani-Ronchi *J. Organomet. Chem.* **1984**, 276, 205; Kao; Gaus; Youngdahl; Darcensbourg *Organometallics* **1984**, 3, 1601.

¹²¹⁵For a review, see Cha *Org. Prep. Proced. Int.* **1989**, 21, 451-477.

¹²¹⁶For other reagents, see Hubert; Eyman; Wiemer *J. Org. Chem.* **1984**, 49, 2279; Corriu; Lanneau; Perrot *Tetrahedron Lett.* **1987**, 28, 3941; Cha; Kim; Yoon; Kim *Tetrahedron Lett.* **1987**, 28, 6231. See also the lists in Ref. 508, pp. 619-622.

¹²¹⁷Bedenbaugh; Bedenbaugh; Bergin; Adkins *J. Am. Chem. Soc.* **1970**, 92, 5774; Burgstahler; Worden; Lewis *J. Org. Chem.* **1963**, 28, 2918.

¹²¹⁸Brown; Rao; Kulkarni *Synthesis* **1979**, 704.

¹²¹⁹Sato; Jinbo; Sato *Synthesis* **1981**, 871.

¹²²⁰Brown; Cha; Yoon; Nazer *J. Org. Chem.* **1987**, 52, 5400.

¹²²¹Cha; Kim; Lee *J. Org. Chem.* **1987**, 52, 5030.

¹²²²For the preparation of this reagent, see Fujisawa; Sato *Org. Synth.* 66, 121.

¹²²³Fujisawa; Mori; Tsuge; Sato *Tetrahedron Lett.* **1983**, 24, 1543.

¹²²⁴Muraki; Mukaiyama *Chem. Lett.* **1974**, 1447, **1975**, 215.

¹²²⁵Zakharkin; Khorlina *J. Gen. Chem. USSR* **1964**, 34, 1021; Zakharkin; Sorokina *J. Gen. Chem. USSR* **1967**, 37, 525.

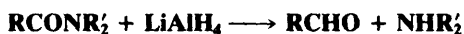
Carboxylic esters have been reduced to aldehydes with DIBALH at -70°C , with di-aminoaluminum hydrides,¹²²⁴ with $\text{LiAlH}_4\text{-Et}_2\text{NH}$,¹²²⁶ and with NaAlH_4 at -65 to -45°C , and (for phenolic esters) with $\text{LiAlH}(\text{O-}t\text{-Bu})_3$ at 0°C .¹²²⁷ Aldehydes have also been prepared by reducing ethyl thiol esters RCOSEt with Et_3SiH and a Pd-C catalyst.¹²²⁸

Anhydrides, both aliphatic and aromatic, as well as mixed anhydrides of carboxylic and carbonic acids, have been reduced to aldehydes in moderate yields with disodium tetracarbonylferrate $\text{Na}_2\text{Fe}(\text{CO})_4$.¹²²⁹

Also see **9-40** and **9-42**.

OS VI, 312; **66**, 121; **69**, 55.

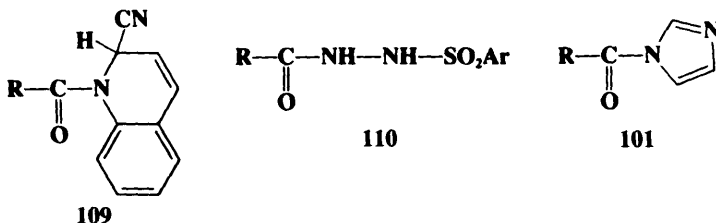
0-85 Reduction of Amides to Aldehydes Hydro-de-dialkylamino-substitution



N,N-Disubstituted amides can be reduced to amines with LiAlH_4 (see **9-39**), but also to aldehydes.¹²³⁰ Keeping the amide in excess gives the aldehyde rather than the amine. Sometimes it is not possible to prevent further reduction and primary alcohols are obtained instead. Other reagents¹²³¹ that give good yields of aldehydes are DIBALH,¹²³² $\text{LiAlH}(\text{O-}t\text{-Bu})_3$, $\text{LiAlH}_4\text{-EtOH}$,¹²³³ NaAlH_4 ,¹²³⁴ and diaminoaluminum hydrides.¹²³⁵

Aldehydes have been prepared from carboxylic acids or acyl halides by first converting them to certain types of amides that are easily reducible. The following are some examples:¹²³⁶

1. *Reissert compounds*¹²³⁷ (**109**) are prepared from the acyl halide by treatment with quinoline and cyanide ion. Treatment of **109** with sulfuric acid gives the corresponding aldehyde.



2. Acyl sulfonylhydrazides (**110**) are cleaved with base to give aldehydes. This is known as the *McFadyen-Stevens reduction* and is applicable only to aromatic aldehydes or aliphatic

¹²²⁴Cha; Kwon *J. Org. Chem.* **1987**, 52, 5486.

¹²²⁷Zakharkin; Khorlina *Tetrahedron Lett.* **1962**, 619, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1963**, 288, **1964**, 435; Zakharkin; Gavrilenko; Maslin; Khorlina *Tetrahedron Lett.* **1963**, 2087; Zakharkin; Gavrilenko; Maslin *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1964**, 867; Weissman; Brown *J. Org. Chem.* **1966**, 31, 283.

¹²²⁸Fukuyama; Lin; Li *J. Am. Chem. Soc.* **1990**, 112, 7050.

¹²²⁹Watanabe; Yamashita; Mitsudo; Igami; Takegami *Bull. Chem. Soc. Jpn.* **1975**, 48, 2490; Watanabe; Yamashita; Mitsudo; Igami; Tomi; Takegami *Tetrahedron Lett.* **1975**, 1063.

¹²³⁰For a review, see Fuson, in Patai, Ref. 446, pp. 220-225.

¹²³¹For a list of reagents, with references, see Ref. 508, pp. 623-624.

¹²³²Zakharkin; Khorlina *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1959**, 2046.

¹²³³Brown; Tsukamoto *J. Am. Chem. Soc.* **1964**, 86, 1089.

¹²³⁴Zakharkin; Maslin; Gavrilenko *Tetrahedron* **1969**, 25, 5555.

¹²³⁵Muraki; Mukaiyama *Chem. Lett.* **1975**, 875.

¹²³⁶For other examples, see Brown; Tsukamoto *J. Am. Chem. Soc.* **1961**, 83, 4549; Doleschall *Tetrahedron* **1976**, 32, 2549; Atta-ur-Rahman; Basha *J. Chem. Soc., Chem. Commun.* **1976**, 594; Izawa; Mukaiyama *Bull. Chem. Soc. Jpn.* **1979**, 52, 555; Craig; Ekwuribe; Fu; Walker *Synthesis* **1981**, 303.

¹²³⁷For reviews of Reissert compounds, see Popp; Uff *Heterocycles* **1985**, 23, 731-740; Popp *Bull. Soc. Chim Belg* **1981**, 90, 609-613, *Adv. Heterocycl. Chem.* **1979**, 24, 187-214, **1968**, 9, 1-25.

aldehydes with no α hydrogen.¹²³⁸ $\text{RCON}=\text{NH}$ (see 0-82) has been proposed as an intermediate in this reaction.¹²³⁹

3. Imidazoles (101)⁶⁶⁴ can be reduced to aldehydes with LiAlH_4 .
4. See also the Sonn-Müller method (6-28).

OS 67, 69. See OS IV, 641, VI, 115 for the preparation of Reissert compounds.

Carbon Nucleophiles

In any heterolytic reaction in which a new carbon-carbon bond is formed¹²⁴⁰ one carbon atom attacks as a nucleophile and the other as an electrophile. The classification of a given reaction as nucleophilic or electrophilic is a matter of convention and is usually based on analogy. Although not discussed in this chapter, 1-12 to 1-28 and 2-15 to 2-20 are nucleophilic substitutions with respect to one reactant, though, following convention, we classify them with respect to the other. Similarly, all the reactions in this section (0-86 to 0-113) would be called electrophilic substitution (aromatic or aliphatic) if we were to consider the reagent as the substrate.

A. Attack at an Alkyl Carbon. In 0-86 to 0-93 the nucleophile is a "carbanion" part of an organometallic compound, often a Grignard reagent. There is much that is still not known about the mechanisms of these reactions and many of them are not nucleophilic substitutions at all. In those reactions that are nucleophilic substitutions, the attacking carbon brings a pair of electrons with it to the new C—C bond, whether or not free carbanions are actually involved. The connection of two alkyl or aryl groups is called *coupling*. Reactions 0-86 to 0-93 include both symmetrical and unsymmetrical coupling reactions. The latter are also called *cross-coupling reactions*. Other coupling reactions are considered in later chapters.

0-86 Coupling of Alkyl Halides. The Wurtz Reaction De-halogen-coupling



The coupling of alkyl halides by treatment with sodium to give a symmetrical product is called the *Wurtz reaction*. Side reactions (elimination and rearrangement) are so common that the reaction is seldom used. Mixed Wurtz reactions of two alkyl halides are even less feasible because of the number of products obtained. A somewhat more useful reaction (though still not very good) takes place when a mixture of an alkyl and an aryl halide is treated with sodium to give an alkylated aromatic compound (the *Wurtz-Fittig reaction*).¹²⁴¹ However, the coupling of two aryl halides with sodium is impractical (but see 3-16). Other metals have also been used to effect Wurtz reactions,¹²⁴² notably silver, zinc,¹²⁴³ iron,¹²⁴⁴ activated copper,¹²⁴⁵ and pyrophoric lead.¹²⁴⁶ Lithium, under the influence of ultrasound,

¹²³⁸Babad; Herbert; Stiles *Tetrahedron Lett.* **1966**, 2927; Dudman; Grice; Reese *Tetrahedron Lett.* **1980**, 21, 4645.

¹²³⁹For discussions, see Cacchi; Paolucci *Gazz. Chem. Ital.* **1974**, 104, 221; Matin; Craig; Chan *J. Org. Chem.* **1974**, 39, 2285.

¹²⁴⁰For a monograph that discusses most of the reactions in this section, see Stowell *Carbanions in Organic Synthesis*; Wiley: New York, 1979. For a review, see Noyori, in Alper *Transition Metal Organometallics in Organic Synthesis*, vol. 1; Academic Press: New York, 1976, pp. 83-187.

¹²⁴¹For an example, see Kwa; Boelhouwer *Tetrahedron* **1970**, 25, 5771.

¹²⁴²For a list of reagents, including metals and other reagents, with references, see Ref. 508, pp. 47-48.

¹²⁴³See, for example, Nosek *Collect. Czech. Chem. Commun.* **1964**, 29, 597.

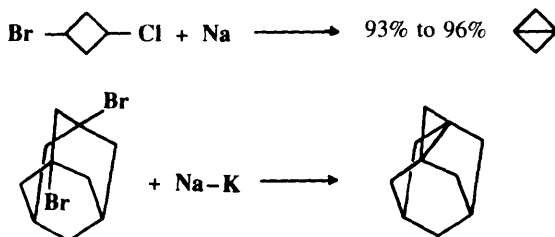
¹²⁴⁴Nozaki; Noyori *Tetrahedron* **1966**, 22, 2163; Onsager *Acta Chem. Scand., Ser. B* **1978**, 32, 15.

¹²⁴⁵Ginah; Donovan; Suchan; Pfennig; Ebert *J. Org. Chem.* **1990**, 55, 584.

¹²⁴⁶Mészáros *Tetrahedron Lett.* **1967**, 4951; Azoo; Grimshaw *J. Chem. Soc. C* **1968**, 2403.

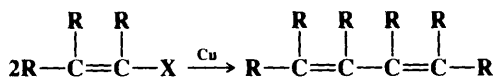
has been used to couple alkyl, aryl, and benzylic halides.¹²⁴⁷ Metallic nickel, prepared by the reduction of nickel halides with Li, dimerizes benzylic halides to give $\text{ArCH}_2\text{CH}_2\text{Ar}$.¹²⁴⁸ The coupling of alkyl halides has also been achieved electrochemically.¹²⁴⁹

One type of Wurtz reaction that is quite useful is the closing of small rings, especially three-membered rings.¹²⁵⁰ For example, 1,3-dibromopropane can be converted to cyclopropane by Zn and NaI.¹²⁵¹ Two highly strained molecules that have been prepared this way are bicyclobutane¹²⁵² and tetracyclo[3.3.1.1^{3,7}.0^{1,3}]decane.¹²⁵³ Three- and four-membered



rings can also be closed in this manner with certain other reagents,¹²⁵⁴ including benzoyl peroxide,¹²⁵⁵ *t*-BuLi,¹²⁵⁶ (phenylsulfonyl)methylene dilithium $\text{PhSO}_2\text{CHLi}_2$,¹²⁵⁷ and lithium amalgam,¹²⁵⁸ as well as electrochemically.¹²⁵⁹

Vinyl halides can be coupled to give 1,3-butadienes by treatment with activated copper powder in a reaction analogous to the Ullmann reaction (3-16).¹²⁶⁰ This reaction is stereospecific, with retention of configuration at both carbons. Vinyl halides can also be



coupled¹²⁶¹ with CuCl,¹²⁶² with Zn-NiCl₂,¹²⁶³ and with *n*-BuLi in ether in the presence of MnCl₂.¹²⁶⁴

¹²⁴⁷Han; Boudjouk *Tetrahedron Lett.* **1981**, 22, 2757.

¹²⁴⁸Inaba; Matsumoto; Rieke *J. Org. Chem.* **1984**, 49, 2093. For some other reagents that accomplish this, see Sayles; Kharasch *J. Org. Chem.* **1961**, 26, 4210; Cooper *J. Am. Chem. Soc.* **1973**, 95, 4158; Ho; Olah *Synthesis* **1977**, 170; Ballatore; Crozet; Surzur *Tetrahedron Lett.* **1979**, 3073; Yamada; Momose *Chem. Lett.* **1981**, 1277; Iyoda; Sakaitani; Otsuka; Oda *Chem. Lett.* **1985**, 127.

¹²⁴⁹Folest; Nedelec; Perichon *J. Chem. Res. (S)* **1989**, 394.

¹²⁵⁰For a review, see Freidlina; Kamyshova; Chukovskaya *Russ. Chem. Rev.* **1982**, 51, 368-376. For reviews of methods of synthesizing cyclopropane rings, see, in Rappoport *The Chemistry of the Cyclopropyl Group*, pt. 1; Wiley: New York, 1987, the reviews by Tsuji; Nishida, pp. 307-373, and Verhé; De Kimpe, pp. 445-564.

¹²⁵¹For a discussion of the mechanism, see Applequist; Pfohl *J. Org. Chem.* **1978**, 43, 867.

¹²⁵²Wiberg; Lampman *Tetrahedron Lett.* **1963**, 2173; Lampman; Aumiller *Org. Synth.* VI, 133.

¹²⁵³Pincock; Schmidt; Scott; Torupka *Can. J. Chem.* **1972**, 50, 3958.

¹²⁵⁴For a list of reagents, with references, see Ref. 508, pp. 87-88.

¹²⁵⁵Kaplan *J. Am. Chem. Soc.* **1967**, 89, 1753; *J. Org. Chem.* **1967**, 32, 4059.

¹²⁵⁶Bailey; Gagnier *Tetrahedron Lett.* **1982**, 23, 5123.

¹²⁵⁷Eisch; Dua; Behrooz *J. Org. Chem.* **1985**, 50, 3674.

¹²⁵⁸Connor; Wilson *Tetrahedron Lett.* **1967**, 4925.

¹²⁵⁹Rifi *J. Am. Chem. Soc.* **1967**, 89, 4442; *Org. Synth.* VI, 153.

¹²⁶⁰Cohen; Poeth *J. Am. Chem. Soc.* **1972**, 94, 4363.

¹²⁶¹For some other methods, see Jones *J. Org. Chem.* **1967**, 32, 1667; Semmelhack; Helquist; Gorzynski *J. Am. Chem. Soc.* **1972**, 94, 9234; Wellmann; Steckhan *Synthesis* **1978**, 901; Miyahara; Shiraishi; Inazu; Yoshino *Bull. Chem. Soc. Jpn.* **1979**, 52, 953; Grigg; Stevenson; Worakun *J. Chem. Soc., Chem. Commun.* **1985**, 971; Vandercse; Fort; Becker; Caubere *Tetrahedron Lett.* **1986**, 27, 3517.

¹²⁶²Kauffmann; Sahn *Angew. Chem. Int. Ed. Engl.* **1967**, 6, 85 [*Angew. Chem.* 79, 101]; Toda; Takehira *J. Chem. Soc., Chem. Commun.* **1975**, 174.

¹²⁶³Takagi; Mimura; Inokawa *Bull. Chem. Soc. Jpn.* **1984**, 57, 3517.

¹²⁶⁴Cahiez; Bernard; Normant *J. Organomet. Chem.* **1976**, 113, 99.

It seems likely that the mechanism of the Wurtz reaction consists of two basic steps. The first is halogen-metal exchange to give an organometallic compound ($RX + M \rightarrow RM$), which in many cases can be isolated (2-38). Following this, the organometallic compound reacts with a second molecule of alkyl halide ($RX + RM \rightarrow RR$). This reaction and its mechanism are considered in the next section (0-87).

OS III, 157; V, 328, 1058; VI, 133, 153.

0-87 The Reaction of Alkyl Halides with Organometallic Reagents¹²⁶⁵

Alkyl-de-halogenation



The reagents lithium dialkylcopper¹²⁶⁶ (also called *Gilman reagents*) react with alkyl bromides, chlorides, and iodides in ether or THF to give good yields of the cross-coupling products.¹²⁶⁷ The reaction is of wide scope.¹²⁶⁸ R may be primary alkyl, allylic, benzylic, aryl, vinylic, or allenic, and may contain keto, COOH, COOR, or CONR₂ groups. The reaction at a vinylic substrate occurs stereospecifically, with retention of configuration.¹²⁶⁹ When the reagent and substrate are both vinylic, yields are low, but the reaction can be made to go (to give 1,3-butadienes) stereospecifically in high yields by the use of ZnBr₂ and a Pd(0) complex.¹²⁷⁰ Many *gem*-dihalides do not react, but when the two halogens are on a carbon α to an aromatic ring¹²⁷¹ or on a cyclopropane ring,¹²⁷² both halogens can be replaced by R, e.g., $PhCHCl_2 \rightarrow PhCHMe_2$. However, 1,2-dibromides give exclusive elimination¹²⁷³ (7-29). R' in R'₂CuLi may be primary alkyl, vinylic, allylic, or aryl. Thus, in the reaction as so far described, neither R nor R' may be secondary or tertiary alkyl. However, secondary and tertiary alkyl coupling can be achieved (on primary RX) by the use of R₂CuLi-PBu₃¹²⁷⁴ (though this procedure introduces problems in the work-up) or by the use of PhS(R')CuLi,¹²⁷⁵ which selectively couples a secondary or tertiary R' with a primary iodide RI to give RR'.¹²⁷⁶ From the opposite standpoint, coupling to a secondary R can be achieved in high yield with the reagents R'₂Cu(CN)Li₂,¹²⁷⁷ where R' is primary alkyl or vinylic (but not aryl).¹²⁷⁸ The reagents RCu(PPh₂)Li, RCu(NR₂)Li, and Cu(PR'₂)Li (R' = cyclohexyl) are more stable than R₂CuLi and can be used at higher

¹²⁶⁵For a review of the reactions in this section, see Naso; Marchese, in Patai; Rappoport. Ref. 88, pt. 2, pp. 1353-1449.

¹²⁶⁶For the structure of Me₂CuLi (a cyclic dimer), see Pearson; Gregory *J. Am. Chem. Soc.* **1976**, 98, 4098. See also Lipshutz; Kozlowski; Breneman *Tetrahedron Lett.* **1985**, 26, 5911. For reviews of the structure and reactions of organocopper compounds, see Power *Prog. Inorg. Chem.* **1991**, 39, 75-112; Collman; Hegedus; Norton; Finke *Principles and Applications of Organotransition Metal Chemistry*, 2nd ed.; University Science Books: Mill Valley, CA, 1987, pp. 682-698.

¹²⁶⁷Corey; Posner *J. Am. Chem. Soc.* **1967**, 89, 3911, **1968**, 90, 5615; Whitesides; Fischer; San Filippo; Bashe; House *J. Am. Chem. Soc.* **1969**, 91, 4871; Bergbreiter; Whitesides *J. Org. Chem.* **1975**, 40, 779.

¹²⁶⁸For a review of this reaction, see Posner *Org. React.* **1975**, 22, 253-400. For a review of organocopper reagents, see Normant *Synthesis* **1972**, 63-80. For examples of the use of this reaction in this synthesis of natural products, see Posner *An Introduction to Synthesis Using Organocopper Reagents*; Wiley: New York, 1980, pp. 68-81. For lists of substrates and reagents, with references, see Ref. 508, pp. 206-210, 304-306, 788.

¹²⁶⁹Corey; Posner, Ref. 1267; Klein; Levene *J. Am. Chem. Soc.* **1972**, 94, 2520.

¹²⁷⁰Jabri; Alexakis; Normant *Tetrahedron Lett.* **1981**, 22, 959, **1982**, 23, 1589, *Bull. Soc. Chim. Fr.* **1983**, II-321, II-332.

¹²⁷¹Posner; Brunelle *Tetrahedron Lett.* **1972**, 293.

¹²⁷²See, for example, Kitatani; Hiyama; Nozaki *Bull. Chem. Soc. Jpn* **1977**, 50, 1600.

¹²⁷³Posner; Ting *Synth. Commun.* **1973**, 3, 281.

¹²⁷⁴Whitesides; Fischer; San Filippo; Bashe; House, Ref. 1267.

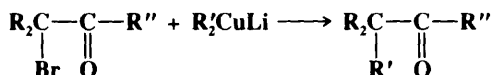
¹²⁷⁵Prepared as in Ref. 1285 or treatment of PhSCu with RLi; Posner; Brunelle; Sinoway *Synthesis* **1974**, 662.

¹²⁷⁶Posner; Whitten; Sterling *J. Am. Chem. Soc.* **1973**, 95, 7788; Posner; Whitten *Tetrahedron Lett.* **1973**, 1815.

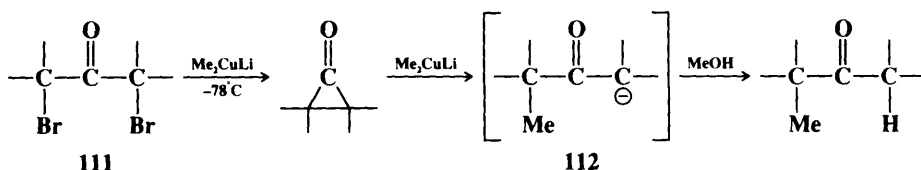
¹²⁷⁷For reviews of these and other "higher order" organocuprates, see Lipshutz; Wilhelm; Kozlowski *Tetrahedron* **1984**, 40, 5005-5038, Lipshutz *Synthesis* **1987**, 325-341, *Synlett* **1990**, 119-128. See also Bertz *J. Am. Chem. Soc.* **1990**, 112, 4031; Lipshutz; Sharma; Ellsworth *J. Am. Chem. Soc.* **1990**, 112, 4032.

¹²⁷⁸Lipshutz; Wilhelm; Floyd *J. Am. Chem. Soc.* **1981**, 103, 7672.

temperatures.¹²⁷⁹ With an allenic substrate, reaction with $R(CN)CuLi$ can give ordinary displacement (with retention of configuration)¹²⁸⁰ or an $SN2'$ reaction to produce an alkyne.¹²⁸¹ In the latter case, a chiral allene gave a chiral alkyne. The fact that R'_2CuLi do not react with ketones provides a method for the alkylation of ketones¹²⁸² (see also **0-95** and **0-99**), though halogen-metal exchange (**2-39**) is a side reaction and can become the main reaction.¹²⁸³



When α,α' -dibromo ketones (**111**) are treated with Me_2CuLi in ether at $-78^\circ C$ and the mixture quenched with methanol, *monomethylation* takes place¹²⁸⁴ (no dimethylation is observed). It has been suggested that the reaction involves cyclization (**0-86**) to a cyclopropanone followed by nucleophilic attack to give the enolate ion **112** which is protonated by



the methanol. If methyl iodide is added instead of methanol, an α,α' -dimethyl ketone is obtained, presumably from $SN2$ attack by **112** on methyl iodide (**0-95**). Only halides that are highly reactive to $SN2$ attack (e.g., methyl and benzylic halides) react successfully with **112**. Primary, secondary, and tertiary monoalkylation of **111** can be achieved if **111** is treated with a lithium *t*-butoxy(alkyl)copper reagent¹²⁸⁵ instead of Me_2CuLi . For example, 2,6-dibromocyclohexanone, treated with lithium *t*-butoxy(*t*-butyl)copper, gave 66% 2-*t*-butylcyclohexanone. This is one of the few methods for introducing a tertiary alkyl group α to a carbonyl group. When dialkylcopperzinc reagents $R_2CuZnCl$ couple with allylic halides, almost complete allylic rearrangement occurs ($SN2'$), and the reaction is diastereoselective if the allylic halide contains a δ alkoxy group.¹²⁸⁶

For the preparation of R'_2CuLi reagents, see **2-35**.

A much older reaction is the coupling of alkyl halides with Grignard reagents.¹²⁸⁷ Grignard reagents have the advantage that they are usually simpler to prepare than the corresponding R'_2CuLi , but the reaction is much narrower in scope. Grignard reagents couple only with active halides: allylic (though allylic rearrangements are common) and benzylic. They also couple with tertiary alkyl halides, but generally in low or moderate yields.¹²⁸⁸ Aryl Grignard

¹²⁷⁹Bertz; Dabbagh; Villacorta *J. Am. Chem. Soc.* **1982**, *104*, 5824; Bertz; Dabbagh *J. Org. Chem.* **1984**, *49*, 1119.

¹²⁸⁰Mooiweer; Elsevier; Wijkens; Vermeer *Tetrahedron Lett.* **1985**, *26*, 65.

¹²⁸¹Corey; Boaz *Tetrahedron Lett.* **1984**, *25*, 3059, 3063. For the reaction of these reagents with haloalkynes, see Yeh; Knochel *Tetrahedron Lett.* **1989**, *30*, 4799.

¹²⁸²Dubois; Lion; Moulineau *Tetrahedron Lett.* **1971**, 177; Dubois; Fournier; Lion *Bull. Soc. Chim. Fr.* **1976**, 1871.

¹²⁸³See Corey; Posner, Ref. 1267; Wakselman; Mondon *Tetrahedron Lett.* **1973**, 4285.

¹²⁸⁴Posner; Sterling *J. Am. Chem. Soc.* **1973**, *95*, 3076. See also Posner; Sterling; Whitten; Lentz; Brunelle *J. Am. Chem. Soc.* **1975**, *97*, 107; Lion; Dubois *Tetrahedron* **1975**, *31*, 1223. Ph_2CuLi behaves similarly; see Lei; Doubleday; Turro *Tetrahedron Lett.* **1986**, *27*, 4671.

¹²⁸⁵Prepared by treating CuI with *t*-BuOLi in THF at $0^\circ C$ and adding RLi to this solution.

¹²⁸⁶Nakamura; Sekiya; Arai; Aoki *J. Am. Chem. Soc.* **1989**, *111*, 3091.

¹²⁸⁷For reviews, see Raston; Salem, in *Hartley The Chemistry of the Metal-Carbon Bond*, vol. 4; Wiley: New York, 1987, pp. 161-306, pp. 269-283; Kharasch; Reinmuth *Grignard Reactions of Nonmetallic Substances*; Prentice-Hall: Englewood Cliffs, NJ, 1954, pp. 1046-1165.

¹²⁸⁸See, for example, Ohno; Shimizu; Ishizaki; Sasaki; Eguchi *J. Org. Chem.* **1988**, *53*, 729.

reagents usually give better yields in these reactions than alkyl Grignard reagents. Furthermore, because Grignard reagents react with the C=O group (**6-29**, **6-32**), they cannot be used to couple with halides containing ketone, COOR, or amide functions. Though the coupling of Grignard reagents with ordinary alkyl halides is usually not useful for synthetic purposes, small amounts of symmetrical coupling product are commonly formed while Grignard reagents are being prepared. Grignard reagents can be made to couple with alkyl halides in good yields by the use of certain catalysts.¹²⁸⁹ Among these are Cu(I) salts, which permit the coupling of Grignard reagents with primary alkyl halides in good yield¹²⁹⁰ (organocopper salts are probably intermediates here), and iron(III)¹²⁹¹ or palladium¹²⁹² complexes, which allow the coupling of Grignard reagents and vinylic halides. Grignard reagents prepared from primary or secondary¹²⁹³ alkyl or aryl halides can be coupled with vinylic or aryl halides in high yields in the presence of a nickel(II) catalyst.¹²⁹⁴ When a chiral nickel(II) catalyst is used, optically active hydrocarbons can be prepared from achiral reagents.¹²⁹⁵ Neopentyl iodides also couple with aryl Grignard reagents in the presence of a nickel(II) catalyst.^{1295a}

Other organometallic compounds¹²⁹⁶ have also been used to couple with alkyl halides.¹²⁹⁷ Organosodium and organopotassium compounds are more reactive than Grignard reagents and couple even with less reactive halides. The difficulty is in preparing and keeping them long enough for the alkyl halide to be added. Alkenes can be prepared by the coupling of vinylic lithium compounds with primary halides¹²⁹⁸ or of vinylic halides with alkyllithiums in the presence of a Pd or Ru catalyst.¹²⁹⁹ When treated with organocopper compounds and Lewis acids (e.g., *n*-BuCu·BF₃), allylic halides give substitution with almost complete allylic rearrangement, irrespective of the degree of substitution at the two ends of the allylic system.¹³⁰⁰

Organoaluminum compounds couple very well with tertiary (to give products containing a quaternary carbon) and benzylic halides at -78°C.¹³⁰¹ This reaction can also be applied to allylic, secondary, and some primary halides, but several days standing at room temperature is required (see also **0-90**). Products containing a quaternary carbon can also be

¹²⁸⁹For reviews, see Erdik *Tetrahedron* **1984**, *40*, 641-657; Kochi, Ref. 1077, pp. 374-398.

¹²⁹⁰Tamura; Kochi *J. Am. Chem. Soc.* **1971**, *93*, 1485; *Synthesis* **1971**, 303; *J. Organomet. Chem.* **1972**, *42*, 205; Onuma; Hashimoto *Bull. Chem. Soc. Jpn.* **1972**, *45*, 2582; Derguini-Boumechal; Linstrumelle *Tetrahedron Lett.* **1976**, 3225; Mirviss *J. Org. Chem.* **1989**, *54*, 1948.

¹²⁹¹Tamura; Kochi *Synthesis* **1971**, 303; *J. Am. Chem. Soc.* **1971**, *93*, 1487; Smith; Kochi *J. Org. Chem.* **1976**, *41*, 502; Walborsky; Banks *J. Org. Chem.* **1981**, *46*, 5074; Molander; Rahn; Shubert; Bonde *Tetrahedron Lett.* **1983**, *24*, 5449.

¹²⁹²Dang; Linstrumelle *Tetrahedron Lett.* **1978**, 191; Ratovelomanana; Linstrumelle; Normant *Tetrahedron Lett.* **1985**, *26*, 2575; Rossi; Carpita *Tetrahedron Lett.* **1986**, *27*, 2529; Minato; Suzuki; Tamao *J. Am. Chem. Soc.* **1987**, *109*, 1257; Fiandanese; Marchese; Mascolo; Naso; Ronzini *Tetrahedron Lett.* **1988**, *29*, 3705. For other references, see Ref. 508, pp. 201-202.

¹²⁹³Hayashi; Konishi; Kobori; Kumada; Higuchi; Hirotsu *J. Am. Chem. Soc.* **1984**, *106*, 158.

¹²⁹⁴Corriu; Masse *J. Chem. Soc., Chem. Commun.* **1972**, 144; Tamao; Sumitani; Kumada *J. Am. Chem. Soc.* **1972**, *94*, 4374. For a review, see Kumada *Pure Appl. Chem.* **1980**, *52*, 669-679.

¹²⁹⁵For a review, see Hayashi; Kumada, in Morrison *Asymmetric Synthesis*, vol. 5; Academic Press: New York, 1985, pp. 147-169. See also Cross; Kellogg *J. Chem. Soc., Chem. Commun.* **1987**, 1746; Iida; Yamashita *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2365.

^{1295a}Yuan; Scott *Tetrahedron Lett.* **1991**, *32*, 189.

¹²⁹⁶For lists of reagents and substrates, with references, see Ref. 508, pp. 57-67.

¹²⁹⁷For a review of the coupling of organic halides with organotin, mercury, and copper compounds catalyzed by palladium complexes, see Beletskaya *J. Organomet. Chem.* **1983**, *250*, 551-564. For a review of palladium-assisted coupling, see Larock *Organomercury Compounds in Organic Synthesis*; Springer: New York, 1985, pp. 249-262.

¹²⁹⁸Linstrumelle *Tetrahedron Lett.* **1974**, 3809; Millon; Lorne; Linstrumelle *Synthesis* **1975**, 434; Duhamel; Poirier *J. Am. Chem. Soc.* **1977**, *99*, 8356.

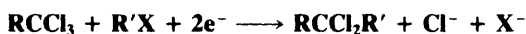
¹²⁹⁹Murahashi; Yamamura; Yanagisawa; Mita; Kondo *J. Org. Chem.* **1979**, *44*, 2408.

¹³⁰⁰Yamamoto; Yamamoto; Yatagai; Maruyama *J. Am. Chem. Soc.* **1980**, *102*, 2318. See also Lipshutz; Ellsworth; Dimock *J. Am. Chem. Soc.* **1990**, *112*, 5869.

¹³⁰¹Miller *J. Org. Chem.* **1966**, *31*, 908; Kennedy *J. Org. Chem.* **1970**, *35*, 532. See also Kennedy; Sivaram *J. Org. Chem.* **1973**, *38*, 2262; Sato; Kodama; Sato *J. Organomet. Chem.* **1978**, *157*, C30.

obtained by treatment of tertiary halides with dialkyl or diaryl zinc reagents in CH_2Cl_2 ,¹³⁰² with Me_4Si and AlCl_3 ,¹³⁰³ or with alkyltitanium reagents RTiCl_3 and R_2TiCl_2 .¹³⁰⁴ The titanium method can also be used with secondary halides ($\text{R}_2\text{CHCl} \rightarrow \text{R}_2\text{CHMe}$), tertiary ethers ($\text{R}_3\text{COR}' \rightarrow \text{R}_3\text{CMe}$), and *gem*-dihalides ($\text{R}_2\text{CCl}_2 \rightarrow \text{R}_2\text{CMe}_2$).¹³⁰⁵ Vinylic aluminum compounds (in the presence of a suitable transition-metal catalyst) couple with allylic halides, acetates, and alcohol derivatives to give 1,4-dienes,¹³⁰⁶ and with vinylic and benzylic halides to give 1,3-dienes and allylic arenes, respectively.¹³⁰⁷ Arylpalladium salts " ArPdX " prepared from arylmercury compounds and lithium palladium chloride couple with allylic chlorides in moderate yields, though allylic rearrangements can occur.¹³⁰⁸ The advantage of this procedure is that the aryl group may contain nitro, ester, or aldehyde groups, etc., which cannot be present in a Grignard reagent. Allylic, benzylic, vinylic, and aryl halides couple with organotin reagents in a reaction catalyzed by palladium complexes.¹³⁰⁹ Such functional groups as COOR , CN , OH , and CHO may be present in either reagent, but the substrate may not bear a β hydrogen on an sp^3 carbon, because that results in elimination. Organosilanes RSiMe_3 or RSiMe_2F (where R can be vinylic, allylic, or alkynyl) couple with vinylic, allylic, and aryl bromides and iodides $\text{R}'\text{X}$, in the presence of certain catalysts, to give RR' in good yields.¹³¹⁰ Alkenylboranes ($\text{R}'_2\text{C}=\text{CHBZ}_2$; Z = various groups) couple in high yields with vinylic, alkynyl, aryl, benzylic, and allylic halides in the presence of tetrakis(triphenylphosphine)palladium $\text{Pd}(\text{PPh}_3)_4$ and a base to give $\text{R}'_2\text{C}=\text{CHR}$.¹³¹¹ 9-Alkyl-9-BBN compounds (p. 785) also couple with vinylic and aryl halides¹³¹² as well as with α -halo ketones, nitriles, and esters.¹³¹³

gem-Dichlorides have been prepared by coupling alkyl halides to RCCl_3 compounds electrochemically, in an undivided cell with a sacrificial anode:¹³¹⁴



R' could also be Cl , in which case the product bears a CCl_3 group.¹³¹⁵

Much study has been devoted to the mechanisms of these reactions,¹³¹⁶ but firm conclusions are still lacking, in part because the mechanisms vary depending on the metal, the R group, the catalyst, if any, and the reaction conditions. Two basic pathways can be envi-

¹³⁰²Reetz; Wenderoth; Peter; Steinbach; Westermann *J. Chem. Soc., Chem. Commun.* **1980**, 1202. See also Klingstedt; Frejd *Organometallics* **1983**, 2, 598.

¹³⁰³Bolestova; Parnes; Latypova; Kursanov *J. Org. Chem. USSR* **1981**, 17, 1203.

¹³⁰⁴Reetz; Westermann; Steinbach *Angew. Chem. Int. Ed. Engl.* **1980**, 19, 900, 901 [*Angew. Chem.* 92, 931, 933].

¹³⁰⁵Reetz; Steinbach; Wenderoth *Synth. Commun.* **1982**, 11, 261.

¹³⁰⁶Lynd; Zweifel *Synthesis* **1974**, 658; Matsushita; Negishi *J. Am. Chem. Soc.* **1981**, 103, 2882; *J. Chem. Soc., Chem. Commun.* **1982**, 160. For similar reactions with other metals, see Larock; Bernhardt; Driggs *J. Organomet. Chem.* **1978**, 156, 45; Yoshida; Tamao; Takahashi; Kumada *Tetrahedron Lett.* **1978**, 2161; Brown; Campbell *J. Org. Chem.* **1980**, 45, 550; Baeckström; Björklund; Högberg; Norin *Acta Chem. Scand., Ser. B* **1984**, 38, 779.

¹³⁰⁷Negishi *Acc. Chem. Res.* **1982**, 15, 340-348; Negishi; Luo *J. Org. Chem.* **1983**, 48, 1560; Negishi; Takahashi; Baba; Van Horn; Okukado *J. Am. Chem. Soc.* **1987**, 109, 2393; Negishi; Takahashi; Baba *Org. Synth.* 66, 60.

¹³⁰⁸Heck *J. Am. Chem. Soc.* **1968**, 90, 5531. For a review of palladium-assisted coupling, see Heck *Palladium Reagents in Organic Syntheses*; Academic Press: New York, 1985, pp. 208-214, 242-249.

¹³⁰⁹For a review, see Stille *Angew. Chem. Int. Ed. Engl.* **1986**, 25, 508-524 [*Angew. Chem.* 98, 504-519]. See also Stille; Simpson *J. Am. Chem. Soc.* **1987**, 109, 2138; Bumagin; Andryukhova; Beletskaya *Doklad. Chem.* **1989**, 307, 211; Stork; Isaacs *J. Am. Chem. Soc.* **1990**, 112, 7399; Laborde; Lesheski; Kiely *Tetrahedron Lett.* **1990**, 31, 1837. For a review of the mechanism, see Bumagin; Beletskaya *Russ. Chem. Rev.* **1990**, 59, 1174-1184.

¹³¹⁰Hatanaka; Hiyama *J. Org. Chem.* **1988**, 53, 918, **1989**, 54, 268.

¹³¹¹Brown; Molander *J. Org. Chem.* **1981**, 46, 645; Miyaura; Yamada; Sugimoto; Suzuki *J. Am. Chem. Soc.* **1985**, 107, 972; Sato; Miyaura; Suzuki *Chem. Lett.* **1989**, 1405; Rivera; Soderquist *Tetrahedron Lett.* **1991**, 32, 2311; and references cited in these papers. For a review, see Matteson *Tetrahedron* **1989**, 45, 1859-1885.

¹³¹²Miyaura; Ishiyama; Sasaki; Ishikawa; Satoh; Suzuki *J. Am. Chem. Soc.* **1989**, 111, 314. See also Soderquist; Santiago *Tetrahedron Lett.* **1990**, 31, 5541.

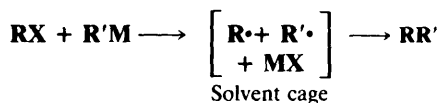
¹³¹³Brown; Joshi; Pyun; Singaram *J. Am. Chem. Soc.* **1989**, 111, 1754. For another such coupling, see Matteson; Tripathy; Sarkar; Sadhu *J. Am. Chem. Soc.* **1989**, 111, 4399.

¹³¹⁴Nédélec; Ait Haddou Mouloud; Folest; Périchon *J. Am. Chem. Soc.* **1988**, 53, 4720.

¹³¹⁵For the transformation $\text{RX} \rightarrow \text{RCF}_3$, see Chen; Wu *J. Chem. Soc., Chem. Commun.* **1989**, 705.

¹³¹⁶For a review, see Beletskaya; Artamkina; Reutov *Russ. Chem. Rev.* **1976**, 45, 330-347.

sioned: a nucleophilic substitution process (which might be S_N1 or S_N2) and a free-radical mechanism. This could be an SET pathway, or some other route that provides radicals. In either case the two radicals $R\cdot$ and $R'\cdot$ would be in a solvent cage:



It is necessary to postulate the solvent cage because, if the radicals were completely free, the products would be about 50% RR' , 25% RR , and 25% $R'R'$. This is generally not the case; in most of these reactions RR' is the predominant or exclusive product.¹³¹⁷ An example where an S_N2 mechanism has been demonstrated (by the finding of inversion of configuration at R) is the reaction between allylic or benzylic lithium reagents with secondary halides.¹³¹⁸ Similarly, inversion has been shown in the reaction of 2-bromobutane with Ph_2CuLi ¹²⁷⁴ (though the same reaction with 2-iodobutane has been reported to proceed with racemization¹³¹⁹). The fact that in some of these cases the reaction can be successfully applied to aryl and vinylic substrates indicates that a simple S_N process cannot be the only mechanism. One possibility is that the reagents first undergo an exchange reaction: $ArX + RM \rightarrow RX + ArM$, and then a nucleophilic substitution takes place. On the other hand, there is much evidence that many coupling reactions involving organometallic reagents with simple alkyl groups occur by free-radical mechanisms. Among the evidence¹³²⁰ is the observation of CIDNP in reactions of alkyl halides with simple organolithium reagents¹³²¹ (see p. 187), the detection of free radicals by esr spectroscopy¹³²² (p. 186), and the formation of 2,3-dimethyl-2,3-diphenylbutane when the reaction was carried out in the presence of cumene¹³²³ (this product is formed when a free radical abstracts a hydrogen from cumene to give $Ph\dot{C}Me_2$, which dimerizes). Evidence for free-radical mechanisms has also been found for the coupling of alkyl halides with simple organosodium compounds (Wurtz),¹³²⁴ with Grignard reagents,¹³²⁵ and with lithium dialkylcopper reagents.¹³²⁶ Free radicals have also been implicated in the metal-ion-catalyzed coupling of alkyl and aryl halides with Grignard reagents.¹³²⁷

For symmetrical coupling of organometallic reagents ($2RM \rightarrow RR$), see 4-33 to 4-35.

OS I, 186; III, 121; IV, 748; V, 1092; VI, 407, 675; VII, 77, 172, 245, 326, 485; 66, 60; 68, 130, 162; 69, 120.

¹³¹⁷When a symmetrical distribution of products is found, this is evidence for a free-radical mechanism: the solvent cage is not efficient and breaks down.

¹³¹⁸Sauer; Braig *Tetrahedron Lett.* **1969**, 4275; Sommer; Korte *J. Org. Chem.* **1970**, 35, 22; Korte; Kinner; Kaska *Tetrahedron Lett.* **1970**, 603. See also Schlosser; Fouquet *Chem. Ber.* **1974**, 107, 1162, 1171.

¹³¹⁹Lipshutz; Wilhelm *J. Am. Chem. Soc.* **1982**, 104, 4696; Lipshutz; Wilhelm; Nugent; Little; Baizer *J. Org. Chem.* **1983**, 48, 3306.

¹³²⁰For other evidence, see Muraoka; Nojima; Kusabayashi; Nagase *J. Chem. Soc., Perkin Trans. 2* **1986**, 761.

¹³²¹Ward; Lawler; Cooper *J. Am. Chem. Soc.* **1969**, 91, 746; Lepley; Landau *J. Am. Chem. Soc.* **1969**, 91, 748; Podoplelov; Leshina; Sagdeev; Kamkha; Shein *J. Org. Chem. USSR* **1976**, 12, 488. For a review, see Ward; Lawler; Cooper, in Lepley; Closs *Chemically Induced Magnetic Polarization*; Wiley: New York, 1973, pp. 281-322.

¹³²²Russell; Lamson *J. Am. Chem. Soc.* **1969**, 91, 3967.

¹³²³Bryce-Smith *Bull. Soc. Chim. Fr.* **1963**, 1418.

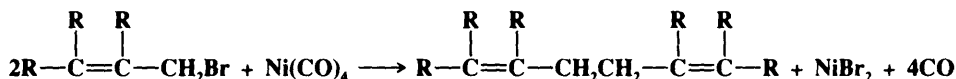
¹³²⁴Garst; Cox *J. Am. Chem. Soc.* **1970**, 92, 6389; Kasukhin; Gragerov *J. Org. Chem. USSR* **1971**, 7, 2087; Garst; Hart *J. Chem. Soc., Chem. Commun.* **1975**, 215.

¹³²⁵Gough; Dixon *J. Org. Chem.* **1968**, 33, 2148; Ward; Lawler; Marzilli *Tetrahedron Lett.* **1970**, 521; Kasukhin; Ponomarchuk; Buteiko *J. Org. Chem. USSR* **1972**, 8, 673; Singh; Tayal; Nigam *J. Organomet. Chem.* **1972**, 42, C9.

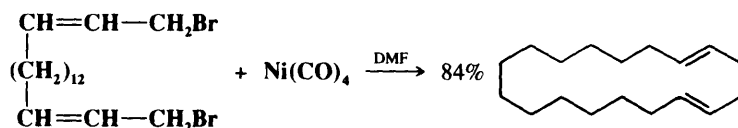
¹³²⁶Ashby; DePriest; Tuncay; Srivastava *Tetrahedron Lett.* **1982**, 23, 5251; Ashby; Coleman *J. Org. Chem.* **1987**, 52, 4554; Bertz; Dabbagh; Muijce *J. Am. Chem. Soc.* **1991**, 113, 631.

¹³²⁷Norman; Waters *J. Chem. Soc.* **1957**, 950; Frey *J. Org. Chem.* **1961**, 26, 5187; Slauch *J. Am. Chem. Soc.* **1961**, 83, 2734; Davies; Done; Hey *J. Chem. Soc. C* **1969**, 1392, 2021, 2056; Abraham; Hogarth *J. Organomet. Chem.* **1968**, 12, 1, 497; Tamura; Kochi *J. Am. Chem. Soc.* **1971**, 93, 1483, 1485, 1487, *J. Organomet. Chem.* **1971**, 31, 289, **1972**, 42, 205; Lehr; Lawler *J. Am. Chem. Soc.* **1986**, 106, 4048.

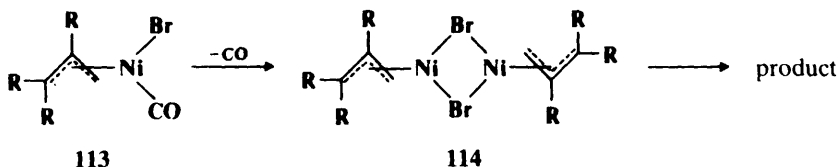
0-88 Allylic and Propargylic Coupling with a Halide Substrate De-halogen-coupling



Because of the presence of the 1,5-diene moiety in many naturally occurring compounds, a great deal of effort has been expended in searching for methods to couple¹³²⁸ allylic groups.¹³²⁹ In one of these methods, allylic halides, tosylates, and acetates can be symmetrically coupled by treatment with nickel carbonyl¹³³⁰ at room temperature in a solvent such as THF or DMF to give 1,5-dienes.¹³³¹ The order of halide reactivity is $\text{I} > \text{Br} > \text{Cl}$. With unsymmetrical allylic substrates, coupling nearly always takes place at the less-substituted end. The reaction can be performed intramolecularly; large (11- to 20-membered) rings can be made in good yields (60 to 80%) by the use of high dilution. An example¹³³² is

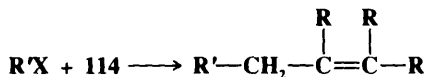


It is likely that the mechanism involves reaction of the allylic compound with $\text{Ni}(\text{CO})_4$ to give one or more π -allyl complexes, one of which may be **113**, which can then lose CO to



give a π -allylnickel bromide (**114**) which reacts further, perhaps with CO, to give the product. The complexes **114** can be isolated from the solution and crystallized as stable solids.

Unsymmetrical coupling can be achieved by treating an alkyl halide directly with **114**, in a polar aprotic solvent.¹³³³ In this case too, unsymmetrical allylic groups couple at the less



¹³²⁸For a review of some allylic coupling reactions, see Magid *Tetrahedron* **1980**, *36*, 1901-1930, pp. 1910-1924.

¹³²⁹In this section are discussed methods in which one molecule is a halide. For other allylic coupling reactions, see **0-87**, **0-90**, and **0-91**.

¹³³⁰For a review of the use of organonickel compounds in organic synthesis, see Tamao; Kumada, in Hartley, Ref. 1287, pp. 819-887.

¹³³¹For reviews, see Collman et al., Ref. 1266, pp. 739-748; Billington *Chem. Soc. Rev.* **1985**, *14*, 93-120; Kochi, Ref. 1077, pp. 398-408; Semmelhack *Org. React.* **1972**, *19*, 115-198, pp. 162-170; Baker *Chem. Rev.* **1973**, *73*, 487-530, pp. 512-517; Heimbach; Jolly; Wilke *Adv. Organomet. Chem.* **1970**, *8*, 29-86, pp. 30-39.

¹³³²Corey; Wat *J. Am. Chem. Soc.* **1967**, *89*, 2757. See also Corey; Helquist *Tetrahedron Lett.* **1975**, 4091; Reijnders; Blankert; Buck *Recl. Trav. Chim. Pays-Bas* **1978**, *97*, 30.

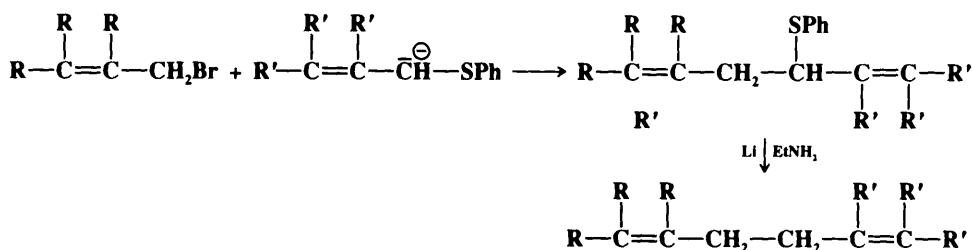
¹³³³Corey; Semmelhack *J. Am. Chem. Soc.* **1967**, *89*, 2755. For a review, see Semmelhack, Ref. 1331, pp. 147-162. For a discussion of the preparation and handling of π -allylnickel halides, see Semmelhack, Ref. 1331, pp. 144-146.

substituted end. The mechanism here cannot be simple nucleophilic substitution, since aryl and vinylic halides undergo the reaction as well as or better than simple primary bromides. There is evidence that free radicals are involved.¹³³⁴ Hydroxy or carbonyl groups in the alkyl halide do not interfere. When **114** reacts with an allylic halide, a mixture of three products is obtained because of halogen-metal interchange. For example, allyl bromide treated with **114** prepared from methallyl bromide gave an approximately statistical mixture of 1,5-hexadiene, 2-methyl-1,5-hexadiene, and 2,5-dimethyl-1,5-hexadiene.¹³³⁵

The reaction between primary and secondary halides and allyltributylstannane provides another method for unsymmetrical coupling $RX + CH_2=CHCH_2SnBu_3 \rightarrow RCH_2CH=CH_2$.¹³³⁶

Symmetrical coupling of allylic halides can also be accomplished by heating with magnesium in ether,¹³³⁷ with a cuprous iodide-dialkylamide complex,¹³³⁸ with $CrCl_3-LiAlH_4$,¹³³⁹ with Te^{2-} ions,¹³⁴⁰ with ion powder in DMF,¹³⁴¹ or electrochemically.¹³⁴² The coupling of two different allylic groups has been achieved by treatment of an allylic bromide with an allylic Grignard reagent in THF containing HMPA,¹³⁴³ or with an allylic tin reagent.¹³⁴⁴ This type of coupling can be achieved with almost no allylic rearrangement in the substrate (and almost complete allylic rearrangement in the reagent) by treatment of allylic halides with lithium allylic boron ate complexes $(RCH=CHCH_2BR'_3 Li^+)$.¹³⁴⁵

In another method for the coupling of two different allylic groups,¹³⁴⁶ a carbanion derived from a β,γ -unsaturated thioether couples with an allylic halide.¹³⁴⁷ The product contains an SPh group that must be removed (with Li in ethylamine) to give the 1,5-diene, but this



method has the advantage that, unlike most of the methods previously discussed, the coupling preserves the original positions and configurations of the two double bonds; no allylic rearrangements take place.

¹³³⁴Hegedus; Thompson *J. Am. Chem. Soc.* **1985**, 107, 5663.

¹³³⁵Corey; Semmelhack; Hegedus *J. Am. Chem. Soc.* **1968**, 90, 2416.

¹³³⁶See Keck; Yates *J. Am. Chem. Soc.* **1982**, 104, 5829; Migita; Nagai; Kosugi *Bull. Chem. Soc. Jpn* **1983**, 56, 2480.

¹³³⁷Turk; Chanan *Org. Synth.* **III**, 121.

¹³³⁸Kitagawa; Oshima; Yamamoto; Nozaki *Tetrahedron Lett.* **1975**, 1859.

¹³³⁹Okude; Hiyama; Nozaki *Tetrahedron Lett.* **1977**, 3829.

¹³⁴⁰Clive; Anderson; Moss; Singh *J. Org. Chem.* **1982**, 47, 1641.

¹³⁴¹Hall; Hurley *Can. J. Chem.* **1969**, 47, 1238.

¹³⁴²Tokuda; Endate; Sugimoto *Chem. Lett.* **1988**, 945.

¹³⁴³Stork; Grieco; Gregson *Tetrahedron Lett.* **1969**, 1393; Grieco *J. Am. Chem. Soc.* **1969**, 91, 5660.

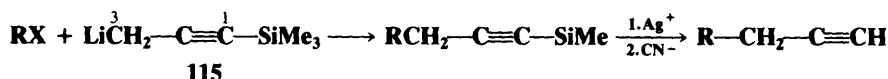
¹³⁴⁴Godschalk; Stille *Tetrahedron Lett.* **1980**, 21, 2599; **1983**, 24, 1905; Hosomi; Imai; Endo; Sakurai *J. Organomet. Chem.* **1985**, 285, 95. See also Yanagisawa; Norikate; Yamamoto *Chem. Lett.* **1988**, 1899.

¹³⁴⁵Yamamoto; Yatagai; Maruyama *J. Am. Chem. Soc.* **1981**, 103, 1969.

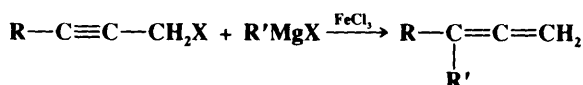
¹³⁴⁶For other procedures, see Axelrod; Milne; van Tamelen *J. Am. Chem. Soc.* **1970**, 92, 2139; Morizawa; Kanemoto; Oshima; Nozaki *Tetrahedron Lett.* **1982**, 23, 2953.

¹³⁴⁷Biellmann; Ducep *Tetrahedron Lett.* **1969**, 3707.

In a method for propargylating an alkyl halide without allylic rearrangement, the halide is treated with lithio-1-trimethylsilylpropyne (**115**) which is a lithium compound protected



by an SiMe₃ group.¹³⁴⁸ Attack by the ambident nucleophile at its 1 position (which gives an allene) takes place only to a small extent, because of steric blockage by the large SiMe₃ group. The SiMe₃ group is easily removed by treatment with Ag⁺ followed by CN⁻. **115** is prepared by treating propynyllithium with Me₃SiCl to give MeC≡CSiMe₃ from which a proton is removed with BuLi. R may be primary or allylic.¹³⁴⁹ On the other hand, propargylic halides can be alkylated with essentially complete allylic rearrangement, to give allenes, by treatment with Grignard reagents and metallic salts,¹³⁵⁰ or with dialkylcuprates R₂Cu.¹³⁵¹



OS III, 121; IV, 748; VI, 722.

0-89 Coupling of Organometallic Reagents with Esters of Sulfuric and Sulfonic Acids
Alkyl-de-sulfonyloxy-substitution, etc.



Lithium dialkylcopper reagents couple with alkyl tosylates.¹³⁵² High yields are obtained with primary tosylates; secondary tosylates give lower yields.¹³⁵³ Aryl tosylates do not react. Vinylic triflates¹³⁵⁴ couple very well to give alkenes.¹³⁵⁵ Vinylic triflates also couple with allylic cuprates, to give 1,4-dienes.¹³⁵⁶ Tosylates and other sulfonates and sulfates also couple with Grignard reagents,¹³⁵⁷ most often those prepared from aryl or benzylic halides.¹³⁵⁸ Alkyl sulfates and sulfonates generally make better substrates in reactions with Grignard reagents than the corresponding halides (**0-87**). The method is useful for primary and secondary R. Allylic tosylates can be symmetrically coupled with Ni(CO)₄ (see **0-88**). Propargylic tosylates couple with vinylic cuprates to give vinylic allenes.¹³⁵⁹ Vinylic triflates, in the presence of Pd(Ph₃P)₄ and LiCl, couple with organotin compounds R'SnMe₃, where R' can be alkyl,

¹³⁴⁸Corey; Kirst; Katzenellenbogen *J. Am. Chem. Soc.* **1970**, 92, 6314.

¹³⁴⁹For an alternative procedure, see Ireland; Dawson; Lipinski *Tetrahedron Lett.* **1970**, 2247.

¹³⁵⁰Pasto; Chou; Waterhouse; Shults; Hennion *J. Org. Chem.* **1978**, 43, 1385; Jeffery-Luong; Linstrumelle *Tetrahedron Lett.* **1980**, 21, 5019.

¹³⁵¹Pasto; Chou; Fritzen; Shults; Waterhouse; Hennion *J. Org. Chem.* **1978**, 43, 1389. See also Tanigawa; Murahashi *J. Org. Chem.* **1980**, 45, 4536.

¹³⁵²Johnson; Dutra *J. Am. Chem. Soc.* **1973**, 95, 7777, 7783. For examples, see Posner *An Introduction to Synthesis Using Organocopper Reagents*. Ref. 1268, pp. 85-90.

¹³⁵³Secondary tosylates give higher yields when they contain an O or S atom: Hanessian; Thavonekham; DeHoff *J. Org. Chem.* **1989**, 54, 5831.

¹³⁵⁴For a review of coupling reactions of vinylic triflates, see Scott; McMurry *Acc. Chem. Res.* **1988**, 21, 47-54.

¹³⁵⁵McMurry; Scott *Tetrahedron Lett.* **1980**, 21, 4313; Tsushima; Araki; Murai *Chem. Lett.* **1989**, 1313.

¹³⁵⁶Lipshutz; Elworthy *J. Org. Chem.* **1990**, 55, 1695.

¹³⁵⁷For a review, see Kharasch; Reinmuth. Ref. 1287, pp. 1277-1286.

¹³⁵⁸For an example involving an allylic rearrangement (conversion of a silylalkyne to a silyllallene), see Danheiser; Tsai; Fink *Org. Synth.* 66, 1.

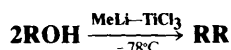
¹³⁵⁹Baudouy; Goré *J. Chem. Res. (S)* **1981**, 278. See also Elsevier; Vermeer *J. Org. Chem.* **1989**, 54, 3726.

allylic, vinylic, or alkynyl.¹³⁶⁰ The reaction has been performed intramolecularly, to prepare large-ring lactones.¹³⁶¹

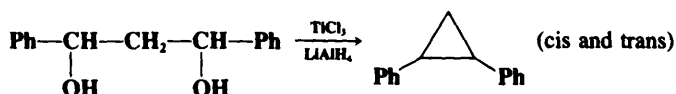
OS I, 471; II, 47, 360; VII, 351; 66, 1; 68, 116.

0-90 Coupling Involving Alcohols

De-hydroxyl-coupling



Allylic or benzylic alcohols can be symmetrically coupled¹³⁶² by treatment with methyllithium and titanium trichloride at -78°C ¹³⁶³ or by refluxing with TiCl_3 and LiAlH_4 .¹³⁶⁴ When the substrate is an allylic alcohol, the reaction is not regiospecific, but a mixture of normal coupling and allylically rearranged products is found. A free-radical mechanism is involved.¹³⁶⁵ Another reagent that symmetrically couples allylic and benzylic alcohols is NbCl_5 - NaAlH_4 .¹³⁶⁶ The TiCl_3 - LiAlH_4 reagent can also convert 1,3-diols to cyclopropanes, provided that at least one α phenyl is present,¹³⁶⁷ e.g.,



Tertiary alcohols react with trimethylaluminum at 80 to 200°C to give methylation.¹³⁶⁸ The presence of side products from elimination and rearrangement, as well as the lack of



stereospecificity,¹³⁶⁹ indicate an $\text{S}_\text{N}1$ mechanism. The reaction can also be applied to primary and secondary alcohols if these contain an aryl group in the α position. Higher trialkylaluminums are far less suitable, because reduction competes with alkylation (see also reactions of Me_3Al with ketones, 6-29, and with carboxylic acids, 6-32). Me_2TiCl_2 also reacts with tertiary alcohols in the same way.¹³⁷⁰ Allylic alcohols couple with a reagent prepared from MeLi , CuI , and $\text{R}'\text{Li}$ in the presence of $(\text{Ph}_3\text{PNMePh})^+ \text{I}^-$ to give alkenes that are products of allylic rearrangement.¹³⁷¹ The reaction gives good yields with primary, secondary, and

¹³⁶⁰Scott; Stille *J. Am. Chem. Soc.* **1986**, *108*, 3033; Kwon; McKee; Stille *J. Org. Chem.* **1990**, *55*, 3114. For discussions of the mechanism, see Stang; Kowalski; Schiavelli; Longford *J. Am. Chem. Soc.* **1989**, *111*, 3347; Stang; Kowalski *J. Am. Chem. Soc.* **1989**, *111*, 3356.

¹³⁶¹Stille; Tanaka *J. Am. Chem. Soc.* **1987**, *109*, 3785.

¹³⁶²For a review, see Lai *Org. Prep. Proceed. Int.* **1980**, *12*, 363-391, pp. 377-388.

¹³⁶³Sharpless; Hanzlik; van Tamelen *J. Am. Chem. Soc.* **1968**, *90*, 209.

¹³⁶⁴McMurry; Silvestri; Fleming; Hoz; Grayston *J. Org. Chem.* **1978**, *43*, 3249. For another method, see Nakanishi; Shundo; Nishibuchi; Otsuji *Chem. Lett.* **1979**, 955.

¹³⁶⁵van Tamelen; Åkermark; Sharpless *J. Am. Chem. Soc.* **1969**, *91*, 1552.

¹³⁶⁶Sato; Oshima *Chem. Lett.* **1982**, 157. For a reagent that couples benzhydrols, see Pri-Bar; Buchman; Blum *Tetrahedron Lett.* **1977**, 1443.

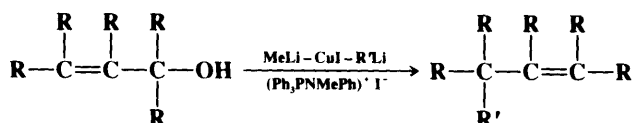
¹³⁶⁷Baumstark; McCloskey; Tolson; Syriopoulos *Tetrahedron Lett.* **1977**, 3003; Walborsky; Murati *J. Am. Chem. Soc.* **1980**, *102*, 426.

¹³⁶⁸Meisters; Mole *J. Chem. Soc., Chem. Commun.* **1972**, 595; Harney; Meisters; Mole *Aust. J. Chem.* **1974**, *27*, 1639.

¹³⁶⁹Salomon; Kochi *J. Org. Chem.* **1973**, *38*, 3715.

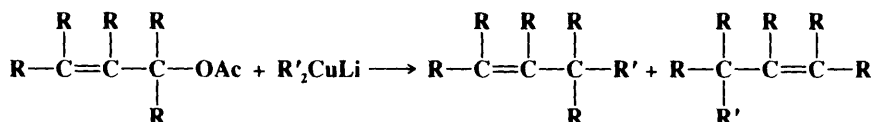
¹³⁷⁰Rectz; Westermann; Steinbach *J. Chem. Soc., Chem. Commun.* **1981**, 237.

¹³⁷¹Tanigawa; Ohta; Sonoda; Murahashi *J. Am. Chem. Soc.* **1978**, *100*, 4610; Goering; Tseng *J. Org. Chem.* **1985**, *50*, 1597. For another procedure, see Yamamoto; Maruyama *J. Organomet. Chem.* **1978**, *156*, C9.



tertiary alcohols, and with alkyl and aryllithiums.¹³⁷² Allylic alcohols also couple with certain Grignard reagents¹³⁷³ in the presence of a nickel complex to give both normal products and the products of allylic rearrangement.

0-91 Coupling of Organometallic Reagents with Carboxylic Esters Alkyl-de-acyloxy-substitution



Lithium dialkylcopper reagents couple with allylic acetates to give normal coupling products or those resulting from allylic rearrangement, depending on the substrate.¹³⁷⁴ A mechanism involving a σ -allylic copper(III) complex has been suggested.¹³⁷⁵ With propargyl substrates, the products are allenes.¹³⁷⁶ Allenes are also obtained when propargyl acetates are treated



with methylmagnesium iodide.¹³⁷⁷ Lithium dialkylcopper reagents also give normal coupling products with enol acetates of β -dicarbonyl compounds.¹³⁷⁸ It is also possible to carry out the coupling of allylic acetates with Grignard reagents, if catalytic amounts of cuprous salts are present.¹³⁷⁹ With this method yields are better and regioselectivity can be controlled by a choice of cuprous salts. Allylic, benzylic, and cyclopropylmethyl acetates couple with trialkylaluminums,¹³⁸⁰ and allylic acetates couple with aryl and vinylic tin reagents, in the presence of a palladium-complex catalyst.¹³⁸¹ Allylic acetates can be symmetrically

¹³⁷²For the allylation of benzylic alcohols, see Cella *J. Org. Chem.* **1982**, 47, 2125.

¹³⁷³Buckwalter; Burfitt; Felkin; Joly-Goudket; Naemura; Salomon; Wenkert; Wovkulich *J. Am. Chem. Soc.* **1978**, 100, 6445; Felkin; Joly-Goudket; Davies *Tetrahedron Lett.* **1981**, 22, 1157; Consiglio; Morandini; Piccolo *J. Am. Chem. Soc.* **1981**, 103, 1846, and references cited in these papers. For a review, see Felkin; Swierczewski *Tetrahedron* **1975**, 31, 2735-2748. For other procedures, see Mukaiyama; Imaoka; Izawa *Chem. Lett.* **1977**, 1257; Fujisawa; Iida; Yukizaki; Sato *Tetrahedron Lett.* **1983**, 24, 5745.

¹³⁷⁴Rona; Tokes; Tremble; Crabbé *Chem. Commun.* **1969**, 43; Anderson; Henrick; Siddall *J. Am. Chem. Soc.* **1970**, 92, 735; Goering; Singleton *J. Am. Chem. Soc.* **1976**, 98, 7854; Gallina; Ciattini *J. Am. Chem. Soc.* **1979**, 101, 1035; Goering; Kantner *J. Org. Chem.* **1984**, 49, 422. For examples of the use of this reaction with allylic and propargyl substrates, see Posner. Ref. 1352, pp. 91-104.

¹³⁷⁵Goering; Kantner *J. Org. Chem.* **1983**, 48, 721; Goering; Kantner; Seitz *J. Org. Chem.* **1985**, 50, 5495.

¹³⁷⁶Crabbé; Barreiro; Dollat; Luche *J. Chem. Soc., Chem. Commun.* **1976**, 183, and references cited therein.

¹³⁷⁷Roumestant; Gore *Bull. Soc. Chim. Fr.* **1972**, 591, 598.

¹³⁷⁸Casey; Marten *Synth. Commun.* **1973**, 3, 321, *Tetrahedron Lett.* **1974**, 925. See also Posner; Brunelle *J. Chem. Soc., Chem. Commun.* **1973**, 907; Kobayashi; Takei; Mukaiyama *Chem. Lett.* **1973**, 1097.

¹³⁷⁹Tseng; Paisley; Goering *J. Org. Chem.* **1986**, 51, 2884; Tseng; Yen; Goering *J. Org. Chem.* **1986**, 51, 2892; Underiner; Paisley; Schmitter; Lesheski; Goering *J. Org. Chem.* **1989**, 54, 2369; Bäckvall; Sellén; Grant *J. Am. Chem. Soc.* **1990**, 112, 6615. See also Hiyama; Wakasa *Tetrahedron Lett.* **1985**, 26, 3259.

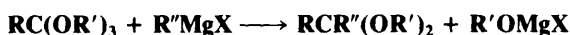
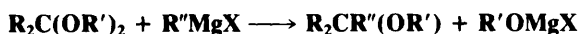
¹³⁸⁰Itoh; Oshima; Sasaki; Yamamoto; Hiyama; Nozaki *Tetrahedron Lett.* **1979**, 4751; Gallina *Tetrahedron Lett.* **1985**, 26, 519; Tolstikov; Dzhemilev *J. Organomet. Chem.* **1985**, 292, 133.

¹³⁸¹Del Valle; Stille; Hegedus *J. Org. Chem.* **1990**, 55, 3019. For another method, see Legros; Fiaud *Tetrahedron Lett.* **1990**, 31, 7453.

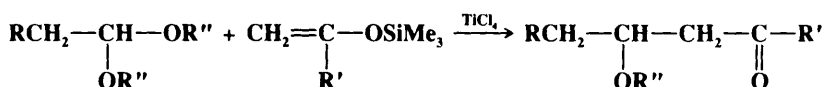
coupled by treatment with $\text{Ni}(\text{CO})_4$ (reaction 0-88) or with Zn and a palladium-complex catalyst,¹³⁸² or converted to unsymmetrical 1,5-dienes by treatment with an allylic stannane $\text{R}_2\text{C}=\text{CHCH}_2\text{SnR}_3$ in the presence of a palladium complex.¹³⁸³

0-92 Coupling of Organometallic Reagents with Compounds Containing the Ether Linkage¹³⁸⁴

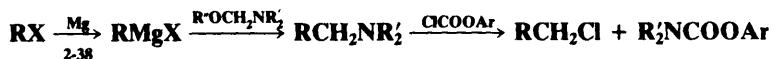
Alkyl-de-alkoxy-substitution



Acetals,¹³⁸⁵ ketals, and ortho esters¹³⁸⁶ react with Grignard reagents to give, respectively, ethers and acetals (or ketals). The latter can be hydrolyzed to aldehydes or ketones (0-6). This procedure is a way of converting a halide $\text{R}''\text{X}$ (which may be alkyl, aryl, vinylic, or alkynyl) to an aldehyde $\text{R}''\text{CHO}$, increasing the length of the carbon chain by one carbon (see also 0-102). The ketone synthesis generally gives lower yields. Acetals, including allylic acetals, also give this reaction with organocopper compounds and BF_3 .¹³⁸⁷ Acetals also undergo substitution when treated with silyl enol ethers or allylic silanes, with a Lewis acid catalyst,¹³⁸⁸ e.g.,



Tertiary amines can be prepared by the reaction of amino ethers with Grignard reagents,¹³⁸⁹ ($\text{R}_2\text{NCH}_2-\text{OR}' + \text{R}''\text{MgX} \rightarrow \text{R}_2\text{NCH}_2-\text{R}''$) or with lithium dialkylcopper reagents.¹³⁹⁰ This method, when followed by treatment of the amine with a chloroformate (see 0-72) allows an alkyl halide RX to be converted to its homolog RCH_2X in only two laboratory steps¹³⁹¹ (see also p. 476):



Ordinary ethers are not cleaved by Grignard reagents (in fact, diethyl ether and THF are the most common solvents for Grignard reagents), though more active organometallic compounds often do cleave them.¹³⁹² Allylic ethers can be cleaved by Grignard reagents in

¹³⁸²Sasaoka; Yamamoto; Kinoshita; Inomata; Kotake *Chem. Lett.* **1985**, 315.

¹³⁸³Trost; Keinan *Tetrahedron Lett.* **1980**, 21, 2595.

¹³⁸⁴For a review, see Trofimov; Korostova *Russ. Chem. Rev.* **1975**, 44, 41-55.

¹³⁸⁵For a review of coupling reactions of acetals, see Mukaiyama; Murakami *Synthesis* **1987**, 1043-1054. For a discussion of the mechanism, see Abell; Massy-Westropp *Aust. J. Chem.* **1985**, 38, 1031. For a list of substrates and reagents, with references, see Ref. 508, pp. 404-405.

¹³⁸⁶For a review of the reaction with ortho esters, see DeWolfe, Ref. 457, pp. 44-45, 224-230.

¹³⁸⁷Normant; Alexakis; Ghribi; Mangeney *Tetrahedron* **1989**, 45, 507; Alexakis; Mangeney; Ghribi; Marek; Sedrani; Guir; Normant *Pure Appl. Chem.* **1988**, 60, 49-56.

¹³⁸⁸See Mori; Ishihara; Flippen; Nozaki; Yamamoto; Bartlett; Heathcock *J. Org. Chem.* **1990**, 55, 6107, and references cited therein.

¹³⁸⁹For example, see Miginiac; Mauzé *Bull. Soc. Chim. Fr.* **1968**, 2544; Eisele; Simchen *Synthesis* **1978**, 757; Kapnang; Charles *Tetrahedron Lett.* **1983**, 24, 1597; Morimoto; Takahashi; Sekiya *J. Chem. Soc., Chem. Commun.* **1984**, 794; Mesnard; Miginiac *J. Organomet. Chem.* **1989**, 373, 1. See also Bourhis; Bosc; Golse *J. Organomet. Chem.* **1983**, 256, 193.

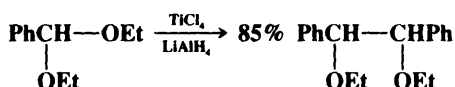
¹³⁹⁰Germon; Alexakis; Normant *Bull. Soc. Chim. Fr.* **1984**, 11-377.

¹³⁹¹Yankee; Charles *Tetrahedron Lett.* **1987**, 28, 427.

¹³⁹²For a review of the reactions of ethers with Grignard reagents, see Kharasch; Reinmuth, Ref. 1287, pp. 1013-1045.

THF if CuBr is present.¹³⁹³ The reaction takes place either with or without allylic rearrangement.¹³⁹⁴ Propargylic ethers give allenes.¹³⁹⁵ Vinylic ethers can also be cleaved by Grignard reagents in the presence of a catalyst, in this case, a nickel complex.¹³⁹⁶ Silyl enol ethers $R_2C=CROSiMe_3$ behave similarly.¹³⁹⁷

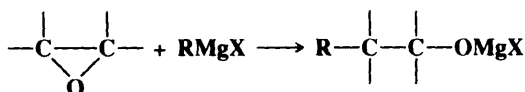
Certain acetals and ketals can be dimerized in a reaction similar to **0-86** by treatment with $TiCl_4$ - $LiAlH_4$, e.g.,¹³⁹⁸



Also see **0-93**.

OS II, 323; III, 701. Also see OS V, 431.

0-93 The Reaction of Organometallic Reagents with Epoxides **3(OC)-seco-Alkyl-de-alkoxy-substitution**



The reaction between Grignard reagents and epoxides is very valuable and is often used to increase the length of a carbon chain by two carbons.¹³⁹⁹ The Grignard reagent may be aromatic or aliphatic, though tertiary Grignard reagents give low yields. As expected for an S_N2 process, attack is at the less substituted carbon. Lithium dialkylcopper reagents also give the reaction,¹⁴⁰⁰ often producing higher yields, and have the additional advantage that they do not react with ester, ketone, or carboxyl groups so that the epoxide ring of epoxy esters, ketones, and carboxylic acids can be selectively attacked, often in a regioselective manner.¹⁴⁰¹ The use of BF_3 increases the reactivity of R_2CuLi , enabling it to be used with thermally unstable epoxides.¹⁴⁰² The reaction has also been performed with other organometallic compounds, e.g., of Li, Al, etc.¹⁴⁰³

¹³⁹³Commercon; Bourgain; Delaumeny; Normant; Villieras *Tetrahedron Lett.* **1975**, 3837; Claesson; Olsson *Chem. Soc., Chem. Commun.* **1987**, 621.

¹³⁹⁴Normant; Commercon; Gendreau; Bourgain; Villieras *Bull. Soc. Chim. Fr.* **1979**, II-309; Gendreau; Normant *Tetrahedron* **1979**, 35, 1517; Calo; Lopez; Pesce *J. Chem. Soc., Perkin Trans. I* **1988**, 1301. See also Valverde; Bernabé; García-Ochoa; Gómez *J. Org. Chem.* **1990**, 55, 2294.

¹³⁹⁵Alexakis; Marek; Mangeney; Normant *Tetrahedron Lett.* **1989**, 30, 2387; *J. Am. Chem. Soc.* **1990**, 112, 8042.

¹³⁹⁶Wenkert; Michelotti; Swindell; Tingoli *J. Org. Chem.* **1984**, 49, 4894; Kociński; Dixon; Wadman *Tetrahedron Lett.* **1988**, 29, 2353.

¹³⁹⁷Hayashi; Katsuro; Kumada *Tetrahedron Lett.* **1980**, 21, 3915.

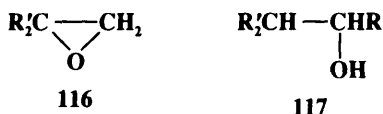
¹³⁹⁸Ishikawa; Mukaiyama *Bull. Chem. Soc. Jpn.* **1978**, 51, 2059.

¹³⁹⁹For a review, see Kharasch; Reinmuth, Ref. 1287, pp. 961-1012. For a thorough discussion, see Schaap; Arens *Recl. Trav. Chim. Pays-Bas* **1968**, 87, 1249. For improved procedures, see Huynh; Derguini-Boumechal; Linstrumelle *Tetrahedron Lett.* **1979**, 1503; Schrupf; Grätz; Meinecke; Fellenberger *J. Chem. Res. (S)* **1982**, 162.

¹⁴⁰⁰For examples of the use of this reactions, see Posner, Ref. 1352, pp. 103-113. See also Lipshutz; Kozłowski; Wilhelm *J. Am. Chem. Soc.* **1982**, 104, 2305.

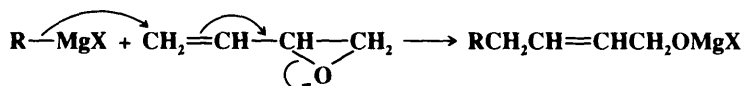
¹⁴⁰¹Johnson; Herr; Wieland *J. Org. Chem.* **1973**, 38, 4263; Hartman; Livinghouse; Rickborn *J. Org. Chem.* **1973**, 38, 4246; Hedelike; Bateman; Bann *J. Org. Chem.* **1975**, 40, 2262; Chono; Shimizu *Tetrahedron Lett.* **1985**, 26, 4682.

When *gem*-disubstituted epoxides (**116**) are treated with Grignard reagents (and sometimes other epoxides), the product may be **117**, that is, the new alkyl group may appear on

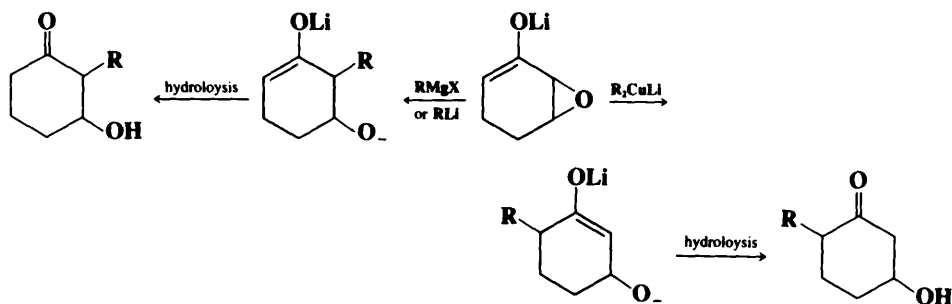


the same carbon as the OH. In such cases, the epoxide is isomerized to an aldehyde or a ketone before reacting with the Grignard reagent. Halohydrins are often side products.

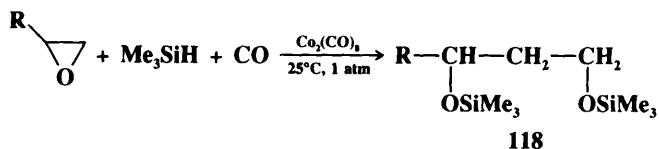
When the substrate is a vinylic epoxide,¹⁴⁰⁴ Grignard reagents generally give a mixture of the normal product and the product of allylic rearrangement.¹⁴⁰⁵



The latter often predominates. In the case of R_2CuLi ,¹⁴⁰⁶ acyclic substrates give mostly allylic rearrangement.¹⁴⁰⁵ The double bond of the “vinylic” epoxide can be part of an enolate ion if the substrate is cyclic. In this case R_2CuLi give exclusive allylic rearrangement ($\text{S}_{\text{N}}2'$), while Grignard and organolithium reagents give normal substitution, e.g.,¹⁴⁰⁷



An organometallic equivalent that opens epoxides is a hydrosilane, e.g., Me_3SiH , and carbon monoxide, catalyzed by dicobalt octacarbonyl:¹⁴⁰⁸



¹⁴⁰⁴For a list of organometallic reagents that react with vinylic epoxides, with references, see Ref. 508, pp. 123-124.

¹⁴⁰⁵Anderson *J. Am. Chem. Soc.* **1970**, 92, 4978; Johnson; Herr; Wieland, Ref. 1401; Marshall; Trometer; Blough; Crute *J. Org. Chem.* **1988**, 53, 4274; Marshall; Trometer; Cleary *Tetrahedron* **1989**, 45, 391.

¹⁴⁰⁶For a review of the reactions of vinylic epoxides with organocopper reagents, see Marshall *Chem. Rev.* **1989**, 89, 1503-1511.

¹⁴⁰⁷Wender; Erhardt; Letendre *J. Am. Chem. Soc.* **1981**, 103, 2114.

¹⁴⁰⁸Murai; Kato; Murai; Toki; Suzuki; Sonoda *J. Am. Chem. Soc.* **1984**, 106, 6093.

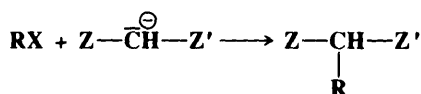
The 1,3-disilyl ether **118** can be hydrolyzed to a 1,3-diol.¹⁴⁰⁹

Aziridines have been similarly opened, to give amines.¹⁴¹⁰

OS **I**, 306; **VII**, 501; **69**, 1, 80.

0-94 Alkylation at a Carbon Bearing an Active Hydrogen

Bis(ethoxycarbonyl)methyl-de-halogenation, etc.



Compounds that contain two (or three, but this is rare) strong electron-withdrawing groups on a carbon atom are more acidic than compounds without such groups (p. 264) and are easily converted to their corresponding enolate ions (p. 72). These enolate ions can attack alkyl halides, resulting in their alkylation.¹⁴¹¹ Z and Z' may be COOR', CHO, COR', CONR', COO⁻, CN,¹⁴¹² NO₂, SOR', SO₂R',¹⁴¹³ SO₂OR', SO₂NR', or similar groups.¹⁴¹⁴ A carbon atom with any two of these (the same or different) will give up a proton (if it has one) to a suitable base. Some commonly used bases are sodium ethoxide and potassium *t*-butoxide, each in its respective alcohol as solvent. With particularly acidic compounds (e.g., β-diketones—Z, Z' = COR'), sodium hydroxide in water or aqueous alcohol or acetone, or even sodium carbonate,¹⁴¹⁵ is a strong enough base for the reaction. If at least one Z group is COOR', saponification is a possible side reaction. In addition to the groups listed above, Z may also be phenyl, but if two phenyl groups are on the same carbon, the acidity is less than in the other cases and a stronger base must be used. However, the reaction can be successfully carried out with diphenylmethane with NaNH₂ as the base.¹⁴¹⁶ The solvent used in the reaction must not be acidic enough to protonate either the enolate ion or the base, which in most cases rules out water. The use of polar aprotic solvents, e.g., DMF or Me₂SO, markedly increases the rate of alkylation¹⁴¹⁷ but also increases the extent of alkylation at the oxygen rather than the carbon (p. 368). Phase transfer catalysis has also been used.¹⁴¹⁸

Usually the reaction is carried out on a CH₂ group connected to two Z groups. In such cases it is possible to alkylate twice, first removing the proton with a base, then alkylating with RX, then removing the proton from ZCHRZ', and finally alkylating the resulting enolate ion with the same or a different RX. The reaction is successful for primary and secondary alkyl, allylic (with allylic rearrangement possible), and benzylic RX, but fails for tertiary halides, since these undergo elimination under the reaction conditions (see, however,

¹⁴⁰⁹For another method of converting epoxides to 1,3-diols, see Pelter; Bugden; Rosser *Tetrahedron Lett.* **1985**, 26, 5097.

¹⁴¹⁰See, for example Eis; Ganem *Tetrahedron Lett.* **1985**, 26, 1153; Onistschenko; Buchholz; Stamm *Tetrahedron* **1987**, 43, 565.

¹⁴¹¹For discussions of reactions 0-94 and 0-95, see House *Modern Synthetic Reactions*, 2nd ed.; W. A. Benjamin: New York, 1972, pp. 492-570, 586-595; Carruthers *Some Modern Methods of Organic Synthesis*, 3rd ed.; Cambridge University Press: Cambridge, 1986, pp. 1-26.

¹⁴¹²For reviews of the reactions of malononitrile CH₂(CN)₂, see Fatiadi *Synthesis* **1978**, 165-204, 241-282; Freeman *Chem. Rev.* **1969**, 69, 591-624.

¹⁴¹³For a review of compounds with two SO₂R groups on the same carbon (*gem*-disulfones), see Neplyuev; Bazarova; Lozinskii *Russ. Chem. Rev.* **1986**, 55, 883-900.

¹⁴¹⁴For lists of examples, with references, see Ref. 508, pp. 764-772ff, 894-896.

¹⁴¹⁵See, for example, Fedoryński; Wojciechowski; Matacz; Mąkosza *J. Org. Chem.* **1978**, 43, 4682.

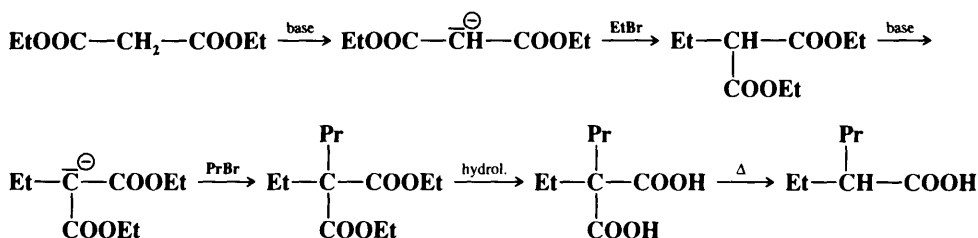
¹⁴¹⁶Murphy; Hamrick; Hauser *Org. Synth.* **V**, 523.

¹⁴¹⁷Zaugg; Horrom; Borgwardt, Ref. 306; Zaugg; Dunnigan; Michaels; Swett; Wang; Sommers; DeNet *J. Org. Chem.* **1961**, 26, 644; Johnstone; Tuli; Rose *J. Chem. Res. (S)* **1980**, 283.

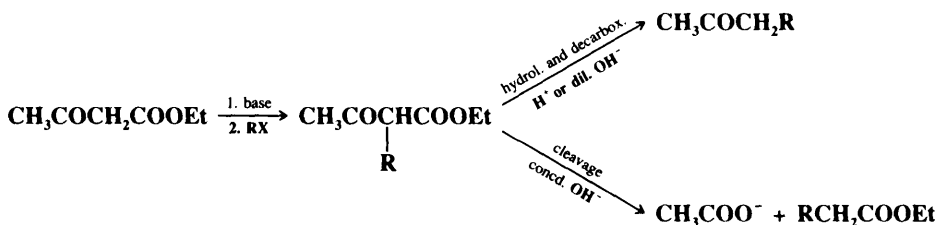
¹⁴¹⁸See Sukhanov; Trappel'; Chetverikov; Yanovskaya *J. Org. Chem. USSR* **1985**, 21, 2288; Tundo; Venturello; Angeletti *J. Chem. Soc., Perkin Trans. I* **1987**, 2159.

p. 466). Various functional groups may be present in RX as long as they are not sensitive to base. Side reactions that may cause problems are the above-mentioned competing O-alkylation, elimination (if the enolate ion is a strong enough base), and dialkylation.

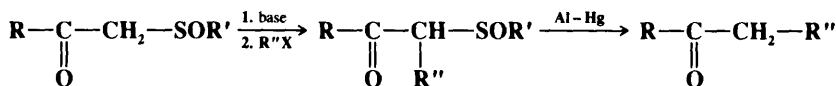
An important example of this reaction is the *malonic ester synthesis*, in which both Z groups are COOEt. The product can be hydrolyzed and decarboxylated (2-40) to give a carboxylic acid. An illustration is the preparation of 2-ethylpentanoic acid from malonic ester:



It is obvious that many carboxylic acids of the formulas RCH_2COOH and $\text{RR}'\text{CHCOOH}$ can be synthesized by this method (for some other ways of preparing such acids, see 0-96, 0-98, and 0-99). Another important example is the *acetoacetic ester synthesis*, in which Z is COOEt and Z' is COCH_3 . In this case the product can be decarboxylated with acid or dilute base (2-40) to give a ketone or cleaved with concentrated base (2-43) to give a carboxylic ester and a salt of acetic acid:



Another way of preparing ketones involves alkylation¹⁴¹⁹ of β -keto sulfoxides¹⁴²⁰ or sulfones,¹⁴²¹ e.g.,



since the product in this case is easily reduced to a ketone in high yields with aluminum amalgam or by electrolysis.¹⁴²² The β -keto sulfoxides or sulfones are easily prepared (0-109). Other examples of the reaction are the *cyanoacetic ester synthesis*, in which Z is COOEt and Z' is CN (as in the malonic ester synthesis, the product here can be hydrolyzed and decarboxylated), and the *Sorensen* method of amino acid synthesis, in which the reaction is applied to N-acetylaminomalonic ester $(\text{EtOOC})_2\text{CHNHCOCH}_3$. Hydrolysis and decarboxylation of the product in this case gives an α -amino acid. The amino group is also frequently protected by conversion to a phthalimido group.

¹⁴¹⁹For a review of the synthetic uses of β -keto sulfoxides, sulfones, and sulfides, see Trost *Chem. Rev.* **1978**, 78, 363-382. For a review of asymmetric synthesis with chiral sulfoxides, see Solladié *Synthesis* **1981**, 185-196.

¹⁴²⁰Gassman; Richmond *J. Org. Chem.* **1966**, 31, 2355. Such sulfoxides can be alkylated on the other side of the C=O group by the use of two moles of base: Kuwajima; Iwasawa *Tetrahedron Lett.* **1974**, 107.

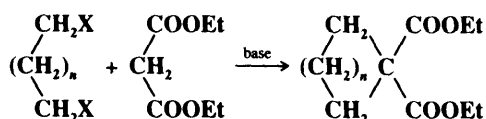
¹⁴²¹House; Larson *J. Org. Chem.* **1968**, 33, 61; Kurth; O'Brien *J. Org. Chem.* **1985**, 3846.

¹⁴²²Lamm; Samuelsson *Acta Chem. Scand.* **1969**, 23, 691.

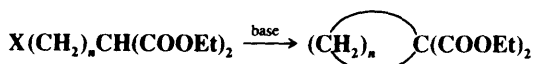
The reaction is not limited to $Z-CH_2-Z'$ compounds. Other acidic CH hydrogens, which include, for example, the methyl hydrogens of α -aminopyridines, the methyl hydrogens of ynamines of the form $CH_3C\equiv CNR_2$ ¹⁴²³ (the product in this case can be hydrolyzed to an amide $RCH_2CH_2CONR_2$), the CH_2 hydrogens of cyclopentadiene and its derivatives (p. 46), hydrogens connected to a triple-bond carbon (**0-100**), and the hydrogen of HCN (**0-101**) can also be removed with a base and the resulting ion alkylated (see also **0-95** to **0-98**).

Alkylation takes place at the most acidic position of a reagent molecule; for example, acetoacetic ester (CH_3COCH_2COOEt) is alkylated at the methylene and not at the methyl group, because the former is more acidic than the latter and hence gives up its proton to the base. However, if 2 moles of base are used, then not only is the most acidic proton removed but also the second most acidic. Alkylation of this doubly charged anion then takes place at the less acidic position (see p. 366). This technique has been used to alkylate many compounds in the second most acidic position.¹⁴²⁴

When ω,ω' -dihalides are used, ring closures can be effected:¹⁴²⁵



This method has been used to close rings of from three ($n = 0$) to seven members, although five-membered ring closures proceed in highest yields. Another ring-closing method involves internal alkylation.¹⁴²⁶



This method has been shown to be applicable to medium rings (10 to 14 members) without the use of high-dilution techniques.¹⁴²⁷

The mechanism of these reactions is usually S_N2 with inversion taking place at a chiral RX, though there is strong evidence that an SET¹⁴²⁸ mechanism is involved in certain cases,¹⁴²⁹ especially where the nucleophile is an α -nitro carbanion¹⁴³⁰ and/or the substrate contains a nitro or cyano¹⁴³¹ group. Tertiary alkyl groups can be introduced by an S_N1 mechanism if the ZCH_2Z' compound (not the enolate ion) is treated with a tertiary carbocation generated in situ from an alcohol or alkyl halide and BF_3 or $AlCl_3$,¹⁴³² or with a tertiary alkyl perchlorate.¹⁴³³

¹⁴²³Corey; Cane *J. Org. Chem.* **1970**, 35, 3405.

¹⁴²⁴For a list of references, see Ref. 508, pp. 772-773. See also Ref. 426.

¹⁴²⁵Zefirov; Kuznetsova; Kozhushkov; Surmina; Rashchupkina *J. Org. Chem. USSR* **1983**, 19, 474.

¹⁴²⁶For example, see Knipe; Stirling *J. Chem. Soc. B* **1968**, 67; Gosselck; Winkler *Tetrahedron Lett.* **1970**, 2437; Walborsky; Murari *Can. J. Chem.* **1984**, 62, 2464. For a review of this method as applied to the synthesis of β -lactams, see Bose; Manhas; Chatterjee; Abdulla *Synth. Commun.* **1971**, 1, 51-73. For a list of examples, see Ref. 508, pp. 81, 83-84.

¹⁴²⁷Deslongchamps; Lamothe; Lin *Can. J. Chem.* **1984**, 62, 2395, **1987**, 65, 1298; Brillon; Deslongchamps *Can. J. Chem.* **1987**, 65, 43, 56.

¹⁴²⁸These SET mechanisms are often called $S_{RN}1$ mechanisms. See also Ref. 75.

¹⁴²⁹Kerber; Urry; Kornblum *J. Am. Chem. Soc.* **1965**, 87, 4520; Kornblum; Michel; Kerber *J. Am. Chem. Soc.* **1966**, 88, 5660, 5662; Russell; Danen *J. Am. Chem. Soc.* **1966**, 88, 5663; Russell; Ros *J. Am. Chem. Soc.* **1985**, 107, 2506; Ashby; Argyropoulos *J. Org. Chem.* **1985**, 50, 3274; Bordwell; Wilson *J. Am. Chem. Soc.* **1987**, 109, 5470; Bordwell; Harrelson *J. Am. Chem. Soc.* **1989**, 111, 1052.

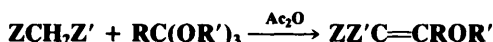
¹⁴³⁰For a review of mechanisms with these nucleophiles, see Bowman *Chem. Soc. Rev.* **1988**, 17, 283-316.

¹⁴³¹Kornblum; Fifolt *Tetrahedron* **1989**, 45, 1311.

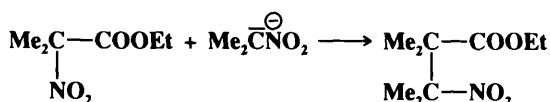
¹⁴³²For example, see Boldt; Militzer *Tetrahedron Lett.* **1966**, 3599; Crimmins; Hauser *J. Org. Chem.* **1967**, 32, 2615; Boldt; Militzer; Thielecke; Schulz *Liebigs Ann. Chem.* **1968**, 718, 101.

¹⁴³³Boldt; Thielecke *Angew. Chem. Int. Ed. Engl.* **1966**, 5, 1044 [*Angew. Chem.* 78, 1058]; Boldt; Ludwig; Militzer *Chem. Ber.* **1970**, 103, 1312.

Other leaving groups are sometimes used. Sulfates, sulfonates, and epoxides give the expected products. Acetals can behave as substrates, one OR group being replaced by ZCHZ' in a reaction similar to 0-92.¹⁴³⁴ Ortho esters behave similarly, but the product loses R'OH to give an enol ether.¹⁴³⁵

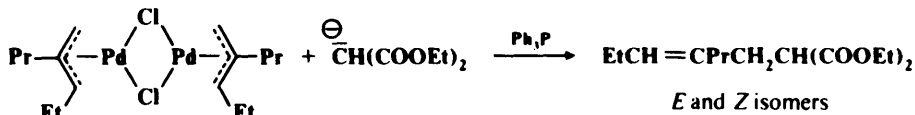


The SO₂Ph group of allylic sulfones can be a leaving group if a palladium(0) complex is present.¹⁴³⁶ The NR₂ group from Mannich bases such as RCOCH₂CH₂NR₂ can also act as a leaving group in this reaction (elimination-addition mechanism, p. 338). A nitro group can be displaced¹⁴³⁷ from α-nitro esters, ketones, nitriles, and α,α-dinitro compounds,¹⁴³⁸ and even from simple tertiary nitro compounds of the form R₃CNO₂¹⁴³⁹ or ArR₂CNO₂¹⁴⁴⁰ by salts of nitroalkanes, e.g.,



These reactions take place by SET mechanisms.¹⁴⁴¹ However, with α-nitro sulfones it is the sulfone group that is displaced, rather than the nitro group.¹⁴⁴² The SO₂R group of allylic sulfones can be replaced by CHZZ' (C=CCH₂-SO₂R → C=CCH₂-CHZZ') if an Mo(CO)₆ catalyst is used.¹⁴⁴³ Alkylation α to a nitro group can be achieved with the Katritzky pyrylium-pyridinium reagents.¹⁴⁴⁴ This reaction probably has a free-radical mechanism.¹⁴⁴⁵

Palladium can be the leaving atom if the substrate is a π-allylpalladium complex (an η³ complex). Ions of ZCHZ' compounds react with such complexes¹⁴⁴⁶ in the presence of triphenylphosphine,¹⁴⁴⁷ e.g.,



¹⁴³⁴Yufit; Krasnaya; Levchenko; Kucherov *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1967**, 123; Aleskerov; Yufit; Kucherov *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1972**, 21, 2279.

¹⁴³⁵For a review, see DeWolfe, Ref. 457, pp. 231-266.

¹⁴³⁶Trost; Schmuff; Miller *J. Am. Chem. Soc.* **1980**, 102, 5979.

¹⁴³⁷For reviews, see Kornblum, in Patai, Ref. 346, pt. 1, pp. 361-393; Kornblum *Angew. Chem. Int. Ed. Engl.* **1975**, 14, 734-745 [*Angew. Chem.* 87, 797-808]. For reviews of aliphatic S_N reactions in which NO₂ is a leaving group, see Tamura; Kamimura; Ono *Synthesis* **1991**, 423-434; Kornblum, in Feuer; Nielsen, Ref. 1198, pp. 46-85.

¹⁴³⁸Kornblum; Kelly; Kestner *J. Org. Chem.* **1985**, 50, 4720.

¹⁴³⁹Kornblum; Erickson *J. Org. Chem.* **1981**, 46, 1037.

¹⁴⁴⁰Kornblum; Carlson; Widmer; Fifolt; Newton; Smith *J. Org. Chem.* **1978**, 43, 1394.

¹⁴⁴¹For a review of the mechanism, see Beletskaya; Drozd *Russ. Chem. Rev.* **1979**, 48, 431-448. See also Kornblum; Wade *J. Org. Chem.* **1987**, 52, 5301; Ref. 1430; Ref. 1437.

¹⁴⁴²Kornblum; Boyd; Ono *J. Am. Chem. Soc.* **1974**, 96, 2580.

¹⁴⁴³Trost; Merlic *J. Org. Chem.* **1990**, 55, 1127.

¹⁴⁴⁴Katritzky; de Ville; Patel *Tetrahedron* **1981**, 37, Suppl. 1, 25; Katritzky; Kashmiri; Wittmann *Tetrahedron* **1984**, 40, 1501.

¹⁴⁴⁵Katritzky; Chen; Marson; Maia; Kashmiri *Tetrahedron* **1986**, 42, 101.

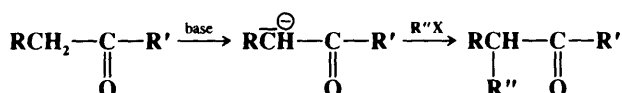
¹⁴⁴⁶For a review of the use of η³-allylpalladium complexes to form C—C bonds, see Tsuji, in Hartley; Patai, Ref. 1403, vol. 3, 1985, pp. 163-199.

¹⁴⁴⁷For reviews, see Trost *Angew. Chem. Int. Ed. Engl.* **1989**, 28, 1173-1192 [*Angew. Chem.* 101, 1199-1219], *Chemtracts: Org. Chem.* **1988**, 1, 415-435, *Aldrichimica Acta* **1981**, 14, 43-50, *Acc. Chem. Res.* **1980**, 13, 385-393, *Tetrahedron* **1977**, 33, 2615-2649; Tsuji; Minami *Acc. Chem. Res.* **1987**, 20, 140-145; Tsuji *Tetrahedron* **1986**, 42, 4361-4401, *Organic Synthesis with Palladium Compounds*; Springer: Berlin, 1981, pp. 45-51, 125-132; Heck *Palladium Reagents in Organic Synthesis*; Academic Press: New York, 1985, pp. 130-166; Hegedus, in Buncl; Durst *Comprehensive Carbanion Chemistry*, vol. 5, pt. B; Elsevier: New York, 1984, pp. 30-44.

When the Pd bears chiral ligands, these reactions can be enantioselective.¹⁴⁴⁸ π -Allyl-molybdenum compounds behave similarly.¹⁴⁴⁹ Because palladium compounds are expensive, a catalytic synthesis, which uses much smaller amounts of the complex, was developed. That is, a substrate such as an allylic acetate, alcohol, amine, or nitro compound¹⁴⁵⁰ is treated with the nucleophile, and a catalytic amount of a palladium salt is added. The π -allylpalladium complex is generated in situ. Alkene-palladium complexes (introducing the nucleophile at a vinylic rather than an allylic carbon) can also be used.¹⁴⁵¹

OS **I**, 248, 250; **II**, 262, 279, 384, 474; **III**, 213, 219, 397, 405, 495, 705; **IV**, 10, 55, 288, 291, 623, 641, 962; **V**, 76, 187, 514, 523, 559, 743, 767, 785, 848, 1013; **VI**, 223, 320, 361, 482, 503, 587, 781, 991; **VII**, 339, 411; **66**, 75; **68**, 56; **69**, 38. See also OS **68**, 210.

0-95 Alkylation of Ketones, Nitriles, and Carboxylic Esters α -Acylalkyl-de-halogenation, etc.



Ketones,¹⁴⁵² nitriles,¹⁴⁵³ and carboxylic esters¹⁴⁵⁴ can be alkylated in the α position in a reaction similar to **0-94**,¹⁴¹¹ but a stronger base must be employed, since only one activating group is present. The most common bases¹⁴⁵⁵ are Et_2NLi (LDA), $(\text{iso-Pr})_2\text{NLi}$, $t\text{-BuOK}$, NaNH_2 , and KH . The base lithium N-isopropyl-N-cyclohexylamide is particularly successful for carboxylic esters¹⁴⁵⁶ and nitriles.¹⁴⁵⁷ Solid KOH in Me_2SO has been used to methylate ketones, in high yields.¹⁴⁵⁸ Some of these bases are strong enough to convert the ketone, nitrile, or ester completely to its enolate ion conjugate base; others (especially $t\text{-BuOK}$) convert a significant fraction of the molecules. In the latter case, the aldol reaction (**6-39**) or Claisen condensation (**0-108**) may be side reactions, since both the free molecule and its conjugate base are present at the same time. It is therefore important to use a base strong enough to convert the starting compound completely. Protic solvents are generally not suitable because they protonate the base (though of course this is not a problem with a conjugate pair, such as $t\text{-BuOK}$ in $t\text{-BuOH}$). Some common solvents are 1,2-dimethoxyethane, THF, DMF, and liquid NH_3 . Phase transfer catalysis has been used to alkylate many nitriles, as well as some esters and ketones.¹⁴⁵⁹

As in **0-94**, the alkyl halide may be primary or secondary. Tertiary halides give elimination. Even primary and secondary halides give predominant elimination if the enolate ion is a strong enough base (e.g., the enolate ion from Me_3CCOMe).¹⁴⁶⁰ Tertiary alkyl groups, as

¹⁴⁴⁸For a review, see Consiglio; Waymouth *Chem. Rev.* **1989**, 89, 257-276.

¹⁴⁴⁹Trost; Lautens *Tetrahedron* **1987**, 43, 4817; *J. Am. Chem. Soc.* **1987**, 109, 1469.

¹⁴⁵⁰Tamura; Kai; Kakihana; Hayashi; Tsuji; Nakamura; Oda *J. Org. Chem.* **1986**, 51, 4375.

¹⁴⁵¹Hegedus; Williams; McGuire; Hayashi *J. Am. Chem. Soc.* **1980**, 102, 4973; Hegedus, Ref. 1447, pp. 9-20.

¹⁴⁵²For a review of the alkylation and acylation of ketones and aldehydes, see Caine, in *Augustine Carbon-Carbon Bond Formation*, vol. 1; Marcel Dekker: New York, 1979, pp. 85-352.

¹⁴⁵³For a review, see Arseniyadis; Kyler; Watt *Org. React.* **1984**, 31, 1-364. For a list of references, see Ref. 508, pp. 910-913.

¹⁴⁵⁴For a review, see Petragnani; Yonashiro *Synthesis* **1982**, 521-578. For a list of references, see Ref. 508, pp. 873-890ff.

¹⁴⁵⁵For a list of some bases, with references, see Ref. 508, pp. 738-740.

¹⁴⁵⁶Rathke; Lindert *J. Am. Chem. Soc.* **1971**, 93, 2319; Bos; Pabon *Recl. Trav. Chim. Pays-Bas* **1980**, 99, 141. See also Cregge; Herrmann; Lee; Richman; Schlessinger *Tetrahedron Lett.* **1973**, 2425.

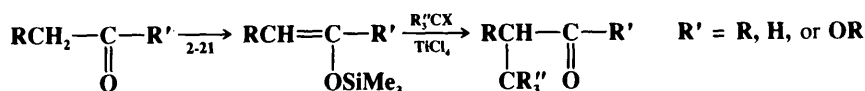
¹⁴⁵⁷Watt *Tetrahedron Lett.* **1974**, 707.

¹⁴⁵⁸Langhals; Langhals *Tetrahedron Lett.* **1990**, 31, 859.

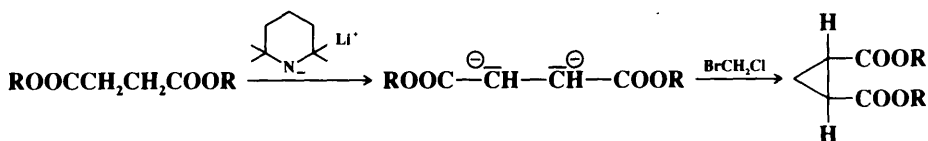
¹⁴⁵⁹For reviews, see Makosza *Russ. Chem. Rev.* **1977**, 46, 1151-1166; *Pure Appl. Chem.* **1975**, 43, 439-462; Starks; Liotta, Ref. 404, pp. 170-217; Weber; Gokel *Phase Transfer Catalysis in Organic Synthesis*, Ref. 404, pp. 136-204.

¹⁴⁶⁰Zook; Kelly; Posey *J. Org. Chem.* **1968**, 33, 3477.

well as other groups that normally give S_N1 reactions, can be introduced if the reaction is performed on a silyl enol ether¹⁴⁶¹ of a ketone, aldehyde, or ester with a Lewis acid catalyst.¹⁴⁶²

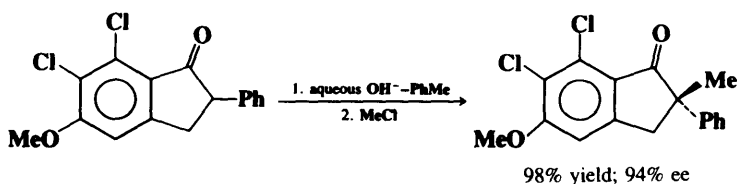


Vinyllic and aryl halides can be used to vinylate or arylate carboxylic esters (but not ketones) by the use of NiBr_2 as a catalyst.¹⁴⁶³ However, ketones have been vinylated by treating their enol acetates with vinyllic bromides in the presence of a Pd compound catalyst.¹⁴⁶⁴ Also as in **0-94**, this reaction can be used to close rings.¹⁴⁶⁵ In one example of this, rings have been closed by treating a diion of a dialkyl succinate with a $1,\omega$ -dihalide or ditosylate,¹⁴⁶⁶ e.g.:



This was applied to the synthesis of 3-, 4-, 5-, and 6-membered rings. When the R groups were chiral (e.g., menthyl) the product was formed with greater than 90% enantiomeric excess.¹⁴⁶⁶

An efficient enantioselective alkylation has been reported:¹⁴⁶⁷



The indanone substrate was methylated in 94% enantiomeric excess, by the use of a chiral catalyst, *N*-(*p*-(trifluoromethyl)benzyl)cinchoninium bromide, under phase transfer conditions.¹⁴⁶⁸ In another method enantioselective alkylation can be achieved by using a chiral base to form the enolate.¹⁴⁶⁹

¹⁴⁶¹For a list of alkylations of silyl enol ethers, see Ref. 508, pp. 750-754.

¹⁴⁶²Chan; Paterson; Pinsonnault *Tetrahedron Lett.* **1977**, 4183; Reetz; Maier *Angew. Chem. Int. Ed. Engl.* **1978**, 17, 48 [*Angew. Chem.* **90**, 50]; Reetz; Schweltnus; Hübner; Massa; Schmidt *Chem. Ber.* **1983**, 116, 3708. Lion; Dubois *Bull. Soc. Chim. Fr.* **1982**, II-375; Reetz; Sauerwald *J. Organomet. Chem.* **1990**, 382, 121; Reetz; Chatziiosifidis; Hübner; Heimbach *Org. Synth. VII*, 424. For a review, see Reetz *Angew. Chem. Int. Ed. Engl.* **1982**, 21, 96-108 [*Angew. Chem.* **94**, 97-109].

¹⁴⁶³Millard; Rathke *J. Am. Chem. Soc.* **1977**, 99, 4833.

¹⁴⁶⁴Kosugi; Hagiwara; Migita *Chem. Lett.* **1983**, 839. For other methods, see Negishi; Akiyoshi *Chem. Lett.* **1987**, 1007; Chang; Rosenblum; Simms *Org. Synth.* **66**, 95.

¹⁴⁶⁵For example, see Etheredge *J. Org. Chem.* **1966**, 31, 1990; Wilcox; Whitney *J. Org. Chem.* **1967**, 32, 2933; Bird; Stirling *J. Chem. Soc. B* **1968**, 111; Stork; Boeckman *J. Am. Chem. Soc.* **1973**, 95, 2016; Stork; Cohen *J. Am. Chem. Soc.* **1974**, 96, 5270. In the last case, the substrate moiety is an epoxide function.

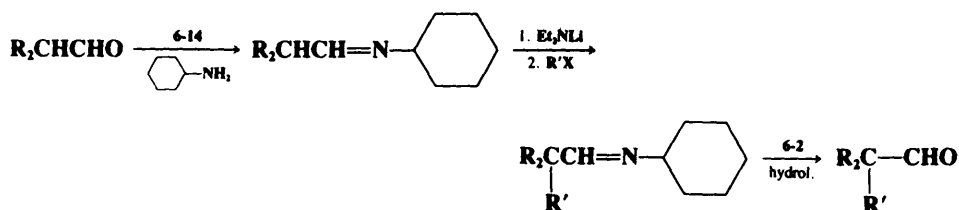
¹⁴⁶⁶Misumi; Iwanaga; Furuta; Yamamoto *J. Am. Chem. Soc.* **1985**, 107, 3343; Furuta; Iwanaga; Yamamoto *Org. Synth.* **67**, 76.

¹⁴⁶⁷For reviews of stereoselective alkylation of enolates, see Nográdi *Stereoselective Synthesis*; VCH: New York, 1986, pp. 236-245; Evans, in Morrison *Asymmetric Synthesis*, vol. 3; Academic Press: New York, 1984, pp. 1-110.

¹⁴⁶⁸Hughes; Dolling; Ryan; Schoenewaldt; Grabowski *J. Org. Chem.* **1987**, 52, 4745.

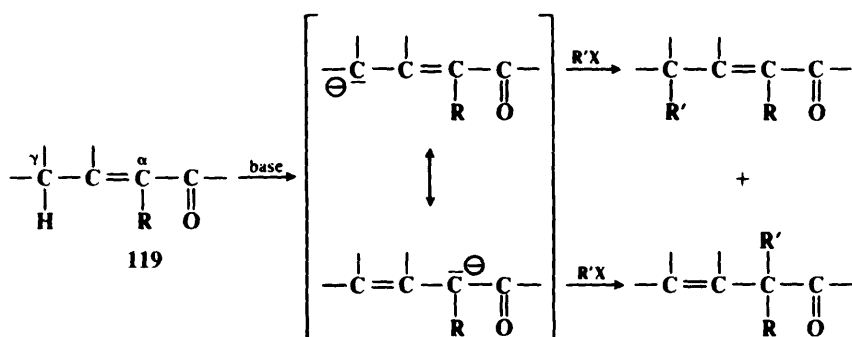
¹⁴⁶⁹For example, see Murakata; Nakajima; Koga *J. Chem. Soc., Chem. Commun.* **1990**, 1657. For a review, see Cox; Simpkins *Tetrahedron: Asymmetry* **1991**, 2, 1-26, pp. 6-13.

The reaction can be applied to aldehydes, indirectly, by alkylating an imine derivative of the aldehyde.¹⁴⁷⁰ The derivative is easily prepared (**6-14**) and the product easily hydrolyzed to the aldehyde (**6-2**). Either or both R groups may be hydrogen, so that mono-, di-, and



trisubstituted acetaldehydes can be prepared by this method. R' may be primary alkyl, allylic, or benzylic. Direct alkylation of aldehydes is not generally possible because base treatment of aldehydes normally gives rapid aldol reaction (**6-39**), though aldehydes bearing only one α hydrogen have been alkylated with allylic and benzylic halides in good yields by the use of the base KH to prepare the potassium enolate,¹⁴⁷¹ or in moderate yields, by the use of a phase transfer catalyst.¹⁴⁷² Hydrazones and other compounds with C=N bonds can be similarly alkylated.¹⁴⁷⁰ The use of chiral amines or hydrazines¹⁴⁷³ (followed by hydrolysis **6-2** of the alkylated imine) can lead to chiral alkylated ketones in high optical yields¹⁴⁷⁴ (for an example, see p. 118).

In α,β -unsaturated ketones, nitriles, and esters (e.g., **119**), the γ hydrogen assumes the acidity normally held by the position α to the carbonyl group, especially when R is not



hydrogen and so cannot compete. This principle, called *vinylology*, operates because the resonance effect is transmitted through the double bond. However, because of the resonance, alkylation at the α position (with allylic rearrangement) competes with alkylation at the γ position and usually predominates.

¹⁴⁷⁰Cuvigny; Normant *Bull. Soc. Chim. Fr.* **1970**, 3976. For reviews, see Fraser, in Buncl; Durst, Ref. 1447, pp. 65-105; Whitesell; Whitesell *Synthesis* **1983**, 517-536. For a list of references, see Ref. 508, pp. 758-761. For a method in which the metalated imine is prepared from a nitrile, see Goering; Tseng *J. Org. Chem.* **1981**, *46*, 5250.

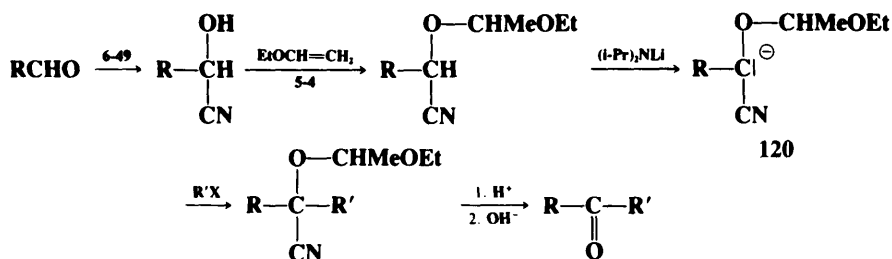
¹⁴⁷¹Groenewegen; Kallenberg; van der Gen *Tetrahedron Lett.* **1978**, 491; Artaud; Torossian; Viout *Tetrahedron* **1985**, *41*, 5031.

¹⁴⁷²Dietl; Brannock *Tetrahedron Lett.* **1973**, 1273; Purohit; Subramanian *Chem. Ind. (London)* **1978**, 731; Buschmann; Zech *Liebigs Ann. Chem.* **1979**, 1585.

¹⁴⁷³For a review of the alkylation of chiral hydrazones, see Enders, in Morrison, Ref. 1467, pp. 275-339.

¹⁴⁷⁴Meyers; Williams; Erickson; White; Druehinger *J. Am. Chem. Soc.* **1981**, *103*, 3081; Meyers; Williams; White; Erickson *J. Am. Chem. Soc.* **1981**, *103*, 3088; Enders; Bockstiegel *Synthesis* **1989**, 493; Enders; Kipphardt; Fey *Org. Synth.* **65**, 183.

α -Hydroxynitriles (cyanohydrins), protected by conversion to acetals with ethyl vinyl ether (5-4), can be easily alkylated with primary or secondary alkyl or allylic halides.¹⁴⁷⁵



R can be aryl or saturated or unsaturated alkyl. Since the cyanohydrins¹⁴⁷⁶ are easily formed from aldehydes (6-49) and the product is easily hydrolyzed to a ketone, this is a method for converting an aldehyde RCHO to a ketone RCOR'¹⁴⁷⁷ (for other methods, see 0-97, 0-105, and 8-9).¹⁴⁷⁸ In this procedure the normal mode of reaction of a carbonyl carbon is reversed. The C atom of an aldehyde molecule is normally electrophilic and is attacked by nucleophiles (Chapter 16), but by conversion to the protected cyanohydrin this carbon atom has been induced to perform as a nucleophile.¹⁴⁷⁹ The German word *umpolung*¹⁴⁸⁰ is used to describe this kind of reversal (another example is found in 0-97). Since the ion 120 serves as a substitute for the unavailable $\text{R}-\text{C}^{\ominus}=\text{O}$ anion, it is often called a "masked" $\text{R}-\text{C}^{\ominus}=\text{O}$ ion. This method fails for formaldehyde (R = H), but other masked formaldehydes have proved successful.¹⁴⁸¹

When the compound to be alkylated is a nonsymmetrical ketone, the question arises as to which side will be alkylated. If an α phenyl or α vinylic group is present on one side, alkylation goes predominantly on that side. When only alkyl groups are present, the reaction is generally not regioselective; mixtures are obtained in which sometimes the more alkylated and sometimes the less alkylated side is predominantly alkylated. Which product is found in higher yield depends on the nature of the substrate, the base,¹⁴⁸² the cation, and the solvent. In any case, di- and trisubstitution are frequent¹⁴⁸³ and it is often difficult to stop with the introduction of just one alkyl group.¹⁴⁸⁴

¹⁴⁷⁵Stork; Maldonado *J. Am. Chem. Soc.* **1971**, 93, 5286; Stork; Depeyay; D'Angelo *Tetrahedron Lett.* **1975**, 389. See also Rasmussen; Heilmann *Synthesis* **1978**, 219; Ahlbrecht; Raab; Vonderheid *Synthesis* **1979**, 127; Hünig; Marschner; Peters; von Schnering *Chem. Ber.* **1989**, 122, 2131, and other papers in this series.

¹⁴⁷⁶For a review of 120, see Albright *Tetrahedron* **1983**, 39, 3207-3233.

¹⁴⁷⁷For similar methods, see Stetter; Schmitz; Schreckenberg *Chem. Ber.* **1977**, 110, 1971; Hünig; *Chimia* **1982**, 36, 1.

¹⁴⁷⁸For a review of methods of synthesis of aldehydes, ketones, and carboxylic acids by coupling reactions, see Martin, *Synthesis* **1979**, 633-665.

¹⁴⁷⁹For reviews of such reversals of carbonyl group reactivity, see Block *Reactions of Organosulfur Compounds*; Academic Press: New York, 1978, pp. 56-67; Gröbel; Seebach *Synthesis* **1977**, 357-402; Lever *Tetrahedron* **1976**, 32, 1943-1971; Seebach; Kolb *Chem. Ind. (London)* **1974**, 687-692; Seebach *Angew. Chem. Int. Ed. Engl.* **1969**, 8, 639-649 [*Angew. Chem.* 81, 690-700]. For a compilation of references to masked acyl and formyl anions, see Hase; Koskimies *Aldrichimica Acta* **1981**, 14, 73-77. For tables of masked reagents, see Hase, Ref. 1480, pp. xiii-xiv, 7-18, 219-317. For lists of references, see Ref. 508, pp. 709-711.

¹⁴⁸⁰For a monograph, see Hase *Umpoled Synthons*; Wiley: New York, 1987. For a review see Seebach *Angew. Chem. Int. Ed. Engl.* **1979**, 18, 239-258 [*Angew. Chem.* 91, 259-278].

¹⁴⁸¹Possel; van Leusen *Tetrahedron Lett.* **1977**, 4229; Stork; Ozorio; Leong *Tetrahedron Lett.* **1978**, 5175.

¹⁴⁸²Sterically hindered bases may greatly favor one enolate over the other. See, for example, Prieto; Suarez; Larson *Synth. Commun.* **1988**, 18, 253; Gaudemar; Bellassoued *Tetrahedron Lett.* **1989**, 30, 2779.

¹⁴⁸³For a procedure for completely methylating the α positions of a ketone, see Lissel; Neumann; Schmidt *Liebigs Ann. Chem.* **1987**, 263.

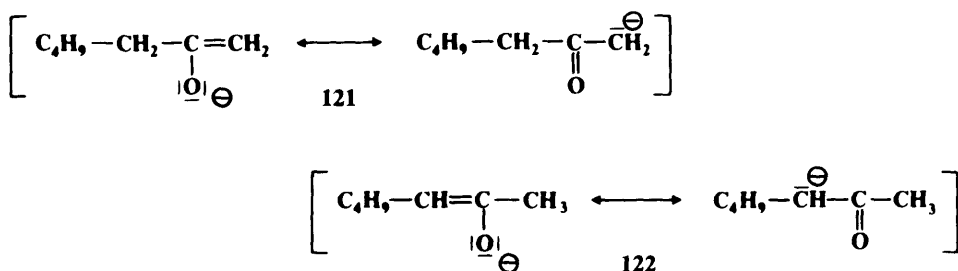
¹⁴⁸⁴For some methods of reducing dialkylation, see Hooz; Oudenes *Synth. Commun.* **1980**, 10, 139; Morita; Suzuki; Noyori *J. Org. Chem.* **1989**, 54, 1785.

Several methods have been developed for ensuring that alkylation takes place regioselectively on the *desired* side of a ketone.¹⁴⁸⁵ Among these are:

1. Block one side of the ketone by introducing a removable group. Alkylation takes place on the other side; the blocking group is then removed. A common reaction for this purpose is formylation with ethyl formate (0-109); this generally blocks the less hindered side. The formyl group is easily removed by alkaline hydrolysis (2-43).

2. Introduce an activating group on one side; alkylation then takes place on that side (0-94); the activating group is then removed.

3. Prepare the desired one of the two possible enolate ions.¹⁴⁸⁶ The two ions, e.g., **121** and **122** for 2-heptanone,



interconvert rapidly only in the presence of the parent ketone or any stronger acid.¹⁴⁸⁷ In the absence of such acids, it is possible to prepare either **121** or **122** and thus achieve selective alkylation on either side of the ketone.¹⁴⁸⁸ The desired enolate ion can be obtained by treatment of the corresponding enol acetate with two equivalents of methyllithium in 1,2-dimethoxyethane. Each enol acetate gives the corresponding enolate, e.g.,



The enol acetates, in turn, can be prepared by treatment of the parent ketone with an appropriate reagent.¹⁴⁸⁸ Such treatment generally gives a mixture of the two enol acetates in which one or the other predominates, depending on the reagent. The mixtures are easily separable.¹⁴⁸⁸ An alternate procedure involves conversion of a silyl enol ether¹⁴⁸⁹ (see 2-23) or a dialkylboron enol ether¹⁴⁹⁰ (an enol borinate, see p. 481) to the corresponding enolate ion. If the less hindered enolate ion is desired (e.g., **121**), it can be prepared directly from the ketone by treatment with lithium diisopropylamide in THF or 1,2-dimethoxyethane at -78°C .¹⁴⁹¹

¹⁴⁸⁵For a review, see House *Rec. Chem. Prog.* **1968**, 28, 99-120. For a review with respect to cyclohexenones, see Podraza *Org. Prep. Proced. Int.* **1991**, 23, 217-235.

¹⁴⁸⁶For reviews, see d'Angelo *Tetrahedron* **1976**, 32, 2979-2990; Stork *Pure Appl. Chem.* **1975**, 43, 553-562.

¹⁴⁸⁷House; Trost *J. Org. Chem.* **1965**, 30, 1341.

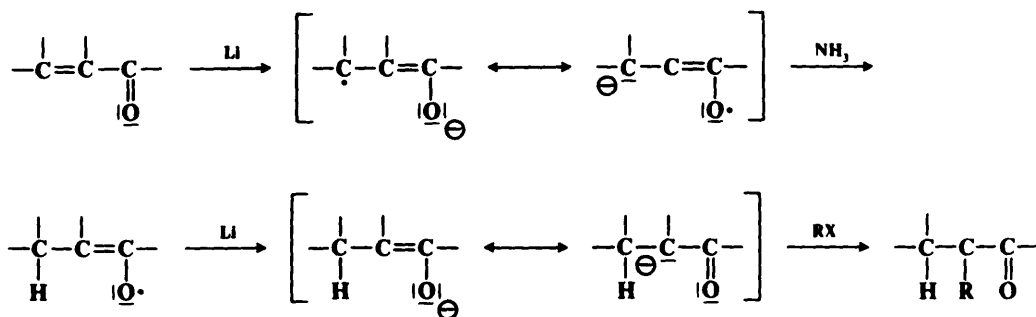
¹⁴⁸⁸House; Trost *J. Org. Chem.* **1965**, 30, 2502; Whitlock; Overman *J. Org. Chem.* **1969**, 34, 1962; House; Gall; Olmstead *J. Org. Chem.* **1971**, 36, 2361. For an improved procedure, see Liotta; Caruso *Tetrahedron Lett.* **1985**, 26, 1599.

¹⁴⁸⁹Stork; Hudrlik *J. Am. Chem. Soc.* **1968**, 90, 4462, 4464. For reviews, see Kuwajima; Nakamura *Acc. Chem. Res.* **1985**, 18, 181-187; Fleming *Chimia* **1980**, 34, 265-271; Rasmussen *Synthesis* **1977**, 91-110.

¹⁴⁹⁰Pasto; Wojtkowski *J. Org. Chem.* **1971**, 36, 1790.

¹⁴⁹¹House; Gall; Olmstead, Ref. 1488. See also Corey; Gross *Tetrahedron Lett.* **1984**, 25, 495.

4. Begin not with the ketone itself, but with an α,β -unsaturated ketone in which the double bond is present on the side where alkylation is desired. Upon treatment with lithium in liquid NH_3 , such a ketone is reduced to an enolate ion. When the alkyl halide is added,

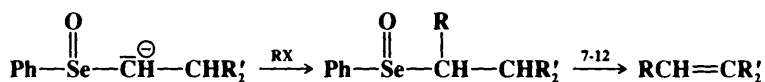


it must react with the enolate ion on the side where the double bond was.¹⁴⁹² Of course, this method is not actually an alkylation of the ketone, but of the α,β -unsaturated ketone, though the product is the same as if the saturated ketone had been alkylated on the desired side.

Both sides of acetone have been alkylated with different alkyl groups, in one operation, by treatment of the *N,N*-dimethylhydrazone of acetone with *n*-BuLi, followed by a primary alkyl, benzylic, or allylic bromide or iodide; then another mole of *n*-BuLi, a second halide, and finally hydrolysis of the hydrazone.¹⁴⁹³

Among other methods for the preparation of alkylated ketones are: (1) the Stork enamine reaction (2-19), (2) the acetoacetic ester synthesis (0-94), (3) alkylation of β -keto sulfones or sulfoxides (0-94), (4) acylation of $\text{CH}_3\text{SOCH}_2^-$ followed by reductive cleavage (0-109), (5) treatment of α -halo ketones with lithium dialkylcopper reagents (0-87), and (6) treatment of α -halo ketones with trialkylboranes (0-99).

Sulfones¹⁴⁹⁴ and sulfonic esters can also be alkylated in the α position if strong enough bases are used.¹⁴⁹⁵ Alkylation at the α position of selenoxides allows the formation of alkenes, since selenoxides easily undergo elimination (7-12).¹⁴⁹⁶



OS III, 44, 219, 221, 223, 397; IV, 278, 597, 641, 962; V, 187, 514, 559, 848; VI, 51, 115, 121, 401, 818, 897, 958, 991; VII, 153, 208, 241, 424; 65, 32, 183; 66, 87, 95; 67, 76, 141; 69, 55.

¹⁴⁹²Stork; Rosen; Goldman; Coombs; Tsuji *J. Am. Chem. Soc.* **1965**, 87, 275. For a review, see Caine *Org. React.* **1976**, 23, 1-258. For similar approaches, see Coates; Sowerby *J. Am. Chem. Soc.* **1971**, 93, 1027; Näf; Decorzant *Helv. Chim. Acta* **1974**, 57, 1317; Wender; Eissenstat *J. Am. Chem. Soc.* **1978**, 100, 292.

¹⁴⁹³Yamashita; Matsuyama; Tanabe; Suemitsu *Bull. Chem. Soc. Jpn.* **1985**, 58, 407.

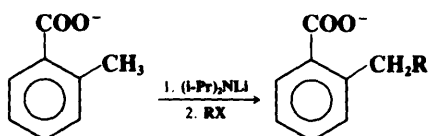
¹⁴⁹⁴For a review, see Magnus *Tetrahedron* **1977**, 33, 2019-2045, pp. 2022-2025. For alkylation of sulfones containing the F_3CSO_2 group, see Hendrickson; Sternbach; Bair *Acc. Chem. Res.* **1977**, 10, 306-312.

¹⁴⁹⁵For examples, see Truce; Hollister; Lindy; Parr *J. Org. Chem.* **1968**, 33, 43; Julia; Arnould *Bull. Soc. Chim. Fr.* **1973**, 743, 746; Bird; Stirling, Ref. 1465.

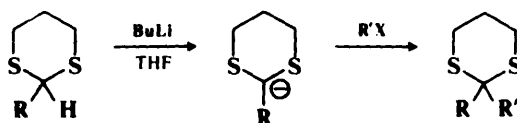
¹⁴⁹⁶Reich; Shah *J. Am. Chem. Soc.* **1975**, 97, 3250.

0-96 Alkylation of Carboxylic Acid Salts **α -Carboxyalkyl-de-halogenation**

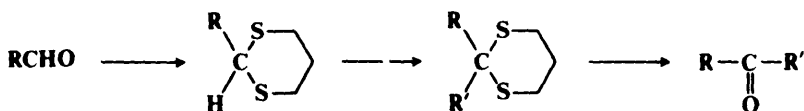
Carboxylic acids can be alkylated in the α position by conversion of their salts to dianions [which actually have the enolate structures $\text{RCH}=\text{C}(\text{O}^-)_2$ ¹⁴⁹⁷] by treatment with a strong base such as lithium diisopropylamide.¹⁴⁹⁸ The use of Li^+ as the counterion is important, because it increases the solubility of the dianionic salt. The reaction has been applied¹⁴⁹⁹ to primary alkyl, allylic, and benzylic halides, and to carboxylic acids of the form RCH_2COOH and $\text{RR}'\text{CHCOOH}$.¹⁴⁵⁴ This method, which is an example of the alkylation of a dianion at its more nucleophilic position (see p. 368), is an alternative to the malonic ester synthesis (0-94) as a means of preparing carboxylic acids and has the advantage that acids of the form $\text{RR}'\text{R}''\text{CCOOH}$ can also be prepared. In a related reaction, methylated aromatic acids can be alkylated at the methyl group by a similar procedure.¹⁵⁰⁰



OS V, 526; VI, 517; VII, 249. See also OS VII, 164.

0-97 Alkylation at a Position α to a Hetero Atom. Alkylation of 1,3-Dithianes**2-(2-Alkyl-1,3-dithianyl)-de-halogenation**

1,3-Dithianes can be alkylated¹⁵⁰¹ if a proton is first removed by treatment with butyllithium in THF.¹⁵⁰² Since 1,3-dithianes can be prepared by treatment of an aldehyde or its acetal (see OS VI, 556) with 1,3-propanedithiol (6-11) and can be hydrolyzed (0-6), this is a method for the conversion of an aldehyde to a ketone¹⁵⁰³ (see also 0-95, 0-105, and 8-9):



¹⁴⁹⁷Mladenova; Blagoev; Gaudemar; Dardoize; Lallemand *Tetrahedron* **1981**, 37, 2153.

¹⁴⁹⁸Cregar *J. Am. Chem. Soc.* **1967**, 89, 2500, **1970**, 92, 1397; Pfeffer; Silbert; Chirinko *J. Org. Chem.* **1972**, 37, 451.

¹⁴⁹⁹For lists of reagents, with references, see Ref. 508, pp. 867-870ff.

¹⁵⁰⁰Cregar *J. Am. Chem. Soc.* **1970**, 92, 1396.

¹⁵⁰¹Corey; Seebach *Angew. Chem. Int. Ed. Engl.* **1965**, 4, 1075, 1077 [*Angew. Chem.* 77, 1134, 1135]; Seebach; Corey *J. Org. Chem.* **1975**, 40, 231. For reviews, see Page; van Niel; Prodger *Tetrahedron* **1989**, 45, 7643-7677; Ager, in Hase, Ref. 1480, pp. 19-37; Seebach *Synthesis* **1969**, 17-36, especially pp. 24-27; Olsen; Currie, in Patai, Ref. 744, pt. 2, pp. 536-547.

¹⁵⁰²For an improved method of removing the proton, see Lipshutz; Garcia *Tetrahedron Lett.* **1990**, 31, 7261.

¹⁵⁰³For examples of the use of this reaction, with references, see Ref. 508, pp. 721-725.

This is another example of umpolung (see 0-95);¹⁴⁷⁸ the normally electrophilic carbon of the aldehyde is made to behave as a nucleophile. The reaction can be applied to the unsubstituted dithiane ($R = H$) and one or two alkyl groups can be introduced, so a wide variety of aldehydes and ketones can be made starting with formaldehyde.¹⁵⁰⁴ R' may be primary or secondary alkyl or benzylic. Iodides give the best results. The reaction has been used to close rings.¹⁵⁰⁵ A similar synthesis of aldehydes can be performed starting with ethyl ethylthiomethyl sulfoxide $\text{EtSOCH}_2\text{SEt}$.¹⁵⁰⁶

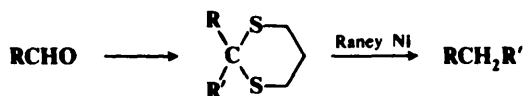
The group **A** may be regarded as a structural equivalent for the carbonyl group **B**, since introduction of **A** into a molecule is actually an indirect means of introducing **B**. It is



convenient to have a word for units within molecules; such a word is *synthon*, introduced by Corey,¹⁵⁰⁷ which is defined as a structural unit within a molecule that can be formed and/or assembled by known or conceivable synthetic operations. There are many other synthons equivalent to **A** and **B**, for example, **C** (by reactions 6-25 and 9-3) and **D** (by reactions 0-2 and 6-24).¹⁵⁰⁸

Carbanions generated from 1,3-dithianes also react with epoxides¹⁵⁰⁹ to give the expected products.

Another useful application of this reaction stems from the fact that dithianes can be desulfurated with Raney nickel (4-36). Aldehydes can therefore be converted to chain-extended hydrocarbons:¹⁵¹⁰



Similar reactions have been carried out with other thioacetals, as well as with compounds containing three thioether groups on a carbon.¹⁵¹¹

The carbanion derived from a 1,3-dithiane is stabilized by two thioether groups. If a strong enough base is used, it is possible to alkylate at a position adjacent to only one such group. For example, benzylic and allylic thioethers (RSCH_2Ar and $\text{RSCH}_2\text{CH}=\text{CH}_2$) and thioethers of the form RSCH_3 ($R = \text{tetrahydrofuryl}$ or $2\text{-tetrahydropyranyl}$)¹⁵¹² have been successfully alkylated at the carbon adjacent to the sulfur atom.¹⁵¹³ In the case of the RSCH_3

¹⁵⁰⁴For a direct conversion of RX to RCHO , see 0-102.

¹⁵⁰⁵For example, see Seebach; Jones; Corey *J. Org. Chem.* **1968**, 33, 300; Hylton; Boeckelheide *J. Am. Chem. Soc.* **1968**, 90, 6887; Ogura; Yamashita; Suzuki; Tsuchihashi *Tetrahedron Lett.* **1974**, 3653.

¹⁵⁰⁶Richman; Herrmann; Schlessinger *Tetrahedron Lett.* **1973**, 3267. See also Ogura; Tsuchihashi *Tetrahedron Lett.* **1971**, 3151; Schill; Jones *Synthesis* **1974**, 117; Hori; Hayashi; Midorikawa *Synthesis* **1974**, 705.

¹⁵⁰⁷Corey *Pure Appl. Chem.* **1967**, 14, 19-37, pp. 20-23.

¹⁵⁰⁸For a long list of synthons for RCO , with references, see Hase; Koskimies *Aldrichimica Acta* **1982**, 15, 35-41.

¹⁵⁰⁹For example, see Corey; Seebach, Ref. 1501; Jones; Grayshan *Chem. Commun.* **1970**, 141, 741.

¹⁵¹⁰For examples, see Hylton; Boeckelheide, Ref. 1505; Jones; Grayshan, Ref. 1509.

¹⁵¹¹For example, see Seebach *Angew. Chem. Int. Ed. Engl.* **1967**, 6, 442 [*Angew. Chem.* **79**, 468]; Olsson *Acta Chem. Scand.* **1968**, 22, 2390; Mori; Hashimoto; Takenaka; Takigawa *Synthesis* **1975**, 720; Lissel *Liebigs Ann. Chem.* **1982**, 1589.

¹⁵¹²Block; Aslam *J. Am. Chem. Soc.* **1985**, 107, 6729.

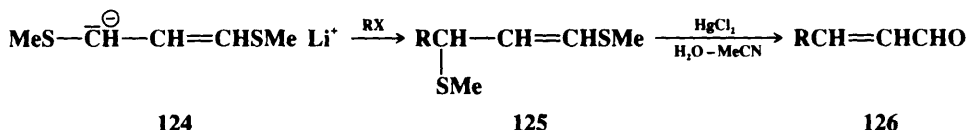
¹⁵¹³Biellmann; Ducep *Tetrahedron Lett.* **1968**, 5629, **1969**, 3707, *Tetrahedron* **1971**, 27, 5861. See also Narasaka; Hayashi; Mukaiyama *Chem. Lett.* **1972**, 259.

compounds, alkylation took place at the methyl group. Stabilization by one thioether group has also been used in a method for the homologization of primary halides.¹⁵¹⁴ Thioanisole is treated with BuLi to give the corresponding anion¹⁵¹⁵ which reacts with the halide to give



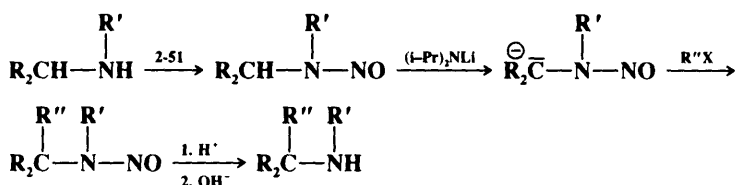
the thioether **123**. **123** is then refluxed with a mixture of methyl iodide and sodium iodide in dimethylformamide. By this sequence an alkyl halide RX is converted to its homolog RCH₂X by a pathway involving two laboratory steps (see also 0-92).

Vinyl sulfides containing an α hydrogen can also be alkylated¹⁵¹⁶ by alkyl halides or epoxides. In one application, the ion **124**, which can be prepared in three steps from epichlorohydrin, reacts with alkyl halides to give the bis(methylthio) compound **125**,¹⁵¹⁷ which



is easily hydrolyzed¹⁵¹⁸ with HgCl₂ in aqueous MeCN. This is a method for converting an alkyl halide RX to an α,β-unsaturated aldehyde (**126**) using **124**, which is the synthetic equivalent of the unknown $\text{HC}^{\ominus}=\text{CH}-\text{CHO}$ ion.¹⁵¹⁹ Even simple alkyl aryl sulfides RCH₂SAr and RR'CHSAr have been alkylated α to the sulfur.¹⁵²⁰

Alkylation can also be carried out, in certain compounds, at positions α to other hetero atoms,¹⁵²¹ for example, at a position α to the nitrogen of tertiary amines.¹⁵²² Alkylation α to the nitrogen of primary or secondary amines is not generally feasible because an NH hydrogen is usually more acidic than a CH hydrogen. It has been accomplished, however, by replacing the NH hydrogens with other (removable) groups.¹⁵²³ In one example, a secondary amine is converted to its N-nitroso derivative (**2-51**).¹⁵²⁴ The N-nitroso product is



¹⁵¹⁴Corey; Jautelat *Tetrahedron Lett.* **1968**, 5787.

¹⁵¹⁵Corey; Seebach *J. Org. Chem.* **1966**, 31, 4097.

¹⁵¹⁶Oshima; Shimoji; Takahashi; Yamamoto; Nozaki *J. Am. Chem. Soc.* **1973**, 95, 2694.

¹⁵¹⁷Corey; Erickson; Noyori *J. Am. Chem. Soc.* **1971**, 93, 1724.

¹⁵¹⁸Corey; Shulman *J. Org. Chem.* **1970**, 35, 777. See, however, Mura; Majetich; Grieco; Cohen *Tetrahedron Lett.* **1975**, 4437.

¹⁵¹⁹For references to other synthetic equivalents of this ion, see Funk; Bolton *J. Am. Chem. Soc.* **1968**, 110, 1290.

¹⁵²⁰Dolak; Bryson *Tetrahedron Lett.* **1977**, 1961.

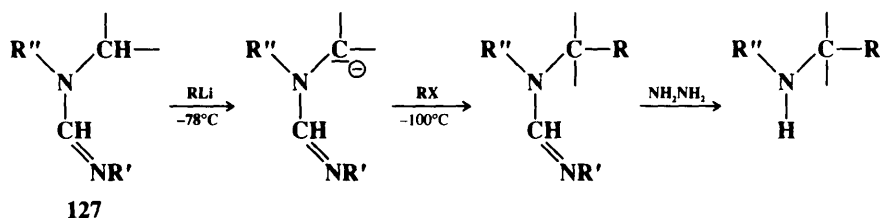
¹⁵²¹For a review of anions α to a selenium atom on small rings, see Krief *Top. Curr. Chem.* **1987**, 135, 1-75. For alkylation α to boron, see Pelter; Smith; Brown *Borane Reagents*; Academic Press: New York, 1988, pp. 336-341.

¹⁵²²Lepley; Khan *J. Org. Chem.* **1966**, 31, 2061, 2064, *Chem. Commun.* **1967**, 1198; Lepley; Giumanini *J. Org. Chem.* **1966**, 31, 2055; Ahlbrecht; Dollinger *Tetrahedron Lett.* **1984**, 25, 1353.

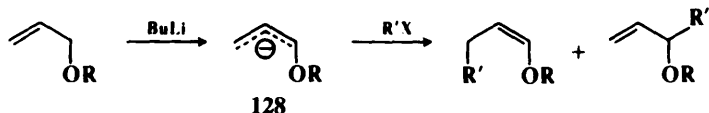
¹⁵²³For a review, see Beak; Zajdel; Reitz *Chem. Rev.* **1984**, 84, 471-523.

¹⁵²⁴Seebach; Enders; Renger *Chem. Ber.* **1977**, 110, 1852; Renger; Kalinowski; Seebach *Chem. Ber.* **1977**, 110, 1866. For a review, see Seebach; Enders *Angew. Chem. Int. Ed. Engl.* **1975**, 14, 15-32 [*Angew. Chem.* **87**, 1-17].

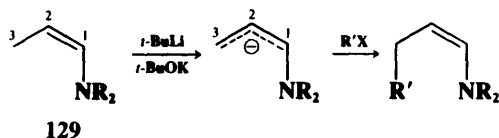
easily hydrolyzed to the product amine (**9-53**).¹⁵²⁵ Alkylation of secondary and primary amines has also been accomplished with more than ten other protecting groups, involving conversion of amines to amides, carbamates,¹⁵²⁶ formamidines,¹⁵²⁷ and phosphoramides.¹⁵²³ In the case of formamidines (**127**) use of a chiral R' leads to a chiral amine, in high enantiomeric excess, even when R is not chiral.¹⁵²⁸



A proton can be removed from an allylic ether by treatment with an alkyl lithium at about -70°C (at higher temperatures the Wittig rearrangement—**8-23**—takes place) to give the ion **128**, which reacts with alkyl halides to give the two products shown.¹⁵²⁹ Similar



reactions¹⁵³⁰ have been reported for allylic¹⁵³¹ and vinylic tertiary amines. In the latter case, enamines **129**, treated with a strong base, are converted to anions that are then alkylated, generally at C-3.¹⁵³² (For direct alkylation of enamines at C-2, see **2-19**.)



It is also possible to alkylate a methyl, ethyl, or other primary group of an aryl ester ArCOOR, where Ar is a 2,4,6-trialkylphenyl group.¹⁵³³ Since esters can be hydrolyzed to alcohols, this constitutes an indirect alkylation of primary alcohols. Methanol has also been alkylated by converting it to ⁻CH₂O.¹⁵³⁴

OS VI, 316, 364, 542, 704, 869; **67**, 60.

¹⁵²⁵Fridman; Mukhametshin; Novikov *Russ. Chem. Rev.* **1971**, *40*, 34-50, pp. 41-42.

¹⁵²⁶For the use of *t*-butyl carbamates, see Beak; Lee *Tetrahedron Lett.* **1989**, *30*, 1197.

¹⁵²⁷For a review, see Meyers *Aldrichimica Acta* **1985**, *18*, 59-68.

¹⁵²⁸Meyers; Fuentes; Kubota *Tetrahedron* **1984**, *40*, 1361; Gawley; Hart; Goicoechea-Pappas; Smith *J. Org. Chem.* **1986**, *51*, 3076; Meyers; Dickman *J. Am. Chem. Soc.* **1987**, *109*, 1263; Gawley *J. Am. Chem. Soc.* **1987**, *109*, 1265; Meyers; Miller; White *J. Am. Chem. Soc.* **1988**, *110*, 4778; Gonzalez; Meyers *Tetrahedron Lett.* **1989**, *30*, 43, 47.

¹⁵²⁹Evans; Andrews; Buckwalter *J. Am. Chem. Soc.* **1974**, *96*, 5560; Still; Macdonald *J. Am. Chem. Soc.* **1974**, *96*, 5561; Ref. 1519. For a similar reaction with triple-bond compounds, see Hommes; Verkruijsse; Brandsma *Recl. Trav. Chim. Pays-Bas* **1980**, *99*, 113, and references cited therein.

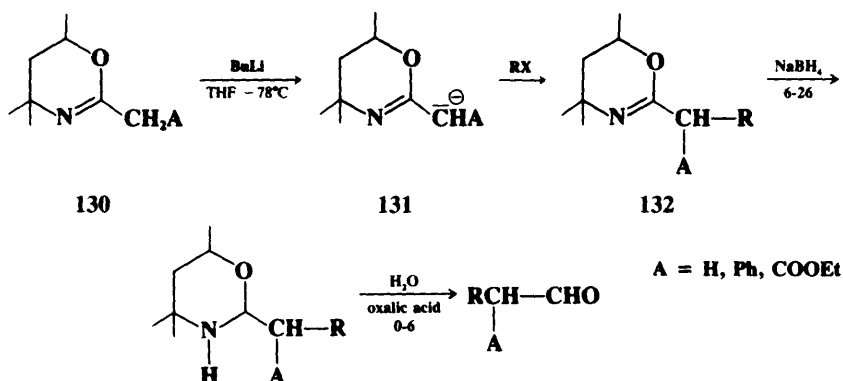
¹⁵³⁰For a review of allylic and benzylic carbanions substituted by hetero atoms, see Biellmann; Ducep *Org. React.* **1982**, *27*, 1-344.

¹⁵³¹Martin; DuPriest *Tetrahedron Lett.* **1977**, 3925 and references cited therein.

¹⁵³²For a review, see Ahlbrecht *Chimia* **1977**, *31*, 391-403.

¹⁵³³Beak; McKinnie *J. Am. Chem. Soc.* **1977**, *99*, 5213; Beak; Carter *J. Org. Chem.* **1981**, *46*, 2363.

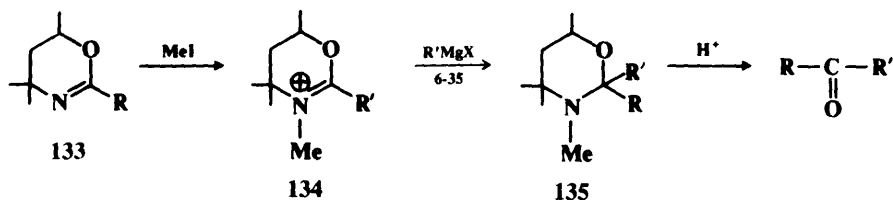
¹⁵³⁴Seebach; Meyer *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 438 [*Angew. Chem.* **88**, 484].

0-98 Alkylation of Dihydro-1,3-Oxazine. The Meyers Synthesis of Aldehydes, Ketones, and Carboxylic Acids

A synthesis of aldehydes¹⁵³⁵ developed by Meyers¹⁵³⁶ begins with the commercially available dihydro-1,3-oxazine derivatives **130** (A = H, Ph, or COOEt).¹⁵³⁷ Though the ions (**131**) prepared from **130** are ambident, they are regioselectively alkylated at carbon by a wide variety of alkyl bromides and iodides. R can be primary or secondary alkyl, allylic, or benzylic and can carry another halogen or a CN group.¹⁵³⁸ The alkylated oxazine **132** is then reduced and hydrolyzed to give an aldehyde containing two more carbons than the starting RX. This method thus complements **0-97** which converts RX to an aldehyde containing one more carbon. Since A can be H, mono- or disubstituted acetaldehydes can be produced by this method.

The ion **131** also reacts with epoxides, to form γ -hydroxy aldehydes after reduction and hydrolysis,¹⁵³⁹ and with aldehydes and ketones (**6-41**). Similar aldehyde synthesis has also been carried out with thiazoles¹⁵⁴⁰ and thiazolines¹⁵⁴¹ (five-membered rings containing N and S in the 1 and 3 positions).

The reaction has been extended to the preparation of ketones:¹⁵⁴² treatment of a dihydro-1,3-oxazine (**133**) with methyl iodide forms the iminium salt **134** (**0-43**) which, when treated with a Grignard reagent or organolithium compound (**6-35**), produces **135** which can be



¹⁵³⁵For examples of the preparation of aldehydes and ketones by the reactions in this section, see Ref. 508, pp. 729-732.

¹⁵³⁶Meyers; Nabeya; Adickes; Politzer; Malone; Kovelesky; Nolen; Portnoy *J. Org. Chem.* **1973**, 38, 36.

¹⁵³⁷For reviews of the preparation and reactions of **130** see Schmidt *Synthesis* **1972**, 333-350; Collington *Chem. Ind. (London)* **1973**, 987-991.

¹⁵³⁸Meyers; Malone; Adickes *Tetrahedron Lett.* **1970**, 3715.

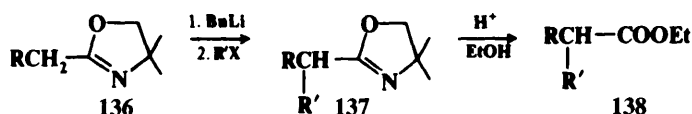
¹⁵³⁹Adickes; Politzer; Meyers *J. Am. Chem. Soc.* **1969**, 91, 2155.

¹⁵⁴⁰Altman; Richheimer *Tetrahedron Lett.* **1971**, 4709.

¹⁵⁴¹Meyers; Durandetta *J. Org. Chem.* **1975**, 40, 2021.

¹⁵⁴²Meyers; Smith *J. Am. Chem. Soc.* **1970**, 92, 1084; *J. Org. Chem.* **1972**, 37, 4289.

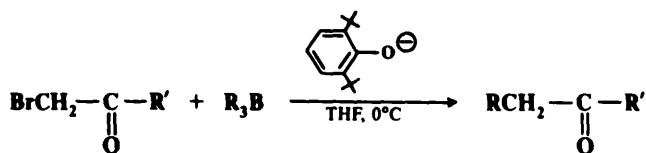
hydrolyzed to a ketone. R can be alkyl, cycloalkyl, aryl, benzylic, etc., and R' can be alkyl, aryl, benzylic, or allylic. **130**, **132**, and **133** themselves do not react with Grignard reagents. In another procedure, 2-oxazolines¹⁵⁴³ (**136**) can be alkylated to give **137**,¹⁵⁴⁴ which are easily



converted directly to the esters **138** by heating in 5 to 7% ethanolic sulfuric acid. **136** and **137** are thus synthons for carboxylic acids; this is another indirect method for the α alkylation of a carboxylic acid,¹⁵⁴⁵ representing an alternative to the malonic ester synthesis (**0-94**) and to **0-96** and **0-99**. The method can be adapted to the preparation of optically active carboxylic acids by the use of a chiral reagent.¹⁵⁴⁶ Note that, unlike **130**, **136** can be alkylated even if R is alkyl. However, the C=N bond of **136** and **137** cannot be effectively reduced, so that aldehyde synthesis is not feasible here.¹⁵⁴⁷

OS VI, 905.

0-99 Alkylation with Trialkylboranes Alkyl-de-halogenation



Trialkylboranes react rapidly and in high yields with α -halo ketones,¹⁵⁴⁸ α -halo esters,¹⁵⁴⁹ α -halo nitriles,¹⁵⁵⁰ and α -halo sulfonyl derivatives (sulfones, sulfonic esters, sulfonamides)¹⁵⁵¹ in the presence of a base to give, respectively, alkylated ketones, esters, nitriles, and sulfonyl derivatives.¹⁵⁵² Potassium *t*-butoxide is often a suitable base, but potassium 2,6-di-*t*-butylphenoxide at 0°C in THF gives better results in most cases, possibly because the large bulk of the two *t*-butyl groups prevents the base from coordinating with the R₃B.¹⁵⁵³ The trialkylboranes are prepared by treatment of 3 moles of an alkene with 1 mole of BH₃

¹⁵⁴³For a review, see Meyers; Mihelich *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 270-281 [*Angew. Chem.* **88**, 321-332].

¹⁵⁴⁴Meyers; Temple; Nolen; Mihelich *J. Org. Chem.* **1974**, *39*, 2778; Meyers; Mihelich; Nolen *J. Org. Chem.* **1974**, *39*, 2783; Meyers; Mihelich; Kamata *J. Chem. Soc., Chem. Commun.* **1974**, 768.

¹⁵⁴⁵For reviews, see Meyers, *Pure Appl. Chem.* **1979**, *51*, 1255-1268. *Acc. Chem. Res.* **1978**, *11*, 375-381. See also Hoobler; Bergbreiter; Newcomb *J. Am. Chem. Soc.* **1978**, *100*, 8182; Meyers; Snyder; Ackerman *J. Am. Chem. Soc.* **1978**, *100*, 8186.

¹⁵⁴⁶For a review of asymmetric synthesis via chiral oxazolines, see Lutomski; Meyers, in Morrison, Ref. 1467, pp. 213-274.

¹⁵⁴⁷Meyers; Temple *J. Am. Chem. Soc.* **1970**, *92*, 6644, 6646.

¹⁵⁴⁸Brown; Rogić; Rathke *J. Am. Chem. Soc.* **1968**, *90*, 6218.

¹⁵⁴⁹Brown; Rogić; Rathke; Kabalka *J. Am. Chem. Soc.* **1968**, *90*, 818.

¹⁵⁵⁰Brown; Nambu; Rogić *J. Am. Chem. Soc.* **1969**, *91*, 6854.

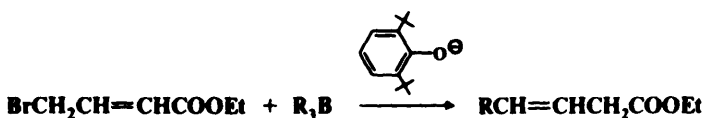
¹⁵⁵¹Truce; Mura; Smith; Young *J. Org. Chem.* **1974**, *39*, 1449.

¹⁵⁵²For reviews, see Negishi; Idacavage *Org. React.* **1985**, *33*, 1-246, pp. 42-43, 143-150; Weill-Raynal *Synthesis* **1976**, 633-651; Brown; Rogić *Organomet. Chem. Synth.* **1972**, *1*, 305-327; Rogić *Intra-Sci. Chem. Rep.* **1973**, *7*(2), 155-167; Brown *Boranes in Organic Chemistry*; Cornell University Press: Ithaca, NY, 1972, pp. 372-391, 404-409; Cragg, Ref. 1167, pp. 275-278, 283-287.

¹⁵⁵³Brown; Nambu; Rogić *J. Am. Chem. Soc.* **1969**, *91*, 6852, 6854, 6855.

(5-12).¹⁵⁵⁴ With appropriate boranes, the R group transferred to α -halo ketones, nitriles, and esters can be vinylic,¹⁵⁵⁵ or (for α -halo ketones and esters) aryl.¹⁵⁵⁶

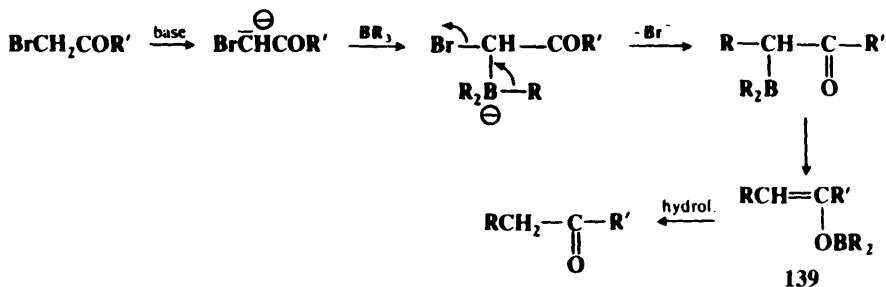
The reaction can be extended to α,α -dihalo esters¹⁵⁵⁷ and α,α -dihalo nitriles.¹⁵⁵⁸ It is possible to replace just one halogen or both. In the latter case the two alkyl groups can be the same or different. When dialkylation is applied to dihalo nitriles, the two alkyl groups can be primary or secondary, but with dihalo esters, dialkylation is limited to primary R. Another extension is the reaction of boranes with γ -halo- α,β -unsaturated esters.¹⁵⁵⁹ Alkylation takes place in the γ position, but the double bond migrates, e.g.,



In this case, however, double-bond migration is an advantage, because nonconjugated β,γ -unsaturated esters are usually much more difficult to prepare than their α,β -unsaturated isomers.

The alkylation of activated halogen compounds is one of several reactions of trialkylboranes developed by H. C. Brown¹⁵⁶⁰ (see also 5-12, 5-19, 8-24 to 8-28, etc.). These compounds are extremely versatile and can be used for the preparation of many types of compounds. In this reaction, for example, an alkene (through the BR_3 prepared from it) can be coupled to a ketone, a nitrile, a carboxylic ester, or a sulfonyl derivative. Note that this is still another indirect way to alkylate a ketone (see 0-95) or a carboxylic acid (see 0-96), and provides an additional alternative to the malonic ester and acetoacetic ester syntheses (0-94).

Although superficially this reaction resembles 0-87 it is likely that the mechanism is quite different, involving migration of an R group from boron to carbon (see also 8-24 to 8-28). The mechanism is not known with certainty,¹⁵⁶¹ but it may be tentatively shown as (illustrated for an α -halo ketone):



¹⁵⁵⁴For an improved procedure, with B-R-9-BBN (see p. 785), see Brown; Rogić *J. Am. Chem. Soc.* **1969**, *91*, 2146; Brown; Rogić; Nambu; Rathke *J. Am. Chem. Soc.* **1969**, *91*, 2147; Katz; Dubois; Lion *Bull. Soc. Chim. Fr.* **1977**, 683.

¹⁵⁵⁵Brown; Bhat; Campbell *J. Org. Chem.* **1986**, *51*, 3398.

¹⁵⁵⁶Brown; Rogić *J. Am. Chem. Soc.* **1969**, *91*, 4304.

¹⁵⁵⁷Brown; Rogić; Rathke; Kabalka *J. Am. Chem. Soc.* **1968**, *90*, 1911.

¹⁵⁵⁸Nambu; Brown *J. Am. Chem. Soc.* **1970**, *92*, 5790.

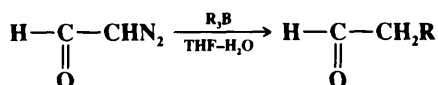
¹⁵⁵⁹Brown; Nambu *J. Am. Chem. Soc.* **1970**, *92*, 1761.

¹⁵⁶⁰Brown *Organic Syntheses via Boranes*; Wiley: New York, 1975. *Hydroboration*; W.A. Benjamin: New York, 1962. *Boranes in Organic Chemistry*, Ref. 1552; Pelter; Smith; Brown, Ref. 1521.

¹⁵⁶¹See Prager; Reece *Aust. J. Chem.* **1975**, *28*, 1775.

The first step is removal of the acidic proton by the base to give an enolate ion which combines with the borane (Lewis acid-base reaction). An R group then migrates, displacing the halogen leaving group.¹⁵⁶² Another migration follows, this time of BR_2 from carbon to oxygen to give the enol borinate **139**¹⁵⁶³ which is hydrolyzed. Configuration at R is retained.¹⁵⁶⁴

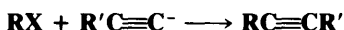
The reaction has also been applied to compounds with other leaving groups. Diazo ketones, diazo esters, diazo nitriles, and diazo aldehydes¹⁵⁶⁵ react with trialkylboranes in a similar manner, e.g.,



The mechanism is probably also similar. In this case a base is not needed, since the carbon already has an available pair of electrons. The reaction with diazo aldehydes¹⁵⁶⁶ is especially notable, since successful reactions cannot be obtained with α -halo aldehydes.¹⁵⁶⁷

OS VI, 919.

0-100 Alkylation at an Alkynyl Carbon Alkynyl-de-halogenation



The reaction between alkyl halides and acetylide ions is useful but of limited scope.¹⁵⁶⁸ Only primary halides unbranched in the β position give good yields, though allylic halides can be used if CuI is present.¹⁵⁶⁹ If acetylene is the reagent, two different groups can be successively attached. Sulfates, sulfonates, and epoxides¹⁵⁷⁰ are sometimes used as substrates. The acetylide ion is often prepared by treatment of an alkyne with a strong base such as NaNH_2 . Magnesium acetylides (ethynyl Grignard reagents; prepared as in **2-21**) are also frequently used, though they react only with active substrates, such as allylic, benzylic, and propargylic halides, and not with primary alkyl halides. Alternatively, the alkyl halide can be treated with a lithium acetylide-ethylenediamine complex.¹⁵⁷¹ If 2 moles of a very strong base are used, alkylation can be effected at a carbon α to a terminal triple bond: $\text{RCH}_2\text{C}\equiv\text{CH} + 2\text{BuLi} \rightarrow \text{RCHC}\equiv\text{C}^- + \text{R}'\text{Br} \rightarrow \text{RR}'\text{CHC}\equiv\text{C}^-$.¹⁵⁷² For another method of alkylating at an alkynyl carbon, see **8-28**.

OS IV, 117; VI, 273, 564, 595; 67, 193. Also see OS IV, 801; VI, 925.

¹⁵⁶²It has been shown that this migration occurs stereospecifically with inversion in the absence of a solvent, but nonstereospecifically in the presence of a solvent such as THF or dimethyl sulfide: Midland; Zolopa; Halterman *J. Am. Chem. Soc.* **1979**, 101, 248. See also Midland; Preston *J. Org. Chem.* **1980**, 45, 747.

¹⁵⁶³Pasto; Wojtkowski *Tetrahedron Lett.* **1970**, 215, Ref. 1490.

¹⁵⁶⁴Brown; Rogić; Rathke; Kabalka *J. Am. Chem. Soc.* **1969**, 91, 2150.

¹⁵⁶⁵Hooz; Linke *J. Am. Chem. Soc.* **1968**, 90, 5936, 6891; Hooz; Gunn; Kono *Can. J. Chem.* **1971**, 49, 2371; Mikhailov; Gurskii *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1973**, 22, 2588.

¹⁵⁶⁶Hooz; Morrison *Can. J. Chem.* **1970**, 48, 868.

¹⁵⁶⁷For an improved procedure, see Hooz; Bridson; Calzada; Brown; Midland; Levy *J. Org. Chem.* **1973**, 38, 2574.

¹⁵⁶⁸For reviews, see Ben-Efraim, in Patai *The Chemistry of the Carbon-Carbon Triple Bond*; Wiley: New York, 1978, pp. 790-800; Ziegenbein, in Vieh *Acetylenes*; Marcel Dekker: New York, 1969, pp. 185-206, 241-244. For a discussion of the best ways of preparing various types of alkyne, see Bernadou; Mesnard; Miginiac *J. Chem. Res. (S)* **1978**, 106, 1979, 190.

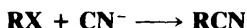
¹⁵⁶⁹Bourgain; Normant *Bull. Soc. Chim. Fr.* **1973**, 1777; Jeffery *Tetrahedron Lett.* **1989**, 30, 2225.

¹⁵⁷⁰For example, see Fried; Lin; Ford *Tetrahedron Lett.* **1969**, 1379; Krause; Seebach *Chem. Ber.* **1988**, 121, 1315.

¹⁵⁷¹Smith; Beumel *Synthesis* **1974**, 441.

¹⁵⁷²Bhanu; Scheinmann *J. Chem. Soc., Perkin Trans. 1* **1979**, 1218; Quillinan; Scheinmann *Org. Synth.* VI, 595.

0-101 Preparation of Nitriles Cyano-de-halogenation



The reaction between cyanide ion (isoelectronic with $\text{HC}\equiv\text{C}^-$ and of similar geometry) and alkyl halides is a convenient method for the preparation of nitriles.¹⁵⁷³ Primary, benzylic, and allylic halides give good yields of nitriles; secondary halides give moderate yields. The reaction fails for tertiary halides, which give elimination under these conditions. Many other groups on the molecule do not interfere. Though a number of solvents have been used, the high yields and short reaction times observed with dimethyl sulfoxide make it a very good solvent for this reaction.¹⁵⁷⁴ Other ways to obtain high yields under mild conditions are to use a phase transfer catalyst¹⁵⁷⁵ or ultrasound.¹⁵⁷⁶ This is an important way of increasing the length of a carbon chain by one carbon, since nitriles are easily hydrolyzed to carboxylic acids (6-5).

The cyanide ion is an ambident nucleophile and isocyanides may be side products. If the preparation of isocyanides is desired, they can be made the main products by the use of silver or copper(I) cyanide¹⁵⁷⁷ (p. 368). Vinylic bromides can be converted to vinylic cyanides with CuCN ,¹⁵⁷⁸ with KCN , a crown ether, and a $\text{Pd}(0)$ complex,¹⁵⁷⁹ with KCN and a $\text{Ni}(0)$ catalyst,¹⁵⁸⁰ or with $\text{K}_4\text{Ni}_2(\text{CN})_6$.¹⁵⁸¹ Tertiary halides can be converted to the corresponding nitriles by treatment with trimethylsilyl cyanide in the presence of catalytic amounts of SnCl_4 : $\text{R}_3\text{CCl} + \text{Me}_3\text{SiCN} \rightarrow \text{R}_3\text{CCN}$.¹⁵⁸²

The cyanide nucleophile also reacts with compounds containing other leaving groups. Esters of sulfuric and sulfonic acids behave like halides. Vinylic triflates give vinylic cyanides when treated with LiCN , a crown ether, and a palladium catalyst.¹⁵⁸³ Epoxides give β -hydroxy nitriles. Primary, secondary, and tertiary alcohols are converted to nitriles in good yields by treatment with NaCN , Me_3SiCl , and a catalytic amount of NaI in DMF-MeCN .¹⁵⁸⁴ One alkoxy group of acetals is replaced by CN [$\text{R}_2\text{C}(\text{OR}')_2 \rightarrow \text{R}_2\text{C}(\text{OR}')\text{CN}$] with Me_3SiCN and a catalyst¹⁵⁸⁵ or with $t\text{-BuNC}$ and TiCl_4 .¹⁵⁸⁶ NaCN in HMPA selectively cleaves methyl esters in the presence of ethyl esters: $\text{RCOOMe} + \text{CN}^- \rightarrow \text{MeCN} + \text{RCOO}^-$.¹⁵⁸⁷

OS I, 46, 107, 156, 181, 254, 256, 536; II, 292, 376; III, 174, 372, 557; IV, 438, 496, 576; V, 578, 614.

¹⁵⁷³For reviews, see, in Patai; Rappoport, Ref. 353, the articles by Fatiadi, pt. 2, pp. 1057-1303, and Friedrich, pt. 2, pp. 1343-1390; Friedrich; Wallenfels, in Rappoport *The Chemistry of the Cyano Group*; Wiley: New York, 1970, pp. 77-86.

¹⁵⁷⁴Smiley; Arnold *J. Org. Chem.* **1960**, 25, 257; Friedman; Shechter *J. Org. Chem.* **1960**, 25, 877.

¹⁵⁷⁵For reviews, see Starks; Liotta, Ref. 404, pp. 94-112; Weber; Gokel *Phase Transfer Catalysis in Organic Synthesis*, Ref. 404, pp. 96-108. See also Bram; Loupy; Pedoussaut *Tetrahedron Lett.* **1986**, 27, 4171. *Bull. Soc. Chim. Fr.* **1986**, 124.

¹⁵⁷⁶Ando; Kawate; Ichihara; Hanafusa *Chem. Lett.* **1984**, 725.

¹⁵⁷⁷For an example, see Jackson; McKusick *Org. Synth.* **IV**, 438.

¹⁵⁷⁸For example, see Koelsch *J. Am. Chem. Soc.* **1936**, 58, 1328; Newman; Boden *J. Org. Chem.* **1961**, 26, 2525; Lapouyade; Daney; Lapenue; Bouas-Laurent *Bull. Soc. Chim. Fr.* **1973**, 720.

¹⁵⁷⁹Yamamura; Murahashi *Tetrahedron Lett.* **1977**, 4429.

¹⁵⁸⁰Sakakibara; Yadani; Ibuki; Sakai; Uchino *Chem. Lett.* **1982**, 1565; Procházka; Šíroky *Collect. Czech. Chem. Commun.* **1983**, 48, 1765.

¹⁵⁸¹Corey; Hegedus *J. Am. Chem. Soc.* **1969**, 91, 1233. See also Stuhl *J. Org. Chem.* **1985**, 50, 3934.

¹⁵⁸²Reetz; Chatziosifidis *Angew. Chem. Int. Ed. Engl.* **1981**, 20, 1017 [*Angew. Chem.* 93, 1075].

¹⁵⁸³Piers; Fleming *J. Chem. Soc., Chem. Commun.* **1989**, 756.

¹⁵⁸⁴Davis; Untch *J. Org. Chem.* **1981**, 46, 2985. See also Mizuno; Hamada; Shioiri *Synthesis* **1980**, 1007; Manna; Falck; Mioskowski *Synth. Commun.* **1985**, 15, 663; Camps; Gasol; Guerrero *Synth. Commun.* **1988**, 18, 445.

¹⁵⁸⁵Torii; Inokuchi; Kobayashi *Chem. Lett.* **1984**, 897; Soga; Takenoshita; Yamada; Mukaiyama *Bull. Chem. Soc. Jpn.* **1990**, 63, 3122.

¹⁵⁸⁶Ito; Imai; Segoe; Saegusa *Chem. Lett.* **1984**, 937.

¹⁵⁸⁷Müller; Siegfried *Helv. Chim. Acta* **1974**, 57, 987.

0-102 Direct Conversion of Alkyl Halides to Aldehydes and Ketones Formyl-de-halogenation



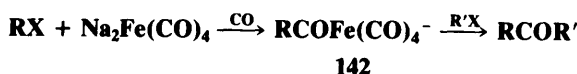
The direct conversion of alkyl bromides to aldehydes, with an increase in the chain length by one carbon, can be accomplished¹⁵⁸⁸ by treatment with sodium tetracarbonylferate(-II)¹⁵⁸⁹ (*Collman's reagent*) in the presence of triphenylphosphine and subsequent quenching of **140** with acetic acid. The reagent $\text{Na}_2\text{Fe}(\text{CO})_4$ can be prepared by treatment of iron pentacarbonyl $\text{Fe}(\text{CO})_5$ with sodium amalgam in THF. Good yields are obtained from primary alkyl bromides; secondary bromides give lower yields. The reaction is not satisfactory for benzylic bromides. The initial species produced from RX and $\text{Na}_2\text{Fe}(\text{CO})_4$ is the ion $\text{RFe}(\text{CO})_4^-$ (**141**) (which can be isolated¹⁵⁹⁰); it then reacts with Ph_3P to give **140**.¹⁵⁹¹

The synthesis can be extended to the preparation of ketones in six distinct ways.¹⁵⁹²

1. Instead of quenching **140** with acetic acid, the addition of a second alkyl halide at this point gives a ketone: $\text{140} + \text{R}'\text{X} \rightarrow \text{RCOR}'$.

2. Treatment of $\text{Na}_2\text{Fe}(\text{CO})_4$ with an alkyl halide in the absence of Ph_3P gives rise to a solution of **141**. Addition of a second alkyl halide produces a ketone: $\text{141} + \text{R}'\text{X} \rightarrow \text{RCOR}'$.

3. Treatment of $\text{Na}_2\text{Fe}(\text{CO})_4$ with an alkyl halide in the presence of CO results in an



acylated iron complex (**142**) that can be isolated.¹⁵⁹⁰ Treatment of this with a second alkyl halide gives a ketone.

4. Treatment of $\text{Na}_2\text{Fe}(\text{CO})_4$ with an acyl halide produces **142** which, when treated with an alkyl halide, gives a ketone or, when treated with an epoxide, gives an α,β -unsaturated ketone.¹⁵⁹³

5. Alkyl halides and tosylates react with $\text{Na}_2\text{Fe}(\text{CO})_4$ in the presence of ethylene to give alkyl ethyl ketones.¹⁵⁹⁴ The reaction was not successful for higher alkenes, except that where the double bond and the tosylate group are in the same molecule, 5- and 6-membered rings can be closed.¹⁵⁹⁵

6. If 1,4-dihalides are treated with $\text{K}_2\text{Fe}(\text{CO})_4$, 5-membered cyclic ketones are prepared.¹⁵⁹⁶

In the first stage of methods 1, 2, and 3, primary bromides, iodides, and tosylates and secondary tosylates can be used. The second stage of the first four methods requires more active substrates, such as primary iodides or tosylates or benzylic halides. Method 5 has been applied to primary and secondary substrates.

¹⁵⁸⁸Cooke *J. Am. Chem. Soc.* **1970**, *92*, 6080.

¹⁵⁸⁹For a review of this reagent, see Collman *Acc. Chem. Res.* **1975**, *8*, 342-347. For a review of the related tetracarbonylhydridoferrates $\text{MHFe}(\text{CO})_4$, see Brunet *Chem. Rev.* **1990**, *90*, 1041-1059.

¹⁵⁹⁰Siegl; Collman *J. Am. Chem. Soc.* **1972**, *94*, 2516.

¹⁵⁹¹For the mechanism of the conversion $\text{141} \rightarrow \text{140}$, see Collman; Finke; Cawse; Brauman *J. Am. Chem. Soc.* **1977**, *99*, 2515, **1978**, *100*, 4766.

¹⁵⁹²For the first four of these methods, see Collman; Winter; Clark *J. Am. Chem. Soc.* **1972**, *94*, 1788; Collman; Hoffman *J. Am. Chem. Soc.* **1973**, *95*, 2689.

¹⁵⁹³Yamashita; Yamamura; Kurimoto; Suemitsu *Chem. Lett.* **1979**, 1067.

¹⁵⁹⁴Cooke; Parlman *J. Am. Chem. Soc.* **1975**, *97*, 6863.

¹⁵⁹⁵McMurry; Andrus *Tetrahedron Lett.* **1980**, *21*, 4687, and references cited therein.

¹⁵⁹⁶Yamashita; Uchida; Tashika; Suemitsu *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2728.

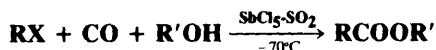
Aryl, benzylic, vinylic, and allylic halides have been converted to aldehydes by treatment with CO and Bu_3SnH , with a $\text{Pd}(0)$ catalyst.¹⁵⁹⁷ Various other groups do not interfere. Symmetrical ketones R_2CO can be prepared by treatment of a primary alkyl or benzylic halide with $\text{Fe}(\text{CO})_5$ and a phase transfer catalyst,¹⁵⁹⁸ or from a halide RX (R = primary alkyl, aryl, allylic, or benzylic) and CO by an electrochemical method involving a nickel complex.¹⁵⁹⁹ Several procedures for the preparation of ketones are catalyzed by palladium complexes, among them the following: Alkyl aryl ketones are formed in good yields by treatment of a mixture of an aryl iodide, an alkyl iodide, and a Zn-Cu couple with CO ($\text{ArI} + \text{RI} + \text{CO} \rightarrow \text{RCOAr}$);¹⁶⁰⁰ vinylic halides react with vinylic tin reagents in the presence of CO to give unsymmetrical divinyl ketones;¹⁶⁰¹ and aryl, vinylic, and benzylic halides can be converted to methyl ketones ($\text{RX} \rightarrow \text{RCOMe}$) by reaction with (α -ethoxyvinyl)tributyltin $\text{Bu}_3\text{SnC}(\text{OEt})=\text{CH}_2$.¹⁶⁰²

The conversion of alkyl halides to aldehydes and ketones can also be accomplished indirectly (0-97). See also 2-32.

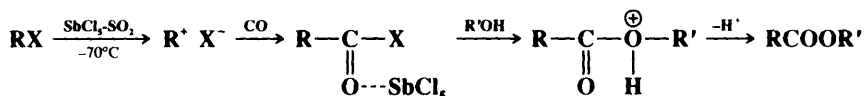
OS VI, 807.

0-103 Conversion of Alkyl Halides, Alcohols, or Alkanes to Carboxylic Acids and Their Derivatives

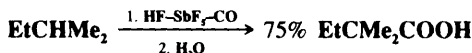
Alkoxy carbonyl-de-halogenation



Several methods, all based on carbon monoxide or metal carbonyls, have been developed for converting an alkyl halide to a carboxylic acid or an acid derivative with the chain extended by one carbon.¹⁶⁰³ When an alkyl halide is treated with $\text{SbCl}_5\text{-SO}_2$ at -70°C , it dissociates into the corresponding carbocation (p. 166). If carbon monoxide and an alcohol are present, a carboxylic ester is formed by the following route:¹⁶⁰⁴



This has also been accomplished with concentrated H_2SO_4 saturated with CO.¹⁶⁰⁵ Not surprisingly, only tertiary halides perform satisfactorily; secondary halides give mostly rearrangement products. An analogous reaction takes place with alkanes possessing a tertiary hydrogen, e.g.,¹⁶⁰⁶



¹⁵⁹⁷Baillargeon; Stille *J. Am. Chem. Soc.* **1986**, *108*, 452. See also Kasahara; Izumi; Yanai *Chem. Ind. (London)* **1983**, 898; Pri-Bar; Buchman *J. Org. Chem.* **1984**, *49*, 4009; Takeuchi; Tsuji; Watanabe *J. Chem. Soc., Chem. Commun.* **1986**, 351; Ben-David; Portnoy; Milstein *J. Chem. Soc., Chem. Commun.* **1989**, 1816.

¹⁵⁹⁸Kimura; Tomita; Nakanishi; Otsuji *Chem. Lett.* **1979**, 321; des Abbayes; Clément; Laurent; Tanguy; Thilmont *Organometallics* **1988**, *7*, 2293.

¹⁵⁹⁹Garnier; Rollin; Périchon *J. Organomet. Chem.* **1989**, *367*, 347.

¹⁶⁰⁰Tamaru; Ochiai; Yamada; Yoshida *Tetrahedron Lett.* **1983**, *24*, 3869.

¹⁶⁰¹Goure; Wright; Davis; Labadie; Stille *J. Am. Chem. Soc.* **1984**, *106*, 6417. For a similar preparation of diallyl ketones, see Merrifield; Godschalk; Stille *Organometallics* **1984**, *3*, 1108.

¹⁶⁰²Kosugi; Sumiya; Obara; Suzuki; Sano; Migita *Bull. Chem. Soc. Jpn.* **1987**, *60*, 767.

¹⁶⁰³For discussions of most of the reactions in this section, see Colquhoun; Holton; Thompson; Twigg *New Pathways for Organic Synthesis*; Plenum: New York, 1984, pp. 199-204, 212-220, 234-235. For lists of reagents, with references, see Ref. 508, pp. 850-851, 855-856, 859-860.

¹⁶⁰⁴Yoshimura; Nojima; Tokura *Bull. Chem. Soc. Jpn.* **1973**, *46*, 2164; Puzitskii; Pirozhkov; Ryabova; Myshenkova; Éidus *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1974**, *23*, 192.

¹⁶⁰⁵Takahashi; Yoneda *Synth. Commun.* **1989**, *19*, 1945.

¹⁶⁰⁶Paatz; Weisgerber *Chem. Ber.* **1967**, *100*, 984.

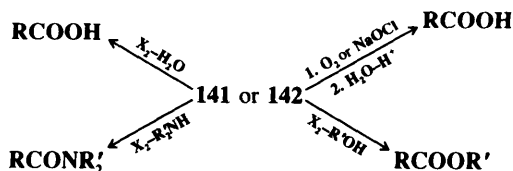
Carboxylic acids or esters are the products, depending on whether the reaction mixture is solvolyzed with water or an alcohol. Alcohols with more than 7 carbons are cleaved into smaller fragments by this procedure.¹⁶⁰⁷ Similarly, tertiary alcohols¹⁶⁰⁸ react with H_2SO_4 and CO (which is often generated from HCOOH and the H_2SO_4 in the solution) to give trisubstituted acetic acids in a process called the *Koch-Haaf reaction* (see also 5-23).¹⁶⁰⁹ If a primary or secondary alcohol is the substrate, the carbocation initially formed rearranges to a tertiary ion before reacting with the CO. Better results are obtained if trifluoromethanesulfonic acid $\text{F}_3\text{CSO}_2\text{OH}$ is used instead of H_2SO_4 .¹⁶¹⁰

Another method¹⁶¹¹ for the conversion of alkyl halides to carboxylic esters is treatment of a halide with nickel carbonyl $\text{Ni}(\text{CO})_4$ in the presence of an alcohol and its conjugate



base.¹⁶¹² When R' is primary, RX may only be a vinylic or an aryl halide; retention of configuration is observed at a vinylic R. Consequently, a carbocation intermediate is not involved here. When R' is tertiary, R may be primary alkyl as well as vinylic or aryl. This is thus one of the few methods for preparing esters of tertiary alcohols. Alkyl iodides give the best results, then bromides. In the presence of an amine, an amide can be isolated directly, at least in some instances.

Still another method for the conversion of halides to acid derivatives makes use of $\text{Na}_2\text{Fe}(\text{CO})_4$. As described in 0-102, primary and secondary alkyl halides and tosylates react with this reagent to give the ion $\text{RFe}(\text{CO})_4^-$ (**141**) or, if CO is present, the ion $\text{RCOFe}(\text{CO})_4^-$ (**142**). Treatment of **141** or **142** with oxygen or sodium hypochlorite gives, after hydrolysis, a carboxylic acid.¹⁶¹³ Alternatively, **141** or **142** reacts with a halogen (for example, I_2) in the



presence of an alcohol to give a carboxylic ester,¹⁶¹⁴ or in the presence of a secondary amine or water to give, respectively, the corresponding amide or free acid. **141** and **142** prepared from primary R give high yields. With secondary R, the best results are obtained in the solvent THF by the use of **142** prepared from secondary tosylates. Ester and keto groups may be present in R without being affected. Carboxylic esters $\text{RCO}_2\text{R}'$ have also been

¹⁶⁰⁷Yoneda; Takahashi; Fukuhara; Suzuki *Bull. Chem. Soc. Jpn.* **1986**, 59, 2819.

¹⁶⁰⁸For reviews of other carbonylation reactions of alcohols and other saturated oxygenated compounds, see Bahrman; Cornils, in *Falbe New Syntheses with Carbon Monoxide*; Springer: New York, 1980, pp. 226-241; Piacenti; Bianchi, in Wender; Pino *Organic Syntheses via Metal Carbonyls*, vol. 2; Wiley: New York, 1977, pp. 1-42.

¹⁶⁰⁹For a review, see Bahrman, in *Falbe*, Ref. 1608, pp. 372-413.

¹⁶¹⁰Booth; El-Fekky *J. Chem. Soc., Perkin Trans. I* **1979**, 2441.

¹⁶¹¹For reviews of methods involving transition metals, see Collman et al., Ref. 1266, pp. 749-768; Anderson; Davies, in Hartley; Patai, Ref. 1403, vol. 3, pp. 335-359, pp. 348-356; Heck *Adv. Catal.* **1977**, 26, 323-349, pp. 323-336; Cassar; Chiusoli; Guerrieri *Synthesis* **1973**, 509-523.

¹⁶¹²Corey; Hegedus *J. Am. Chem. Soc.* **1969**, 91, 1233. See also Crandall; Michaely *J. Organomet. Chem.* **1973**, 51, 375.

¹⁶¹³Collman; Winter; Komoto *J. Am. Chem. Soc.* **1973**, 95, 249.

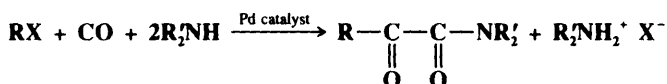
¹⁶¹⁴Ref. 1613; Masada; Mizuno; Suga; Watanabe; Takegami *Bull. Chem. Soc. Jpn.* **1970**, 43, 3824.

prepared by treating primary alkyl halides RX with alkoxides $R'O^-$ in the presence of $Fe(CO)_5$.¹⁶¹⁵ **142** is presumably an intermediate.

Palladium complexes also catalyze the carbonylation of halides.¹⁶¹⁶ Aryl (see **3-15**), vinylic,¹⁶¹⁷ benzylic, and allylic halides (especially iodides) can be converted to carboxylic esters with CO , an alcohol or alkoxide, and a palladium complex.¹⁶¹⁸ Use of an amine instead of the alcohol or alkoxide leads to an amide.¹⁶¹⁹ Benzylic and allylic halides were converted to carboxylic acids electrocatalytically, with CO and a cobalt imine complex.¹⁶²⁰ Vinylic halides were similarly converted with CO and nickel cyanide, under phase-transfer conditions.¹⁶²¹

Rhodium catalysts have also been used. Benzylic halides were converted to carboxylic esters with CO in the presence of a rhodium complex. In this case, the R' could come from an ether R'_2O ,¹⁶²² a borate ester $B(OR')_3$,¹⁶²³ or an Al , Ti , or Zr alkoxide.¹⁶²⁴

A number of double carbonylations have been reported. In these reactions, two molecules of CO are incorporated in the product, leading to α -keto acids or their derivatives.¹⁶²⁵ When the catalyst is a palladium complex, best results are obtained in the formation of α -keto amides.¹⁶²⁶



R is usually aryl or vinylic.¹⁶²⁷ The formation of α -keto acids¹⁶²⁸ or esters¹⁶²⁹ requires more severe conditions. α -Hydroxy acids were obtained from aryl iodides when the reaction was carried out in the presence of an alcohol, which functioned as a reducing agent.¹⁶³⁰ Cobalt catalysts have also been used and require lower CO pressures.¹⁶²⁵

OS V, 20, 739.

¹⁶¹⁵Yamashita; Mizushima; Watanabe; Mitsudo; Takegami *Chem. Lett.* **1977**, 1355. See also Tanguy; Weinberger; des Abbayes *Tetrahedron Lett.* **1983**, 24, 4005.

¹⁶¹⁶For reviews, see Gulevich; Bumagin; Beletskaya *Russ. Chem. Rev.* **1988**, 57, 299-315, pp. 303-309; Heck *Palladium Reagents in Organic Synthesis*, Ref. 1308, pp. 348-356, 366-370.

¹⁶¹⁷For conversion of vinylic triflates to carboxylic esters and amides, see Cacchi; Morera; Ortar *Tetrahedron Lett.* **1985**, 26, 1109.

¹⁶¹⁸Tsuji; Kishi; Imamura; Morikawa *J. Am. Chem. Soc.* **1964**, 86, 4350; Schoenberg; Bartoletti; Heck *J. Org. Chem.* **1974**, 39, 3318; Hidai; Hikita; Wada; Fujikura; Uchida *Bull. Chem. Soc. Jpn.* **1975**, 48, 2075; Bumagin; Gulevich; Beletskaya *J. Organomet. Chem.* **1985**, 285, 415; Milstein *J. Chem. Soc., Chem. Commun.* **1986**, 817; Kiji; Okano; Nishiumi; Konishi *Chem. Lett.* **1988**, 957, **1989**, 1873; Adapa; Prasad *J. Chem. Soc., Perkin Trans. 1* **1989**, 1706.

¹⁶¹⁹Schoenberg; Heck *J. Org. Chem.* **1974**, 39, 3327. See also Lindsay; Widdowson *J. Chem. Soc., Perkin Trans. 1* **1988**, 569. For a review of some methods of amide formation that involve transition metals, see Screttas; Steele *Org. Prep. Proced. Int.* **1990**, 22, 271-314, pp. 288-314.

¹⁶²⁰Folest; Duprilot; Perichon; Robin; Devynck *Tetrahedron Lett.* **1985**, 26, 2633. For other procedures involving a cobalt catalyst, see Francalanci; Gardano; Foà *J. Organomet. Chem.* **1985**, 282, 277; Satyanarayana; Periasamy *Tetrahedron Lett.* **1987**, 28, 2633; Miura; Okuro; Hattori; Nomura *J. Chem. Soc., Perkin Trans. 1* **1989**, 73; Urata; Goto; Fuchikami *Tetrahedron Lett.* **1991**, 32, 3091.

¹⁶²¹Alper; Amer; Vasapollo *Tetrahedron Lett.* **1989**, 30, 2615. See also Amer; Alper *J. Am. Chem. Soc.* **1989**, 111, 927.

¹⁶²²Buchan; Hamel; Woell; Alper *Tetrahedron Lett.* **1985**, 26, 5743.

¹⁶²³Woell; Alper *Tetrahedron Lett.* **1984**, 25, 3791; Alper; Hamel; Smith; Woell *Tetrahedron Lett.* **1985**, 26, 2273.

¹⁶²⁴Woell; Fergusson; Alper *J. Org. Chem.* **1985**, 50, 2134.

¹⁶²⁵For a review, see Collin *Bull. Soc. Chim. Fr.* **1988**, 976-981.

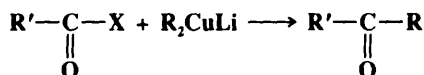
¹⁶²⁶Kobayashi; Tanaka *J. Organomet. Chem.* **1982**, 233, C64; Ozawa; Sugimoto; Yuasa; Santra; Yamamoto; Yamamoto *Organometallics* **1984**, 3, 683.

¹⁶²⁷Son; Yanagihara; Ozawa; Yamamoto *Bull. Chem. Soc. Jpn.* **1988**, 61, 1251.

¹⁶²⁸Tanaka; Kobayashi; Sakakura *J. Chem. Soc., Chem. Commun.* **1985**, 837.

¹⁶²⁹See Ozawa; Kawasaki; Okamoto; Yamamoto; Yamamoto *Organometallics* **1987**, 6, 1640.

¹⁶³⁰Kobayashi; Sakakura; Tanaka *Tetrahedron Lett.* **1987**, 28, 2721.

B. Attack at an Acyl Carbon¹⁶³¹**0-104 The Conversion of Acyl Halides to Ketones with Organometallic Compounds¹⁶³²**
Alkyl-de-halogenation

Acyl halides react cleanly and under mild conditions with lithium dialkylcopper reagents¹⁶³³ to give high yields of ketones.¹⁶³⁴ R' may be primary, secondary, or tertiary alkyl or aryl and may contain iodo, keto, ester, nitro, or cyano groups. R groups that have been used successfully are methyl, primary alkyl, and vinylic. Secondary and tertiary alkyl groups can be introduced by the use of PhS(R)CuLi (p. 451) instead of R₂CuLi,¹⁶³⁵ or by the use of either the mixed homocuprate (R'SO₂CH₂CuR)⁻ Li⁺,¹⁶³⁶ or a magnesium dialkylcopper reagent "RMeCuMgX."¹⁶³⁷ Secondary alkyl groups can also be introduced with the copper-zinc reagents RCu(CN)ZnI.¹⁶³⁸ R may be alkynyl if a cuprous acetylide R'C≡CCu is the reagent.¹⁶³⁹ Organocopper reagents generated in situ from highly reactive copper, and containing such functional groups as cyano, chloro, and ester, react with acyl halides to give ketones.¹⁶⁴⁰

Another type of organometallic reagent¹⁶⁴¹ that gives good yields of ketones when treated with acyl halides are organocadmiums R₂Cd (prepared from Grignard reagents, 2-21). In this case R may be aryl or primary alkyl. In general, secondary and tertiary alkylcadmium reagents are not stable enough to be useful in this reaction.¹⁶⁴² An ester group may be present in either R'COX or R₂Cd. Organozinc compounds behave similarly, but are used less often.¹⁶⁴³ Organomercury compounds¹⁶⁴⁴ and tetraalkylsilanes¹⁶⁴⁵ also give the reaction if an AlX₃ catalyst is present.¹⁶⁴⁶ Organotin reagents R₄Sn react with acyl halides to give high yields of ketones, if a Pd complex is present.¹⁶⁴⁷ Various other groups, for example, nitrile, ester, and aldehyde can be present in the acyl halide without interference. Still

¹⁶³¹For a discussion of many of the reactions in this section, see House, Ref. 1411, pp. 691-694, 734-765.

¹⁶³²For a review, see Cais; Mandelbaum, in Patai, Ref. 446, vol. 1, pp. 303-330.

¹⁶³³For examples of the use of this reaction in the synthesis of natural products, see Posner, Ref. 1352, pp. 81-85. See also Ref. 1268.

¹⁶³⁴Vig; Sharma; Kapur *J. Indian Chem. Soc.* **1969**, *46*, 167; Jukes; Dua; Gilman *J. Organomet. Chem.* **1970**, *21*, 241; Posner; Whitten; McFarland *J. Am. Chem. Soc.* **1972**, *94*, 5106; Luong-Thi; Riviere *J. Organomet. Chem.* **1974**, *77*, C52.

¹⁶³⁵Ref. 1276; Bennett; Nadelson; Alden; Jani *Org. Prep. Proced. Int.* **1976**, *8*, 13.

¹⁶³⁶Johnson; Dhanoa *J. Org. Chem.* **1987**, *52*, 1885.

¹⁶³⁷Bergbreiter; Killough *J. Org. Chem.* **1976**, *41*, 2750.

¹⁶³⁸Knochel; Yeh; Berk; Talbert *J. Org. Chem.* **1988**, *53*, 2390.

¹⁶³⁹Castro; Havlin; Honwad; Malte; Mojé *J. Am. Chem. Soc.* **1969**, *91*, 6464. For methods of preparing acetylenic ketones, see Verkruijsse; Heus-Kloos; Brandsma *J. Organomet. Chem.* **1988**, *338*, 289.

¹⁶⁴⁰Wehmeyer; Rieke *Tetrahedron Lett.* **1988**, *29*, 4513.

¹⁶⁴¹For a list of reagents, with references, see Ref. 508, pp. 686-691.

¹⁶⁴²Cason; Fessenden *J. Org. Chem.* **1960**, *25*, 477.

¹⁶⁴³For examples, see Grey *J. Org. Chem.* **1984**, *49*, 2288; Tamaru; Ochiai; Nakamura; Yoshida *Org. Synth.* **67**, 98.

¹⁶⁴⁴Kurts; Beletskaya; Savchenko; Reutov *J. Organomet. Chem.* **1969**, *17*, P21; Larock; Lu *Tetrahedron Lett.* **1988**, *29*, 6761. See also Bumagin; Kalinovskii; Beletskaya *J. Org. Chem. USSR* **1982**, *18*, 1152.

¹⁶⁴⁵For a review, see Parnes; Bolestova *Synthesis* **1984**, 991-1008, pp. 991-996.

¹⁶⁴⁶In the case of organomercury compounds a palladium catalyst can also be used: Bumagin; More; Beletskaya *J. Organomet. Chem.* **1989**, *365*, 379.

¹⁶⁴⁷Kosugi; Shimizu; Migita *Chem. Lett.* **1977**, 1423; Labadie; Stille *J. Am. Chem. Soc.* **1983**, *105*, 669, 6129; Labadie; Tueting; Stille *J. Org. Chem.* **1983**, *48*, 4634. For the use of R₄Pb see Yamada; Yamamoto *J. Chem. Soc., Chem. Commun.* **1987**, 1302. See also Verlhac; Quintard *Tetrahedron Lett.* **1986**, *27*, 2361.

other reagents are organomanganese compounds¹⁶⁴⁸ (R can be primary, secondary, or tertiary alkyl, vinylic, alkynyl, or aryl), organothallium compounds (R can be primary alkyl or aryl),¹⁶⁴⁹ lithium aryltrialkylborates¹⁶⁵⁰ $\text{ArBR}_3^- \text{Li}^+$ (which transfer an aryl group), and the alkylrhodium(I) complexes bis(triphenylphosphine)carbonylalkylrhodium(I) $\text{Rh}^{\text{I}}\text{R}(\text{CO})(\text{Ph}_3\text{P})_2$. The latter, generated in situ from $\text{Rh}^{\text{I}}\text{Cl}(\text{CO})(\text{Ph}_3\text{P})_2$ (**143**) and a Grignard reagent or organolithium compound, react with acyl halides in THF at -78°C to give good yields of ketones.¹⁶⁵¹ R may be primary alkyl or aryl. An advantage of the rhodium reagents is that they do not react with aldehydes, esters, or nitriles, so that these groups may be present in R'. Another advantage is that the complex **143** is regenerated in reusable form at the end of the reaction.

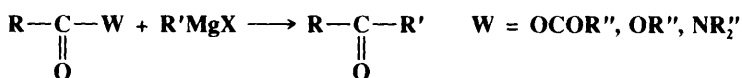
When the organometallic compound is a Grignard reagent,¹⁶⁵² ketones are generally not obtained because the initially formed ketone reacts with a second molecule of RMgX to give the salt of a tertiary alcohol (**6-32**). Ketones *have* been prepared in this manner by the use of low temperatures, inverse addition (i.e., addition of the Grignard reagent to the acyl halide rather than the other way), excess acyl halide, etc., but the yields are usually low, though high yields have been reported in THF at -78°C .¹⁶⁵³ Some ketones are unreactive toward Grignard reagents for steric or other reasons; these can be prepared in this way.¹⁶⁵⁴ Other methods involve running the reaction in the presence of Me_3SiCl ¹⁶⁵⁵ (which reacts with the initial adduct **67** in the tetrahedral mechanism, p. 331), and the use of a combined Grignard–lithium diethylamide reagent.¹⁶⁵⁶ Also, certain metallic halides, notably ferric and cuprous halides, are catalysts that improve the yields of ketone at the expense of tertiary alcohol.¹⁶⁵⁷ For these catalysis, both free-radical and ionic mechanisms have been proposed.¹⁶⁵⁸ The reactions with R_2CuLi , R_2Cd , and the rhodium complexes are successful because these compounds do not generally react with ketones.

Grignard reagents react with ethyl chloroformate to give carboxylic esters $\text{EtOCOR} + \text{RMgX} \rightarrow \text{EtOCOR}$. Acyl halides can also be converted to ketones by treatment with $\text{Na}_2\text{Fe}(\text{CO})_4$ followed by $\text{R}'\text{X}$ (**0-102**, method 4).

OS II, 198; III, 601; IV, 708; VI, 248, 991; VII, 226, 334; **65**, 47; **66**, 87, 116; **67**, 86, 98.

0-105 The Conversion of Anhydrides, Carboxylic Esters, or Amides to Ketones with Organometallic Compounds¹⁶⁵⁹

Alkyl-de-acyloxy-substitution



¹⁶⁴⁸Friour; Alexakis; Cahiez; Normant *Tetrahedron* **1984**, *40*, 683; Friour; Cahiez; Normant *Synthesis* **1985**, 50; Cahiez; Laboue *Tetrahedron Lett.* **1989**, *30*, 7369.

¹⁶⁴⁹Markó; Southern *J. Org. Chem.* **1990**, *55*, 3368.

¹⁶⁵⁰Negishi; Abramovitch; Merrill *J. Chem. Soc., Chem. Commun.* **1975**, 138; Negishi; Chiu; Yoshida *J. Org. Chem.* **1975**, *40*, 1676. See also Miyaura; Sasaki; Itoh; Suzuki *Tetrahedron Lett.* **1977**, 173.

¹⁶⁵¹Hegedus; Kendall; Lo; Sheats *J. Am. Chem. Soc.* **1975**, *97*, 5448. See also Pittman; Hanes *J. Org. Chem.* **1977**, *42*, 1194.

¹⁶⁵²For a review, see Kharasch; Reinmuth, Ref. 1287, pp. 712-724.

¹⁶⁵³Sato; Inoue; Oguro; Sato *Tetrahedron Lett.* **1979**, 4303; Eberle; Kahle *Tetrahedron Lett.* **1980**, *21*, 2303; Föhlisch; Flogaus *Synthesis* **1984**, 734.

¹⁶⁵⁴For example, see Lion; Dubois; Bonzougou *J. Chem. Res., (S)* **1978**, 46; Dubois; Lion; Arouisse *Bull. Soc. Chim. Belg.* **1984**, *93*, 1083.

¹⁶⁵⁵Cooke *J. Org. Chem.* **1986**, *51*, 951.

¹⁶⁵⁶Fehr; Galindo *Helv. Chim. Acta* **1986**, *69*, 228; Fehr; Galindo; Perret *Helv. Chim. Acta* **1987**, *70*, 1745.

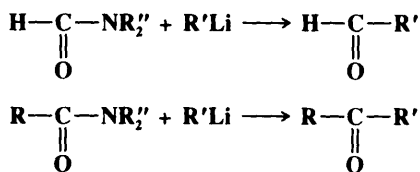
¹⁶⁵⁷For examples, see Cason; Kraus *J. Org. Chem.* **1961**, *26*, 1768, 1772; MacPhee; Dubois *Tetrahedron Lett.* **1972**, 467; Cardellicchio; Fiandanese; Marchese; Ronzini *Tetrahedron Lett.* **1987**, *28*, 2053; Fujisawa; Sato *Org. Synth.* **66**, 116; Babudri; D'Ettole; Fiandanese; Marchese; Naso *J. Organomet. Chem.* **1991**, *405*, 53.

¹⁶⁵⁸For example, see Dubois; Boussu *Tetrahedron Lett.* **1970**, 2523, *Tetrahedron* **1973**, *29*, 3943; MacPhee; Boussu; Dubois *J. Chem. Soc., Perkin Trans. 2* **1974**, 1525.

¹⁶⁵⁹For a review, see Kharasch; Reinmuth, Ref. 1287, pp. 561-562, 846-908.

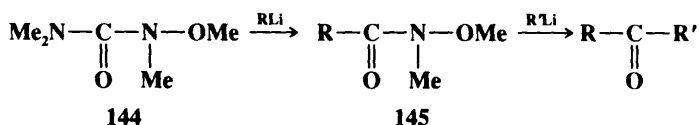
As is the case with acyl halides (**0-104**), anhydrides and carboxylic esters give tertiary alcohols (**6-32**) when treated with Grignard reagents. Low temperatures,¹⁶⁶⁰ the solvent HMPA,¹⁶⁶¹ and inverse addition have been used to increase the yields of ketone.¹⁶⁶² Amides give better yields of ketone at room temperature, but still not very high.¹⁶⁶³ Thiol esters RCOSR' give good yields of ketones when treated with lithium dialkylcopper reagents $\text{R}_2'\text{CuLi}$ ($\text{R}' =$ primary or secondary alkyl or aryl).¹⁶⁶⁴ Ketones can also be prepared by treatment of thioamides with organolithium compounds (alkyl or aryl).¹⁶⁶⁵ Organocadmium reagents are less successful with these substrates than with acyl halides (**0-104**). Esters of formic acid, dialkylformamides, and lithium or sodium formate¹⁶⁶⁶ give good yields of aldehydes, when treated with Grignard reagents.

Alkylolithium compounds have been used to give ketones from carboxylic esters. The reaction must be carried out in a high-boiling solvent such as toluene, since reaction at lower temperatures gives tertiary alcohols.¹⁶⁶⁷ Alkylolithiums also give good yields of carbonyl compounds with *N,N*-disubstituted amides.¹⁶⁶⁸ Dialkylformamides give aldehydes and other disubstituted amides give ketones.



N,N-Disubstituted amides can be converted to alkynyl ketones by treatment with alkynylboranes: $\text{RCONR}_2' + (\text{R}'\text{C}\equiv\text{C})_3\text{B} \rightarrow \text{RCOC}\equiv\text{CR}'$.¹⁶⁶⁹ Alkynyl ketones are also obtained by treatment of anhydrides with lithium alkynyltrifluoroborates $\text{Li}(\text{RC}\equiv\text{C}-\text{BF}_3)$.¹⁶⁷⁰ *N,N*-Disubstituted carbamates ($\text{X} = \text{OR}''$) and carbamoyl chlorides ($\text{X} = \text{Cl}$) react with 2 moles of an alkyl- or aryllithium or Grignard reagent to give symmetrical ketones, in which both R groups are derived from the organometallic compound: $\text{R}_2'\text{NCOX} + 2\text{RMgX} \rightarrow \text{R}_2\text{CO}$.¹⁶⁷¹ *N,N*-Disubstituted amides give ketones in high yields when treated with alkyl-lanthanum triflates $\text{RLa}(\text{OTf})_2$.¹⁶⁷²

By the use of the compound *N*-methoxy-*N,N'*,*N'*-trimethylurea **144**, it is possible to add



¹⁶⁶⁰See, for example, Newman; Smith *J. Org. Chem.* **1948**, *13*, 592; Edwards; Kamman *J. Org. Chem.* **1964**, *29*, 913; Araki; Sakata; Takei; Mukaiyama *Chem. Lett.* **1974**, 687.

¹⁶⁶¹Huet; Emptoz; Jubier *Tetrahedron* **1973**, *29*, 479; Huet; Pellet; Conia *Tetrahedron Lett.* **1976**, 3579.

¹⁶⁶²For a list of preparations of ketones by the reaction of organometallic compounds with carboxylic esters, salts, anhydrides, or amides, with references, see Ref. 508, pp. 685-686, 693-700.

¹⁶⁶³For an improved procedure with amides, see Olah; Prakash; Arvanaghi *Synthesis* **1984**, 228.

¹⁶⁶⁴Anderson; Henrick; Rosenblum *J. Am. Chem. Soc.* **1974**, *96*, 3654. See also Kim; Lee *J. Org. Chem.* **1983**, *48*, 2608.

¹⁶⁶⁵Tominaga; Kohra; Hosomi *Tetrahedron Lett.* **1987**, *28*, 1529.

¹⁶⁶⁶Bogavac; Arsenijević; Pavlov; Arsenijević *Tetrahedron Lett.* **1984**, *25*, 1843.

¹⁶⁶⁷Petrov; Kaplan; Tsir *J. Gen. Chem. USSR* **1962**, *32*, 691.

¹⁶⁶⁸Evans *J. Chem. Soc.* **1956**, 4691. For a review, see Wakefield *Organolithium Methods*; Academic Press: New York, 1988, pp. 82-88.

¹⁶⁶⁹Yamaguchi; Waseda; Hirao *Chem. Lett.* **1983**, 35.

¹⁶⁷⁰Brown; Racherla; Singh *Tetrahedron Lett.* **1984**, *25*, 2411.

¹⁶⁷¹Michael; Hörnfeldt *Tetrahedron Lett.* **1970**, 5219; Scilly, *Synthesis* **1973**, 160.

¹⁶⁷²Collins; Hong *Tetrahedron Lett.* **1987**, *28*, 4391.

two R groups, the same or different, to a CO group. Both reactions can be done in the same vessel without the isolation of **145**.¹⁶⁷³

Hydrogen has been reported to be a leaving group in this reaction: Aromatic aldehydes are converted to methyl ketones ($\text{ArCHO} \rightarrow \text{ArCOCH}_3$) with $\text{Al}(\text{OAr})\text{Me}_2$ ($\text{Ar} = 2,6\text{-di-}i\text{-butyl-4-methylphenyl}$).¹⁶⁷⁴

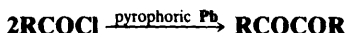
Carboxylic esters can be converted to their homologs ($\text{RCOOEt} \rightarrow \text{RCH}_2\text{COOEt}$) by treatment with Br_2CHLi followed by BuLi at -90°C . The ynolate $\text{RC}\equiv\text{COLi}$ is an intermediate.¹⁶⁷⁵ If the ynolate is treated with 1,3-cyclohexadiene, followed by NaBH_4 , the product is the alcohol $\text{RCH}_2\text{CH}_2\text{OH}$.¹⁶⁷⁶

Ketones can also be obtained by treatment of the lithium salt of a carboxylic acid with an alkyl lithium reagent (**6-31**). For an indirect way to convert carboxylic esters to ketones, see **6-33**.

OS **II**, 282; **III**, 353; **IV**, 285; **VI**, 611; **VII**, 323, 451.

0-106 The Coupling of Acyl Halides

De-halogen-coupling

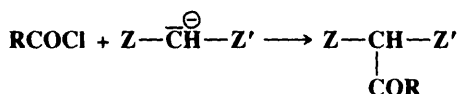


Acyl halides can be coupled with pyrophoric lead to give symmetrical α -diketones in a Wurtz-type reaction.¹⁶⁷⁷ The reaction has been performed with $\text{R} = \text{Me}$ and Ph . Other reagents that give the same reaction are samarium iodide SmI_2 ¹⁶⁷⁸ and hexaethyldistannane Et_6Sn_2 (with palladium catalysts and under CO pressure).¹⁶⁷⁹ Benzoyl chloride was coupled to give benzil by subjecting it to ultrasound in the presence of Li wire: $2\text{PhCOCl} + \text{Li} \rightarrow \text{PhCOCOPh}$.¹²⁴⁷

Unsymmetrical α -diketones RCOCOR' have been prepared by treatment of an acyl halide RCOCl with an acyltin reagent RCOSnBu_3 , with a palladium-complex catalyst.¹⁶⁸⁰

0-107 Acylation at a Carbon Bearing an Active Hydrogen

Bis(ethoxycarbonyl)methyl-de-halogenation, etc.



This reaction is similar to **0-94**, though many fewer examples have been reported.¹⁶⁸¹ Z and Z' may be any of the groups listed in **0-94**.¹⁶⁸² Anhydrides react similarly but are used less often. The product contains three Z groups, since RCO is a Z group. One or two of these can be cleaved (**2-40**, **2-43**). In this way a compound $\text{ZCH}_2\text{Z}'$ can be converted to $\text{ZCH}_2\text{Z}''$ or an acyl halide RCOCl to a methyl ketone RCOCH_3 . O-Acylation is sometimes a side

¹⁶⁷³Hlasta; Court *Tetrahedron Lett.* **1989**, 30, 1773. See also Nahm; Weinreb *Tetrahedron Lett.* **1981**, 22, 3815.

¹⁶⁷⁴Power; Barron *Tetrahedron Lett.* **1990**, 31, 323.

¹⁶⁷⁵Kowalski; Haque; Fields *J. Am. Chem. Soc.* **1985**, 107, 1429; Kowalski; Haque *J. Org. Chem.* **1985**, 50, 5140.

¹⁶⁷⁶Kowalski; Haque *J. Am. Chem. Soc.* **1986**, 108, 1325.

¹⁶⁷⁷Mészáros *Tetrahedron Lett.* **1967**, 4951.

¹⁶⁷⁸Soupe; Namy; Kagan *Tetrahedron Lett.* **1984**, 25, 2869. See also Collin; Namy; Dallemer; Kagan *J. Org. Chem.* **1991**, 56, 3118.

¹⁶⁷⁹Bumagin; Gulevich; Beletskaya *J. Organomet. Chem.* **1985**, 282, 421.

¹⁶⁸⁰Verlhac; Chanson; Jousseau; Quintard *Tetrahedron Lett.* **1985**, 26, 6075. For another procedure, see Olah; Wu *J. Org. Chem.* **1991**, 56, 902.

¹⁶⁸¹For examples of reactions in this section, with references, see Ref. 508, pp. 742, 764-767.

¹⁶⁸²For an improved procedure, see Rathke; Cowan *J. Org. Chem.* **1985**, 50, 2622.

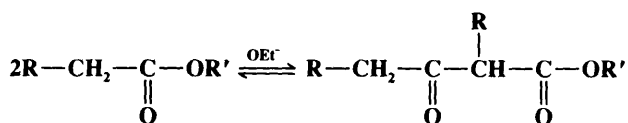
reaction.¹⁶⁸³ When thallium(I) salts of ZCH_2Z' are used, it is possible to achieve regioselective acylation at either the C or the O position. For example, treatment of the thallium(I) salt of $MeCOCH_2COMe$ with acetyl chloride at $-78^\circ C$ gave $>90\%$ O-acylation, while acetyl fluoride at room temperature gave $>95\%$ C-acylation.¹⁶⁸⁴ The use of an alkyl chloroformate gives triesters.¹⁶⁸⁵

The application of this reaction to simple ketones¹⁴⁵² (in parallel with 0-95) requires a strong base, such as $NaNH_2$ or Ph_3CNa , and is often complicated by O-acylation, which in many cases becomes the principal pathway because acylation at the oxygen is usually much faster. It is possible to increase the proportion of C-acylated product by employing an excess (2 to 3 equivalents) of enolate ion (and adding the substrate to this, rather than vice versa), by the use of a relatively nonpolar solvent and a metal ion (such as Mg^{2+}) which is tightly associated with the enolate oxygen atom, by the use of an acyl halide rather than an anhydride,¹⁶⁸⁶ and by working at low temperatures.¹⁶⁸⁷ In cases where the use of an excess of enolate ion results in C-acylation, it is because O-acylation takes place first, and the O-acylated product (an enol ester) is then C-acylated. Simple ketones can also be acylated by treatment of their silyl enol ethers with an acyl chloride in the presence of $ZnCl_2$ or $SbCl_3$.¹⁶⁸⁸ Ketones can be acylated by anhydrides to give β -diketones, with BF_3 as catalyst.¹⁶⁸⁹ Simple esters RCH_2COOEt can be acylated at the α carbon (at $-78^\circ C$) if a strong base such as lithium N-isopropylcyclohexylamide is used to remove the proton.¹⁶⁹⁰

OS II, 266, 268, 594, 596; III, 16, 390, 637; IV, 285, 415, 708; V, 384, 937; VI, 245; VII, 213, 359; 66, 108; 69, 44, 173. See also OS VI, 620; 65, 146.

0-108 Acylation of Carboxylic Esters by Carboxylic Esters. The Claisen and Dieckmann Condensations

Alkoxycarbonylalkyl-de-alkoxy-substitution



When carboxylic esters containing an α hydrogen are treated with a strong base such as sodium ethoxide, a condensation occurs to give a β -keto ester. This reaction is called the *Claisen condensation*. When it is carried out with a mixture of two different esters, each of which possesses an α hydrogen, a mixture of all four products is generally obtained and the reaction is seldom useful synthetically.¹⁶⁹¹ However, if only one of the esters has an α hydrogen, the mixed reaction is frequently satisfactory. Among esters lacking α hydrogens

¹⁶⁸³When phase transfer catalysts are used, O-acylation becomes the main reaction: Jones; Nokkeo; Singh *Synth. Commun.* **1977**, 7, 195.

¹⁶⁸⁴Taylor; Hawks; McKillop *J. Am. Chem. Soc.* **1968**, 90, 2421.

¹⁶⁸⁵See, for example, Skarzewski *Tetrahedron* **1989**, 45, 4593. For a review of triesters, see Newkome; Baker *Org. Prep. Proced. Int.* **1986**, 19, 117-144.

¹⁶⁸⁶See House, Ref. 1411, pp. 762-765; House; Auerbach; Gall; Peet *J. Org. Chem.* **1973**, 38, 514.

¹⁶⁸⁷Seebach; Weller; Protschuk; Beck; Hoekstra *Helv. Chim. Acta* **1981**, 64, 716.

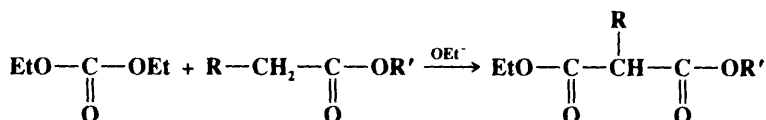
¹⁶⁸⁸Tirpak; Rathke *J. Org. Chem.* **1982**, 47, 5099.

¹⁶⁸⁹For a review, see Hauser; Swamer; Adams *Org. React.* **1954**, 8, 59-196, pp. 98-106.

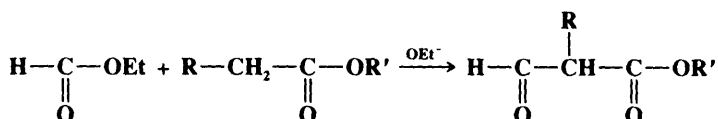
¹⁶⁹⁰For example, see Rathke; Deitch *Tetrahedron Lett.* **1971**, 2953; Logue *J. Org. Chem.* **1974**, 39, 3455; Couffignal; Morcau *J. Organomet. Chem.* **1977**, 127, C65; Ohta; Shimabayashi; Hayakawa; Sumino; Okamoto *Synthesis* **1985**, 45; Hayden; Pucher; Griengl *Monatsh. Chem.* **1987**, 118, 415.

¹⁶⁹¹For a method of allowing certain crossed-Claisen reactions to proceed with good yields, see Tanabe *Bull. Chem. Soc. Jpn.* **1989**, 62, 1917.

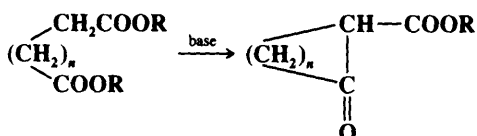
(hence acting as the substrate ester) that are commonly used in this way are esters of aromatic acids, and ethyl carbonate and ethyl oxalate. Ethyl carbonate gives malonic esters.



Ethyl formate serves to introduce the formyl group:

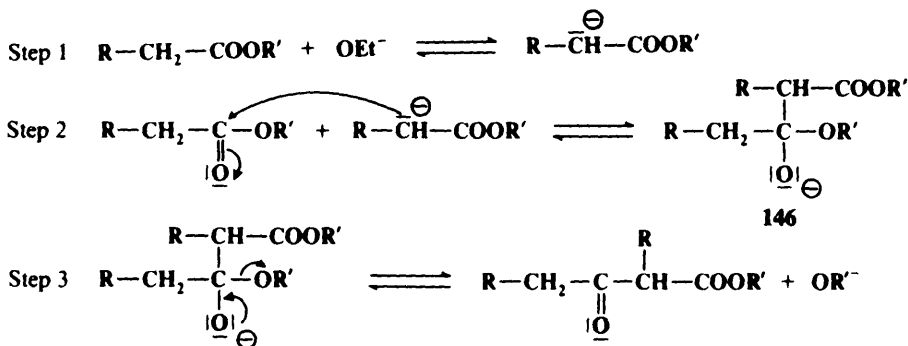


When the two ester groups involved in the condensation are in the same molecule, the product is a cyclic β -keto ester and the reaction is called the *Dieckmann condensation*.¹⁶⁹²



The Dieckmann condensation is most successful for the formation of 5-, 6-, and 7-membered rings. Yields for rings of 9 to 12 members are very low or nonexistent; larger rings can be closed with high-dilution techniques. Reactions in which large rings are to be closed are generally assisted by high dilution, since one end of the molecule has a better chance of finding the other end than of finding another molecule. Dieckmann condensation of unsymmetrical substrates can be made regioselective (unidirectional) by the use of solid-phase supports.¹⁶⁹³

The mechanism of the Claisen and Dieckmann reactions is the ordinary tetrahedral mechanism,¹⁶⁹⁴ with one molecule of ester being converted to a nucleophile by the base and the other serving as the substrate.



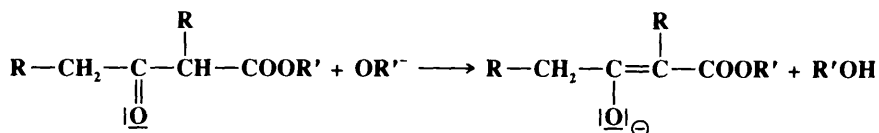
¹⁶⁹²For a review, see Schaefer; Bloomfield *Org. React.* **1967**, *15*, 1-203.

¹⁶⁹³Crowley; Rapoport *J. Org. Chem.* **1980**, *45*, 3215. For another method, see Yamada; Ishii; Kimura; Hosaka *Tetrahedron Lett.* **1981**, *22*, 1353.

¹⁶⁹⁴There is evidence that, at least in some cases, an SET mechanism is involved: Ashby; Park *Tetrahedron Lett.* **1983**, 1667.

This reaction illustrates the striking difference in behavior between carboxylic esters on the one hand and aldehydes and ketones on the other. When a carbanion such as an enolate ion is added to the carbonyl group of an aldehyde or ketone (**6-41**), the H or R is not lost, since these groups are much poorer leaving groups than OR. Instead the intermediate similar to **146** adds a proton at the oxygen to give a hydroxy compound.

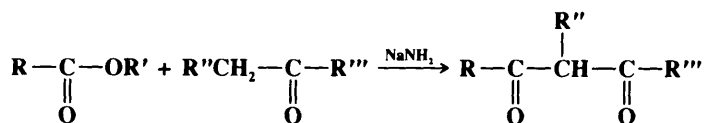
In contrast to **0-94** ordinary esters react quite well, that is, two Z groups are not needed. A lower degree of acidity is satisfactory because it is not necessary to convert the attacking ester entirely to its ion. Step 1 is an equilibrium that lies well to the left. Nevertheless, the small amount of enolate ion formed is sufficient to attack the readily approachable ester substrate. All the steps are equilibria. The reaction proceeds because the product is converted to its conjugate base by the base present (that is, a β -keto ester is a stronger acid than an alcohol):



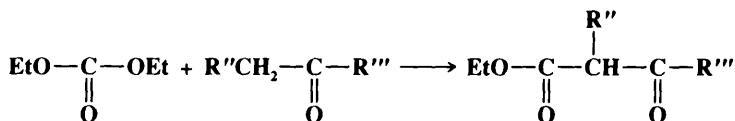
The use of a stronger base, such as NaNH_2 , NaH , or KH ,¹⁶⁹⁵ often increases the yield. For some esters stronger bases *must* be used, since sodium ethoxide is ineffective. Among these are esters of the type $\text{R}_2\text{CHCOOEt}$, the products of which ($\text{R}_2\text{CHCOCR}_2\text{COOEt}$) lack an acidic hydrogen, so that they cannot be converted to enolate ions by sodium ethoxide.¹⁶⁹⁶

OS **I**, 235; **II**, 116, 194, 272, 288; **III**, 231, 300, 379, 510; **IV**, 141; **V**, 288, 687, 989; **66**, 52.

0-109 Acylation of Ketones and Nitriles by Carboxylic Esters α -Acylalkyl-de-alkoxy-substitution



Carboxylic esters can be treated with ketones to give β -diketones in a reaction that is essentially the same as **0-108**. The reaction is so similar that it is sometimes also called the Claisen condensation, though this usage is unfortunate. A fairly strong base, such as sodium amide or sodium hydride, is required. Yields can be increased by the catalytic addition of crown ethers.¹⁶⁹⁷ Esters of formic acid ($\text{R} = \text{H}$) give β -keto aldehydes. Ethyl carbonate gives β -keto esters.



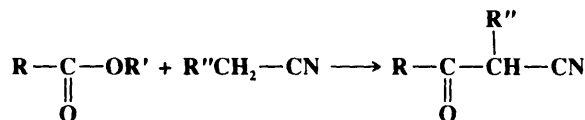
¹⁶⁹⁵Brown *Synthesis* **1975**, 326.

¹⁶⁹⁶For a discussion, see Garst *J. Chem. Educ.* **1979**, 56, 721.

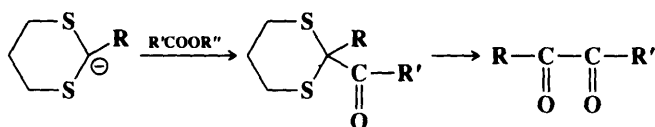
¹⁶⁹⁷Popik; Nikolaev *J. Org. Chem. USSR* **1989**, 25, 1636.

β -Keto esters can also be obtained by treating the lithium enolates of ketones with methyl cyanoformate MeOCOCN ¹⁶⁹⁸ (in this case CN is the leaving group) and by treating ketones with KH and diethyl dicarbonate $(\text{EtOCO})_2\text{O}$.¹⁶⁹⁹

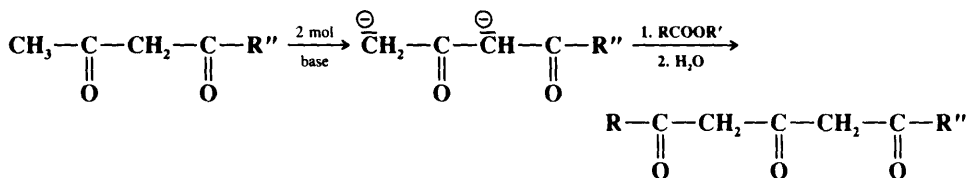
In the case of unsymmetrical ketones, the attack usually comes from the less highly substituted side, so that CH_3 is more reactive than RCH_2 , and the R_2CH group rarely attacks. As in the case of **0-108**, this reaction has been used to effect cyclization, especially to prepare 5- and 6-membered rings. Nitriles are frequently used instead of ketones, the products being β -keto nitriles.



Other carbanionic groups, such as acetylide ions, and ions derived from α -methylpyridines have also been used as nucleophiles. A particularly useful nucleophile is the methylsulfinyl carbanion $\text{CH}_3\text{SOCH}_2^-$,¹⁷⁰⁰ the conjugate base of dimethyl sulfoxide, since the β -keto sulfide produced can easily be reduced to a methyl ketone (p. 465). The methylsulfonyl carbanion $\text{CH}_3\text{SO}_2\text{CH}_2^-$, the conjugate base of dimethyl sulfone, behaves similarly,¹⁷⁰¹ and the product can be similarly reduced. Certain carboxylic esters, acyl halides, and dimethylformamide acylate 1,3-dithianes¹⁷⁰² (see **0-97**) to give, after oxidative hydrolysis with N-bromo- or N-chlorosuccinimide, α -keto aldehydes or α -diketones,⁴⁸² e.g.,



As in **0-94**, a ketone attacks with its second most acidic position if 2 moles of base are used. Thus, β -diketones have been converted to 1,3,5-triketones.¹⁷⁰³



Side reactions are condensation of the ketone with itself (**6-39**), of the ester with itself (**0-108**), and of the ketone with the ester but with the ester supplying the α position (**6-40**). The mechanism is the same as in **0-108**.¹⁷⁰⁴

OS **I**, 238; **II**, 126, 200, 287, 487, 531; **III**, 17, 251, 291, 387, 829; **IV**, 174, 210, 461, 536; **V**, 187, 198, 439, 567, 718, 747; **VI**, 774; **VII**, 351.

¹⁶⁹⁸Mander; Sethi *Tetrahedron Lett.* **1983**, 24, 5425.

¹⁶⁹⁹Hellou; Kingston; Fallis *Synthesis* **1984**, 1014.

¹⁷⁰⁰Becker; Russell *J. Org. Chem.* **1963**, 28, 1896; Corey; Chaykovsky *J. Am. Chem. Soc.* **1964**, 86, 1639; Russell; Sabourin; Hamprecht *J. Org. Chem.* **1969**, 34, 2339. For a review, see Durst *Adv. Org. Chem.* **1969**, 6, 285-388, pp. 296-301.

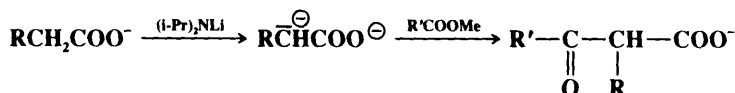
¹⁷⁰¹Becker; Russell, Ref. 1700; Schank; Hasenfratz; Weber *Chem. Ber.* **1973**, 106, 1107; House; Larson, Ref. 1421.

¹⁷⁰²Corey; Seebach, Ref. 1501.

¹⁷⁰³Miles; Harris; Hauser *J. Org. Chem.* **1965**, 30, 1007.

¹⁷⁰⁴Hill; Burkus; Hauser *J. Am. Chem. Soc.* **1959**, 81, 602.

0-110 Acylation of Carboxylic Acid Salts
 α -Carboxyalkyl-de-alkoxy-substitution



We have previously seen (0-96) that dianions of carboxylic acids can be alkylated in the α position. These ions can also be acylated on treatment with a carboxylic ester¹⁷⁰⁵ to give salts of β -keto acids. As in 0-96, the carboxylic acid can be of the form RCH_2COOH or $\text{RR}''\text{CHCOOH}$. Since β -keto acids are so easily converted to ketones (2-40), this is also a method for the preparation of ketones $\text{R}'\text{COCH}_2\text{R}$ and $\text{R}'\text{COCHRR}''$, where R' can be primary, secondary, or tertiary alkyl, or aryl. If the ester is ethyl formate, an α -formyl carboxylate salt ($\text{R}' = \text{H}$) is formed, which on acidification spontaneously decarboxylates into an aldehyde.¹⁷⁰⁶ This is a method, therefore, for achieving the conversion $\text{RCH}_2\text{COOH} \rightarrow \text{RCH}_2\text{CHO}$, and as such is an alternative to the reduction methods discussed in 0-83. When the carboxylic acid is of the form $\text{RR}''\text{CHCOOH}$, better yields are obtained by acylating with acyl halides rather than esters.¹⁷⁰⁷

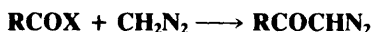
0-111 Preparation of Acyl Cyanides
Cyano-de-halogenation



Acyl cyanides¹⁷⁰⁸ can be prepared by treatment of acyl halides with copper cyanide. The mechanism is not known and might be free-radical or nucleophilic substitution. The reaction has also been accomplished with thallium(I) cyanide,¹⁷⁰⁹ with Me_3SiCN and an SnCl_4 catalyst,¹⁷¹⁰ and with Bu_3SnCN ,¹⁷¹¹ but these reagents are successful only when $\text{R} =$ aryl or tertiary alkyl. KCN has also been used, along with ultrasound,¹⁷¹² as has NaCN with phase transfer catalysts.¹⁷¹³

OS III, 119.

0-112 Preparation of Diazo Ketones
Diazomethyl-de-halogenation



The reaction between acyl halides and diazomethane is of wide scope and is the best way to prepare diazo ketones.¹⁷¹⁴ Diazomethane must be present in excess or the HX produced will react with the diazo ketone (0-71). This reaction is the first step of the Arndt-Eistert synthesis (8-8). Diazo ketones can also be prepared directly from a carboxylic acid and diazomethane or diazoethane in the presence of dicyclohexylcarbodiimide.¹⁷¹⁵

OS III, 119; VI, 386, 613; 69, 180.

¹⁷⁰⁵Kuo; Yahner; Ainsworth *J. Am. Chem. Soc.* **1971**, 93, 6321; Angelo C.R. *Seances Acad. Sci., Ser. C* **1973**, 276, 293.

¹⁷⁰⁶Pfeffer; Silbert *Tetrahedron Lett.* **1970**, 699; Koch; Kop *Tetrahedron Lett.* **1974**, 603.

¹⁷⁰⁷Krapcho; Kashdan; Jahngen; Lovey *J. Org. Chem.* **1977**, 42, 1189; Lion; Dubois *J. Chem. Res., (S)* **1980**, 44.

¹⁷⁰⁸For a review of acyl cyanides, see Hünig; Schaller *Angew. Chem. Int. Ed. Engl.* **1982**, 21, 36-49 [*Angew. Chem.* **94**, 1-15].

¹⁷⁰⁹Taylor; Andrade; John; McKillop *J. Org. Chem.* **1978**, 43, 2280.

¹⁷¹⁰Olah; Arvanaghi; Prakash *Synthesis* **1983**, 636.

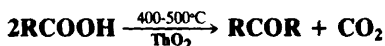
¹⁷¹¹Tanaka *Tetrahedron Lett.* **1980**, 21, 2959. See also Tanaka; Koyanagi *Synthesis* **1981**, 973.

¹⁷¹²Ando; Kawate; Yamawaki; Hanafusa *Synthesis* **1983**, 637.

¹⁷¹³Koenig; Weber *Tetrahedron Lett.* **1974**, 2275. See also Sukata *Bull. Chem. Soc. Jpn.* **1987**, 60, 1085.

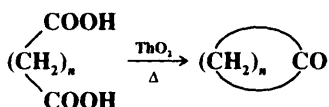
¹⁷¹⁴For reviews, see Fridman; Ismagilova; Zalesov; Novikov *Russ. Chem. Rev.* **1972**, 41, 371-389; Ried; Mengler *Fortshr. Chem. Forsch* **1965**, 5, 1-88.

¹⁷¹⁵Hodson; Holt; Wall *J. Chem. Soc. C* **1970**, 971.

0-113 Ketonic Decarboxylation¹⁷¹⁶**Alkyl-de-hydroxylation**

Carboxylic acids can be converted to symmetrical ketones by pyrolysis in the presence of thorium oxide. In a mixed reaction, formic acid and another acid heated over thorium oxide give aldehydes. Mixed alkyl aryl ketones have been prepared by heating mixtures of ferrous salts.¹⁷¹⁷ When the R group is large, the methyl ester rather than the acid can be decarbomethoxylated over thorium oxide to give the symmetrical ketone.

The reaction has been performed on dicarboxylic acids, whereupon cyclic ketones are obtained:



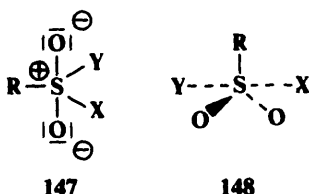
This process, called *Ruzicka cyclization*, is good for the preparation of rings of 6 and 7 members and, with lower yields, of C₈ and C₁₀ to C₃₀ cyclic ketones.¹⁷¹⁸

Not much work has been done on the mechanism of this reaction. However, a free-radical mechanism has been suggested on the basis of a thorough study of all the side products.¹⁷¹⁹

OS I, 192; II, 389; IV, 854; V, 589. Also see OS IV, 55, 560.

Nucleophilic Substitution at a Sulfonyl Sulfur Atom¹⁷²⁰

Nucleophilic substitution at RSO₂X is similar to attack at RCOX. Many of the reactions are essentially the same, though sulfonyl halides are less reactive than halides of carboxylic acids.¹⁷²¹ The mechanisms¹⁷²² are not identical, because a "tetrahedral" intermediate in this case (147) would have five groups on the central atom. Though this is possible (since sulfur



can accommodate up to 12 electrons in its valence shell) it seems more likely that these mechanisms more closely resemble the S_N2 mechanism, with a trigonal bipyramidal transition state (148). There are two major experimental results leading to this conclusion.

¹⁷¹⁶For a review, see Kwart; King, in Patai, Ref. 197, pp. 362-370.

¹⁷¹⁷Granito; Schultz *J. Org. Chem.* **1963**, 28, 879.

¹⁷¹⁸See, for example, Ruzicka; Stoll; Schinz *Helv. Chim. Acta* **1926**, 9, 249, **1928**, 11, 1174; Ruzicka; Brugger; Seidel; Schinz *Helv. Chim. Acta* **1928**, 11, 496.

¹⁷¹⁹Hites; Biemann *J. Am. Chem. Soc.* **1972**, 94, 5772. See also Bouchoule; Blanchard; Thomassin *Bull. Soc. Chim. Fr.* **1973**, 1773.

¹⁷²⁰For a review of mechanisms of nucleophilic substitutions at di-, tri-, and tetracoordinated sulfur atoms, see Ciuffarin; Fava *Prog. Phys. Org. Chem.* **1968**, 6, 81-109.

¹⁷²¹For a comparative reactivity study, see Hirata; Kiyan; Miller *Bull. Soc. Chim. Fr.* **1988**, 694.

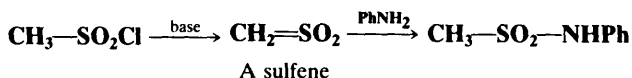
¹⁷²²For a review of mechanisms of nucleophilic substitution at a sulfonyl sulfur, see Gordon; Maskill; Ruasse *Chem. Soc. Rev.* **1989**, 18, 123-151.

1. The stereospecificity of this reaction is more difficult to determine than that of nucleophilic substitution at a saturated carbon, where chiral compounds are relatively easy to prepare, but it may be recalled (p. 98) that optical activity is possible in a compound of the form RSO_2X if one oxygen is ^{16}O and the other ^{18}O . When a sulfonate ester possessing this type of chirality was converted to a sulfone with a Grignard reagent (**0-119**), inversion of configuration was found.¹⁷²³ This is not incompatible with an intermediate such as **147** but it is also in good accord with an $\text{S}_{\text{N}}2$ -like mechanism with backside attack.

2. More direct evidence against **147** (though still not conclusive) was found in an experiment involving acidic and basic hydrolysis of aryl arenesulfonates, where it has been shown by the use of ^{18}O that an intermediate like **147** is not reversibly formed, since ester recovered when the reaction was stopped before completion contained no ^{18}O when the hydrolysis was carried out in the presence of labeled water.¹⁷²⁴

Other evidence favoring the $\text{S}_{\text{N}}2$ -like mechanism comes from kinetics and substituent effects.¹⁷²⁵ However, evidence for the mechanism involving **147** is that the rates did not change much with changes in the leaving group¹⁷²⁶ and the ρ values were large, indicating that a negative charge builds up in the transition state.¹⁷²⁷

In certain cases in which the substrate carries an α hydrogen, there is strong evidence¹⁷²⁸ that at least some of the reaction takes place by an elimination-addition mechanism (E1cB, similar to the one shown on p. 382), going through a sulfene intermediate,¹⁷²⁹ e.g., the reaction between methanesulfonyl chloride and aniline.



In the special case of nucleophilic substitution at a sulfonic ester $\text{RSO}_2\text{OR}'$, where R' is alkyl, $\text{R}'\text{—O}$ cleavage is much more likely than S—O cleavage because the OSO_2R group is such a good leaving group (p. 353).¹⁷³⁰ Many of these reactions have been considered previously (e.g., **0-4**, **0-14**, etc.), because they are nucleophilic substitutions at an alkyl carbon atom and not at a sulfur atom. However, when R' is aryl, then the S—O bond is much more likely to cleave because of the very low tendency aryl substrates have for nucleophilic substitution.¹⁷³¹

¹⁷²³Sabot; Andersen *J. Am. Chem. Soc.* **1969**, *91*, 3603. See also Jones; Cram *J. Am. Chem. Soc.* **1974**, *96*, 2183.

¹⁷²⁴Christman; Oae *Chem. Ind. (London)* **1959**, 1251; Oae; Fukumoto; Kiritani *Bull. Chem. Soc. Jpn.* **1963**, *36*, 346; Kaiser; Zaborsky *J. Am. Chem. Soc.* **1968**, *90*, 4626.

¹⁷²⁵See, for example, Robertson; Rossall *Can. J. Chem.* **1971**, *49*, 1441; Rogne *J. Chem. Soc. B* **1971**, 1855, *J. Chem. Soc., Perkin Trans. 2* **1972**, 489; Gnedin; Ivanov; Spryskov *J. Org. Chem. USSR* **1976**, *12*, 1894; Banjoko; Okwuiwe *J. Org. Chem.* **1980**, *45*, 4966; Ballistreri; Cantone; Maccarone; Tomaselli; Tripolone *J. Chem. Soc., Perkin Trans. 2* **1981**, 438; Suttle; Williams *J. Chem. Soc., Perkin Trans. 2* **1983**, 1563; D'Rozario; Smyth; Williams *J. Am. Chem. Soc.* **1984**, *106*, 5027; Lee; Kang; Lee *J. Am. Chem. Soc.* **1987**, *109*, 7472; Arcoria; Ballistreri; Spina; Tomaselli; Maccarone *J. Chem. Soc., Perkin Trans. 2* **1988**, 1793; Gnedin; Ivanov; Shchukina *J. Org. Chem. USSR* **1988**, *24*, 731.

¹⁷²⁶Ciuffarin; Senatore; Isola *J. Chem. Soc., Perkin Trans. 2* **1972**, 468.

¹⁷²⁷Ciuffarin; Senatore *Tetrahedron Lett.* **1974**, 1635.

¹⁷²⁸For a review, see Opitz *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 107-123 [*Angew. Chem.* **79**, 161-177]. See also King; Lee *J. Am. Chem. Soc.* **1969**, *91*, 6524; Skrypnik; Bezrodnyi *Doklad. Chem.* **1982**, *266*, 341; Farnig; Kice *J. Am. Chem. Soc.* **1981**, *103*, 1137; Thea; Guanti; Hopkins; Williams *J. Am. Chem. Soc.* **1982**, *104*, 1128, *J. Org. Chem.* **1985**, *50*, 5592; Bezrodnyi; Skrypnik *J. Org. Chem. USSR* **1984**, *20*, 1660, 2349; King; Skonieczny *Tetrahedron Lett.* **1987**, *28*, 5001; Pregel; Buncel *J. Chem. Soc., Perkin Trans. 2* **1991**, 307.

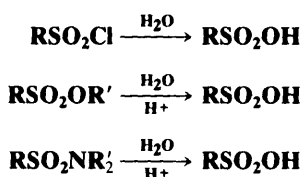
¹⁷²⁹For reviews of sulfenes, see King *Acc. Chem. Res.* **1975**, *8*, 10-17; Nagai; Tokura *Int. J. Sulfur Chem., Part B* **1972**, 207-216; Truce; Liu *Mech. React. Sulfur Compd.* **1969**, *4*, 145-154; Opitz *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 107-123 [*Angew. Chem.* **79**, 161-177]; Wallace *Q. Rev. Chem. Soc.* **1966**, *20*, 67-74.

¹⁷³⁰A number of sulfonates in which R contains α branching, e.g., $\text{Ph}_2\text{C}(\text{CF}_3)\text{SO}_2\text{OR}'$, can be used to ensure that there will be no S—O cleavage; Netscher; Prinzbach *Synthesis* **1987**, 683.

¹⁷³¹See, for example, Oae; Fukumoto; Kiritani *Bull. Chem. Soc. Jpn.* **1963**, *36*, 346; Tagaki; Kurusu; Oae *Bull. Chem. Soc. Jpn.* **1969**, *42*, 2894.

The order of nucleophilicity toward a sulfonyl sulfur has been reported as $\text{OH}^- > \text{RNH}_2 > \text{N}_3^- > \text{F}^- > \text{AcO}^- > \text{Cl}^- > \text{H}_2\text{O} > \text{I}^-$.¹⁷³² This order is similar to that at a carbonyl carbon (p. 351). Both of these substrates can be regarded as relatively hard acids, compared to a saturated carbon which is considerably softer and which has a different order of nucleophilicity (p. 350).

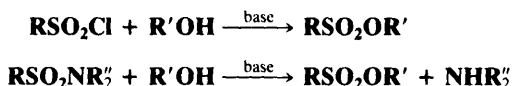
0-114 Attack by OH. Hydrolysis of Sulfonic Acid Derivatives
S-Hydroxy-de-chlorination, etc.



Sulfonyl chlorides as well as esters and amides of sulfonic acids can be hydrolyzed to the corresponding acids. Sulfonyl chlorides can be hydrolyzed with water or with an alcohol in the absence of acid or base. Basic catalysis is also used, though of course the salt is the product obtained. Esters are readily hydrolyzed, many with water or dilute alkali. This is the same reaction as **0-4**, and usually involves $\text{R}'\text{—O}$ cleavage, except when R' is aryl. However, in some cases retention of configuration has been shown at alkyl R' , indicating S—O cleavage in these cases.¹⁷³³ Sulfonamides are generally not hydrolyzed by alkaline treatment, not even with hot concentrated alkali. Acids, however, do hydrolyze them, though less readily than they do sulfonyl halides or sulfonic esters. Of course, ammonia or the amine appears as the salt. However, sulfonamides can be hydrolyzed with base if the solvent is HMPA.¹⁷³⁴

OS **I**, 14; **II**, 471; **III**, 262; **IV**, 34; **V**, 406; **VI**, 652, 727. Also see OS **V**, 673; **VI**, 1016.

0-115 Attack by OR. Formation of Sulfonic Esters
S-Alkoxy-de-chlorination, etc.



Sulfonic esters are most frequently prepared by treatment of the corresponding halides with alcohols in the presence of a base. The method is much used for the conversion of alcohols to tosylates, brosylates, and similar sulfonic esters. Both R and R' may be alkyl or aryl. The base is often pyridine, which functions as a nucleophilic catalyst,¹⁷³⁵ as in the similar alcoholysis of carboxylic acyl halides (**0-20**). Primary alcohols react the most rapidly, and it is often possible to sulfonate selectively a primary OH group in a molecule that also contains secondary or tertiary OH groups. The reaction with sulfonamides has been much less frequently used and is limited to N,N -disubstituted sulfonamides; that is, R'' may not be hydrogen. However, within these limits it is a useful reaction. The nucleophile in this case is actually $\text{R}'\text{O}^-$. However, R'' may be hydrogen (as well as alkyl) if the nucleophile is a phenol, so that the product is RSO_2OAr . Acidic catalysts are used in this case.¹⁷³⁶ Sulfonic acids have been converted directly to sulfonates by treatment with triethyl or trimethyl

¹⁷³²Kice; Kasperek; Patterson *J. Am. Chem. Soc.* **1969**, 91, 5516; Rogne *J. Chem. Soc. B* **1970**, 1056; Ref. 330.

¹⁷³³Chang *Tetrahedron Lett.* **1964**, 305.

¹⁷³⁴Cuvigny; Larchevêque *J. Organomet. Chem.* **1974**, 64, 315.

¹⁷³⁵Rogne *J. Chem. Soc. B* **1971**, 1334. See also Litvinenko; Shatskaya; Savelova *Doklad. Chem.* **1982**, 265, 199.

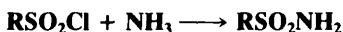
¹⁷³⁶Klamann; Fabienke *Chem. Ber.* **1960**, 93, 252.

orthoformate HC(OR)_3 , without catalyst or solvent;¹⁷³⁷ and with a trialkyl phosphite P(OR)_3 .¹⁷³⁸

OS I, 145; III, 366; IV, 753; VI, 56, 482, 587, 652; VII, 117; 66, 1; 68, 188. Also see OS IV, 529; VI, 324, 757; VII, 495; 66, 185.

0-116 Attack by Nitrogen. Formation of Sulfonamides

S-Amino-de-chlorination



The treatment of sulfonyl chlorides with ammonia or amines is the usual way of preparing sulfonamides. Primary amines give N-alkyl sulfonamides, and secondary amines give N,N-dialkyl sulfonamides. The reaction is the basis of the *Hinsberg test* for distinguishing between primary, secondary, and tertiary amines. N-Alkyl sulfonamides, having an acidic hydrogen, are soluble in alkali, while N,N-dialkyl sulfonamides are not. Since tertiary amines are usually recovered unchanged, primary, secondary, and tertiary amines can be told apart. However, the test is limited for at least two reasons.¹⁷³⁹ (1) Many N-alkyl sulfonamides in which the alkyl group has six or more carbons are insoluble in alkali, despite their acidic hydrogen,¹⁷⁴⁰ so that a primary amine may appear to be a secondary amine. (2) If the reaction conditions are not carefully controlled, tertiary amines may not be recovered unchanged.¹⁷³⁹

A primary or a secondary amine can be protected by reaction with phenacyl-sulfonyl chloride ($\text{PhCOCH}_2\text{SO}_2\text{Cl}$) to give a sulfonamide $\text{RNHSO}_2\text{CH}_2\text{COPh}$ or $\text{R}_2\text{NSO}_2\text{CH}_2\text{COPh}$.¹⁷⁴¹ The protecting group can be removed when desired with zinc and acetic acid. Sulfonyl chlorides react with azide ion to give sulfonyl azides RSO_2N_3 .¹⁷⁴²

OS IV, 34, 943; V, 39, 179, 1055; VI, 78, 652; VII, 501; 69, 158. See also OS VI, 788.

0-117 Attack by Halogen. Formation of Sulfonyl Halides

S-Halo-de-hydroxylation



This reaction, parallel with 0-74, is the standard method for the preparation of sulfonyl halides. Also used are PCl_3 and SOCl_2 , and sulfonic acid salts can also serve as substrates. Sulfonyl bromides and iodides have been prepared from sulfonyl hydrazides ($\text{ArSO}_2\text{NHNH}_2$, themselves prepared by 0-116) by treatment with bromine or iodine.¹⁷⁴³ Sulfonyl fluorides are generally prepared from the chlorides, by halogen exchange.¹⁷⁴⁴

OS I, 84; IV, 571, 693, 846, 937; V, 196. See also OS VII, 495.

0-118 Attack by Hydrogen. Reduction of Sulfonyl Chlorides

S-Hydro-de-chlorination or S-Dechlorination



Sulfinic acids can be prepared by reduction of sulfonyl chlorides. Though mostly done on aromatic sulfonyl chlorides, the reaction has also been applied to alkyl compounds. Besides

¹⁷³⁷Padmapriya; Just; *Lewis Synth. Commun.* **1985**, 15, 1057.

¹⁷³⁸Karaman; Leader; Goldblum; Breuer *Chem. Ind. (London)* **1987**, 857.

¹⁷³⁹For directions for performing and interpreting the Hinsberg test, see Gambill; Roberts; Shechter *J. Chem. Educ.* **1972**, 49, 287.

¹⁷⁴⁰Fanta; Wang *J. Chem. Educ.* **1964**, 41, 280.

¹⁷⁴¹Hendrickson; Bergeron *Tetrahedron Lett.* **1970**, 345.

¹⁷⁴²For an example, see Regitz; Hocker; Liedhegener *Org. Synth.* V, 179.

¹⁷⁴³Poshkus; Herweh; Magnotta *J. Org. Chem.* **1963**, 28, 2766; Litvinenko; Dadali; Savelova; Krichevtsova *J. Gen. Chem. USSR* **1964**, 34, 3780.

¹⁷⁴⁴See Bianchi; Cate *J. Org. Chem.* **1977**, 42, 2031, and references cited therein.

zinc, sodium sulfite, hydrazine, sodium sulfide, and other reducing agents have been used. For reduction of sulfonyl chlorides to thiols, see **9-54**.

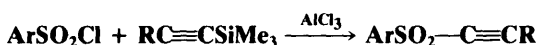
OS **I**, 7, 492; **IV**, 674.

0-119 Attack by Carbon. Preparation of Sulfones

S-Aryl-de-chlorination



Grignard reagents convert aromatic sulfonyl chlorides or aromatic sulfonates to sulfones. Aromatic sulfonates have also been converted to sulfones with organolithium compounds.¹⁷⁴⁵ Vinylic and allylic sulfones have been prepared by treatment of sulfonyl chlorides with a vinylic or allylic stannane and a palladium-complex catalyst.¹⁷⁴⁶ Alkynyl sulfones can be prepared by treatment of sulfonyl chlorides with trimethylsilylalkynes, with an AlCl_3 catalyst.¹⁷⁴⁷



OS **67**, 149.

¹⁷⁴⁵Baarschers *Can. J. Chem.* **1976**, *54*, 3056.

¹⁷⁴⁶Labadie *J. Org. Chem.* **1989**, *54*, 2496.

¹⁷⁴⁷See Waykole; Paquette *Org. Synth.* **67**, 149.

11

AROMATIC ELECTROPHILIC SUBSTITUTION

Most substitutions at an aliphatic carbon are nucleophilic. In aromatic systems the situation is reversed, because the high electron density at the aromatic ring attracts positive species and not negative ones. In electrophilic substitutions the attacking species is a positive ion or the positive end of a dipole or induced dipole. The leaving group (the electrofuge) must necessarily depart without its electron pair. In nucleophilic substitutions, the chief leaving groups are those best able to carry the unshared pair: Br^- , H_2O , OTs^- , etc., that is, the weakest bases. In electrophilic substitutions the most important leaving groups are those that can best exist without the pair of electrons necessary to fill the outer shell, that is, the weakest Lewis acids. The most common leaving group in electrophilic aromatic substitutions is the proton.

MECHANISMS

Electrophilic aromatic substitutions are unlike nucleophilic substitutions in that the large majority proceed by just one mechanism with respect to the substrate.¹ In this mechanism, which we call the *arenium ion mechanism*, the electrophile attacks in the first step, giving rise to a positively charged intermediate (the arenium ion), and the leaving group departs in the second step, so there is a resemblance to the tetrahedral mechanism of Chapter 10, but with the charges reversed. The IUPAC designation for this mechanism is $\text{A}_\text{E} + \text{D}_\text{E}$. Another mechanism, much less common, consists of the opposite behavior: the leaving group departs *before* the electrophile arrives. This mechanism, the SEI mechanism, corresponds to the SN1 mechanism of nucleophilic substitution. Simultaneous attack and departure mechanisms (corresponding to SN2) are not found at all. An addition–elimination mechanism has been postulated in one case (see 1-6).

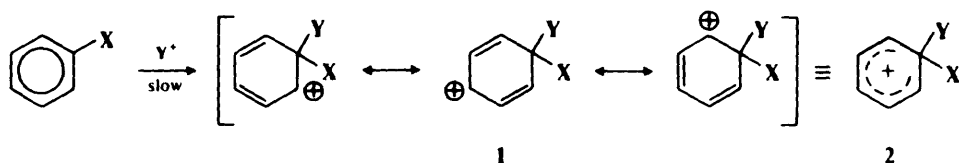
The Arenium Ion Mechanism²

In the arenium ion mechanism the attacking species may be produced in various ways, but what happens to the aromatic ring is basically the same in all cases. For this reason most attention in the study of this mechanism centers around the identity of the attacking entity and how it is produced.

¹For monographs, see Taylor *Electrophilic Aromatic Substitution*; Wiley: New York, 1990; Katritzky; Taylor *Electrophilic Substitution of Heterocycles: Quantitative Aspects* (Vol. 47 of *Adv. Heterocycl. Chem.*); Academic Press: New York, 1990. For a review, see Taylor, in Bamford; Tipper *Comprehensive Chemical Kinetics*, vol. 13; Elsevier: New York, 1972, pp. 1-406.

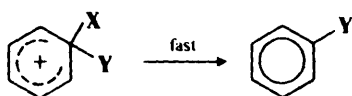
²This mechanism is sometimes called the SE2 mechanism because it is bimolecular, but in this book we reserve that name for aliphatic substrates (see Chapter 12).

The electrophile may be a positive ion or a dipole. If it is a positive ion, it attacks the ring, removing a pair of electrons from the sextet to give a carbocation, which is a resonance hybrid, as shown in **1**, and is frequently represented as in **2**. Ions of this type are called³



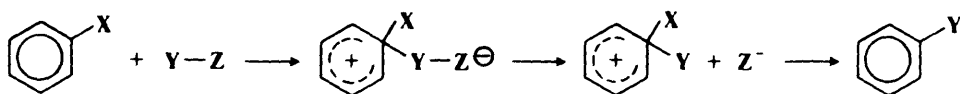
*Wheland intermediates, σ complexes, or arenium ions.*⁴ In the case of benzenoid systems they are cyclohexadienyl cations. It is easily seen that the great stability associated with an aromatic sextet is no longer present in **1**, though the ion is stabilized by resonance of its own. The arenium ion is generally a highly reactive intermediate and must stabilize itself by a further reaction, although it has been isolated (see p. 504).

Carbocations can stabilize themselves in various ways (see p. 174), but for this type of ion the most likely way⁵ is by loss of either X^+ or Y^+ . The aromatic sextet is then restored, and in fact this is the second step of the mechanism:



The second step is nearly always faster than the first, so the first is rate-determining and the reaction is second order (unless the formation of the attacking species is slower still, in which case the aromatic compound does not take part in the rate expression at all). If Y^+ is lost, there is no net reaction, but if X^+ is lost, an aromatic substitution has taken place. If X^+ is a proton, a base is necessary to help remove it.

If the attacking species is not an ion but a dipole, the product must have a negative charge unless part of the dipole, with its pair of electrons, is broken off somewhere in the process, e.g.,



The attacking entity in each case and how it is formed are discussed for each reaction in the reactions section of this chapter.

The evidence for the arenium ion mechanism is mainly of two kinds:

1. Isotope effects. If the hydrogen ion departs before the arrival of the electrophile (SE_1 mechanism) or if the arrival and departure are simultaneous, there should be a substantial isotope effect (i.e., deuterated substrates should undergo substitution more slowly than

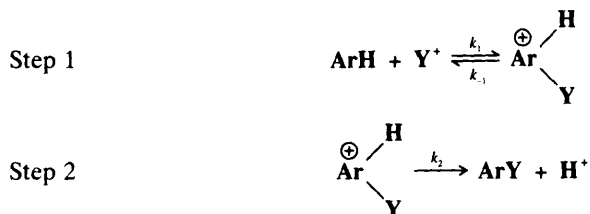
³General agreement on what to call these ions has not yet been reached. The term σ complex is a holdover from the time when much less was known about the structure of carbocations and it was thought they might be complexes of the type discussed in Chapter 3. Other names have also been used. We will call them arenium ions, following the suggestion of Olah *J. Am. Chem. Soc.* **1971**, *94*, 808.

⁴For reviews of arenium ions formed by addition of a proton to an aromatic ring, see Brouwer; Mackor; MacLean, in Olah; Schleyer *Carbanium Ions*, vol. 2; Wiley: New York, 1970, pp. 837-897; Perkampus *Adv. Phys. Org. Chem.* **1966**, *4*, 195-304.

⁵For a discussion of cases in which **1** stabilizes itself in other ways, see de le Mare *Acc. Chem. Res.* **1974**, *7*, 361-368.

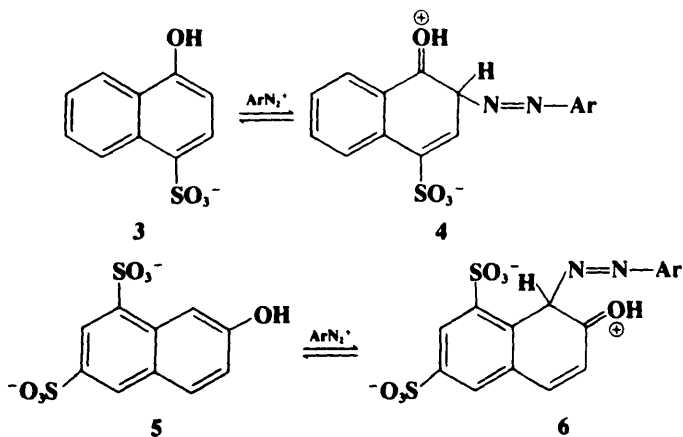
nondeuterated compounds) because, in each case, the C—H bond is broken in the rate-determining step. However, in the arenium ion mechanism, the C—H bond is not broken in the rate-determining step, so no isotope effect should be found. Many such studies have been carried out and, in most cases, especially in the case of nitrations, there is no isotope effect.⁶ This result is incompatible with either the S_E1 or the simultaneous mechanism.

However, in many instances, isotope effects have been found. Since the values are generally much lower than expected for either the S_E1 or the simultaneous mechanisms (e.g., 1 to 3 for k_H/k_D instead of 6 to 7), we must look elsewhere for the explanation. For the case where hydrogen is the leaving group, the arenium ion mechanism can be summarized:



The small isotope effects found most likely arise from the reversibility of step 1 by a *partitioning effect*.⁷ The rate at which ArHY⁺ reverts to ArH should be essentially the same as that at which ArDY⁺ (or ArTY⁺) reverts to ArD (or ArT), since the Ar—H bond is not cleaving. However, ArHY⁺ should go to ArY faster than either ArDY⁺ or ArTY⁺, since the Ar—H bond is broken in this step. If $k_2 \gg k_{-1}$, this does not matter; since a large majority of the intermediates go to product, the rate is determined only by the slow step ($k_1[\text{ArH}][\text{Y}^+]$) and no isotope effect is predicted. However, if $k_2 \approx k_{-1}$, reversion to starting materials is important. If k_2 for ArDY⁺ (or ArTY⁺) is less than k_2 for ArHY⁺, but k_{-1} is the same, then a larger proportion of ArDY⁺ reverts to starting compounds. That is, k_2/k_{-1} (the *partition factor*) for ArDY⁺ is less than that for ArHY⁺. Consequently, the reaction is slower for ArD than for ArH and an isotope effect is observed.

One circumstance that could affect the k_2/k_{-1} ratio is steric hindrance. Thus, diazonium coupling of **3** gave no isotope effect, while coupling of **5** gave a k_H/k_D ratio of 6.55.⁸ For



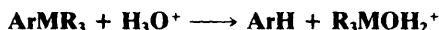
⁶The pioneering studies were by Melander; Melander *Ark. Kemi* **1950**, 2, 211; Berglund-Larsson; Melander *Ark. Kemi* **1953**, 6, 219. See also Zollinger, *Adv. Phys. Org. Chem.* **1964**, 2, 163-200.

⁷For a discussion, see Hammett *Physical Organic Chemistry*, 2nd ed.; McGraw-Hill: New York, 1970. pp. 172-182.

⁸Zollinger *Helv. Chim. Acta* **1955**, 38, 1597, 1617, 1623.

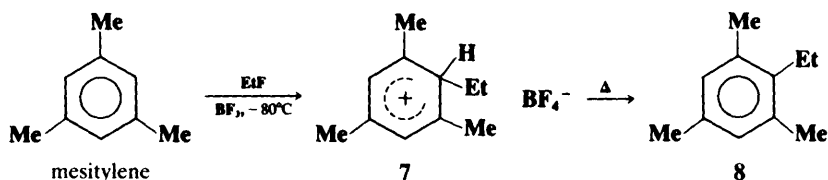
steric reasons it is much more difficult for **6** to lose a proton (it is harder for a base to approach) than it is for **4**, so k_2 is greater for the latter. Since no base is necessary to remove ArN_2^+ , k_{-1} does not depend on steric factors⁹ and is about the same for each. Thus the partition factor k_2/k_{-1} is sufficiently different for **4** and **6** that **5** exhibits a large isotope effect and **3** exhibits none.¹⁰ Base catalysis can also affect the partition factor, since an increase in base concentration increases the rate at which the intermediate goes to product without affecting the rate at which it reverts to starting materials. In some cases, isotope effects can be diminished or eliminated by a sufficiently high concentration of base.

Evidence for the arenium ion mechanism has also been obtained from other kinds of isotope-effect experiments, involving substitutions of the type

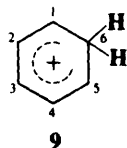


where M is Si, Ge, Sn, or Pb, and R is methyl or ethyl. In these reactions the proton is the electrophile. If the arenium ion mechanism is operating, then the use of D_3O^+ should give rise to an isotope effect, since the D—O bond would be broken in the rate-determining step. Isotope effects of 1.55 to 3.05 were obtained,¹¹ in accord with the arenium ion mechanism.

2. Isolation of arenium ion intermediates. Very strong evidence for the arenium ion mechanism comes from the isolation of arenium ions in a number of instances.¹² For example, **7** was isolated as a solid with melting point -15°C from treatment of mesitylene with ethyl



fluoride and the catalyst BF_3 at -80°C . When **7** was heated, the normal substitution product **8** was obtained.¹³ Even the simplest such ion, the benzenonium ion (**9**) has been prepared in $\text{HF-SbF}_5\text{-SO}_2\text{ClF-SO}_2\text{F}_2$ at -134°C , where it could be studied spectrally.¹⁴ ^{13}C nmr



⁹Snyckers; Zollinger *Helv. Chim. Acta* **1970**, 53, 1294.

¹⁰For some other examples of isotope effects caused by steric factors, see Helgstrand *Acta Chem. Scand.* **1965**, 19, 1583; Nilsson *Acta Chem. Scand.* **1967**, 21, 2423; Baciocchi; Illuminati; Sleiter; Stegel *J. Am. Chem. Soc.* **1967**, 89, 125; Myhre; Beug; James *J. Am. Chem. Soc.* **1968**, 90, 2105; Dubois; Uzan *Bull. Soc. Chim. Fr.* **1968**, 3534; Márton *Acta Chem. Scand.* **1969**, 23, 3321, 3329.

¹¹Bott; Eaborn; Greasley *J. Chem. Soc.* **1964**, 4803.

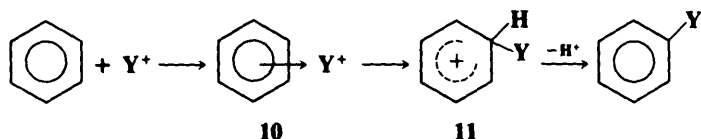
¹²For reviews, see Koptug *Top. Curr. Chem.* **1984**, 122, 1-245; *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1974**, 23, 1031-1045. For a review of polyfluorinated arenium ions, see Shteingarts *Russ. Chem. Rev.* **1981**, 50, 735-749. For a review of the protonation of benzene and simple alkylbenzenes, see Fărcașiu *Acc. Chem. Res.* **1982**, 15, 46-51.

¹³Olah; Kuhn *J. Am. Chem. Soc.* **1958**, 80, 6541. For some other examples, see Ershov; Volod'kin *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1962**, 680; Farrell; Newton; White *J. Chem. Soc. B* **1967**, 637; Kamshii; Koptug *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1974**, 23, 232; Olah; Spear; Messina; Westerman *J. Am. Chem. Soc.* **1975**, 97, 4051; Nambu; Hiraoka; Shigemura; Hamanaka; Ogawa *Bull. Chem. Soc. Jpn.* **1976**, 49, 3637; Chikinev; Bushmelev; Shakirov; Shubin *J. Org. Chem. USSR* **1986**, 22, 1311; Knoche; Schoeller; Schomäcker; Vogel *J. Am. Chem. Soc.* **1988**, 110, 7484; Effenberger *Acc. Chem. Res.* **1989**, 22, 27-35.

¹⁴Olah; Schlossberg; Porter; Mo; Kelly; Mateescu *J. Am. Chem. Soc.* **1972**, 94, 2034.

spectra of the benzenonium ion¹⁵ and the pentamethylbenzenonium ion¹⁶ give graphic evidence for the charge distribution shown in **1**. According to this, the 1, 3, and 5 carbons, each of which bears a charge of about $+\frac{1}{3}$, should have a greater chemical shift in the nmr than the 2 and 4 carbons, which are uncharged. The spectra bear this out. For example, ¹³C nmr chemical shifts for **9** are C-3: 178.1; C-1 and C-5: 186.6; C-2 and C-4: 136.9, and C-6: 52.2.¹⁵

In Chapter 3 it was mentioned that positive ions can form addition complexes with π systems. Since the initial step of electrophilic substitution involves attack by a positive ion on an aromatic ring, it has been suggested¹⁷ that such a complex, called a π complex (represented as **10**), is formed first and then is converted to the arenium ion **11**. Stable solutions of arenium ions or π complexes (e.g., with Br₂, I₂, picric acid, Ag⁺, or HCl) can



be formed at will. For example, π complexes are formed when aromatic hydrocarbons are treated with HCl alone, but the use of HCl plus a Lewis acid (e.g., AlCl₃) gives arenium ions. The two types of solution have very different properties. For example, a solution of an arenium ion is colored and conducts electricity (showing positive and negative ions are present), while a π complex formed from HCl and benzene is colorless and does not conduct a current. Furthermore, when DCl is used to form a π complex, no deuterium exchange takes place (because there is no covalent bond between the electrophile and the ring), while formation of an arenium ion with DCl and AlCl₃ gives deuterium exchange. The relative stabilities of some methylated arenium ions and π complexes are shown in Table 11.1. The arenium ion stabilities listed were determined by the relative basicity of the substrate toward HF.¹⁸ The π complex stabilities are relative equilibrium constants for the reaction¹⁹ between

TABLE 11.1 Relative stabilities of arenium ions and π complexes and relative rates of chlorination and nitration

In each case, p-xylene = 1.00

Substituents	Relative arenium ion stability ¹⁸	Relative π -complex stability ¹⁸	Rate of chlorination ¹⁹	Rate of nitration ²³
None (benzene)	0.09	0.61	0.0005	0.51
Me	0.63	0.92	0.157	0.85
<i>p</i> -Me ₂	1.00	1.00	1.00	1.00
<i>o</i> -Me ₂	1.1	1.13	2.1	0.89
<i>m</i> -Me ₂	26	1.26	200	0.84
1,2,4-Me ₃	63	1.36	340	
1,2,3-Me ₃	69	1.46	400	
1,2,3,4-Me ₄	400	1.63	2000	
1,2,3,5-Me ₄	16,000	1.67	240,000	
Me ₅	29,000		360,000	

¹⁵Olah; Stalal; Asencio; Liang; Forsyth; Mateescu *J. Am. Chem. Soc.* **1978**, *100*, 6299.

¹⁶Lyerla; Yannoni; Bruck; Fyfe *J. Am. Chem. Soc.* **1979**, *101*, 4770.

¹⁷Dewar *Electronic Theory of Organic Chemistry*; Clarendon Press: Oxford, 1949.

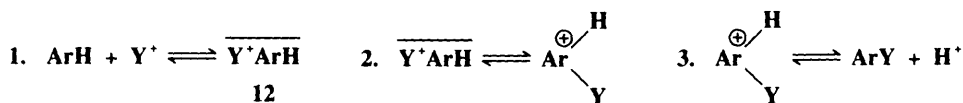
¹⁸Kilpatrick; Luborsky *J. Am. Chem. Soc.* **1953**, *75*, 577.

¹⁹Brown; Brady *J. Am. Chem. Soc.* **1952**, *74*, 3570.

the aromatic hydrocarbon and HCl. As shown in Table 11.1, the relative stabilities of the two types of species are very different: the π complex stability changes very little with methyl substitution, but the arenium ion stability changes a great deal.

How can we tell if **10** is present on the reaction path? If it is present, there are two possibilities: (1) The formation of **10** is rate-determining (the conversion of **10** to **11** is much faster), or (2) the formation of **10** is rapid, and the conversion **10** to **11** is rate-determining. One way to ascertain which species is formed in the rate-determining step in a given reaction is to use the stability information given in Table 11.1. We measure the relative rates of reaction of a given electrophile with the series of compounds listed in Table 11.1. If the relative rates resemble the arenium ion stabilities, we conclude that the arenium ion is formed in the slow step; but if they resemble the stabilities of the π complexes, the latter are formed in the slow step.²⁰ When such experiments are carried out, it is found in most cases that the relative rates are similar to the arenium ion and not to the π complex stabilities. For example, Table 11.1 lists chlorination rates.¹⁹ Similar results were obtained in room-temperature bromination with Br_2 in acetic acid²¹ and in acetylation with $\text{CH}_3\text{CO}^+ \text{SbF}_6^-$.²² It is clear that in these cases the π complex either does not form at all, or if it does, its formation is not rate-determining (unfortunately, it is very difficult to distinguish between these two possibilities).

On the other hand, in nitration with the powerful electrophile NO_2^+ (in the form of $\text{NO}_2^+ \text{BF}_4^-$), the relative rates resembled π complex stabilities much more than arenium ion stabilities (Table 11.1).²³ Similar results were obtained for bromination with Br_2 and FeCl_3 in nitromethane. These results were taken to mean²⁴ that in these cases π complex formation is rate-determining. However, graphical analysis of the NO_2^+ data showed that a straight line could not be drawn when the nitration rate was plotted against π complex stability,²⁵ which casts doubt on the rate-determining formation of a π complex in this case.²⁶ There is other evidence, from positional selectivities (discussed on p. 520), that *some* intermediate is present before the arenium ion is formed, whose formation can be rate-determining with powerful electrophiles. Not much is known about this intermediate, which is given the nondescriptive name *encounter complex* and generally depicted as **12**. The arenium complex mechanism is therefore written as²⁷



²⁰Condon *J. Am. Chem. Soc.* **1952**, *74*, 2528.

²¹Brown; Stock *J. Am. Chem. Soc.* **1957**, *79*, 1421.

²²Olah; Kuhn; Flood; Hardie *J. Am. Chem. Soc.* **1964**, *86*, 2203.

²³Olah; Kuhn; Flood *J. Am. Chem. Soc.* **1961**, *83*, 4571, 4581.

²⁴Olah; Kuhn; Flood; Hardie *J. Am. Chem. Soc.* **1964**, *86*, 1039, 1044; Ref. 23.

²⁵Rys; Skrabal; Zollinger *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 874-883 [*Angew. Chem.* *84*, 921-930]. See also DeHaan; Covey; Delker; Baker; Feigon; Miller; Stelter *J. Am. Chem. Soc.* **1979**, *101*, 1336; Santiago; Houk; Perrin *J. Am. Chem. Soc.* **1979**, *101*, 1337.

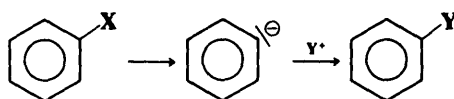
²⁶For other evidence against π complexes, see Tolgyesi *Can. J. Chem.* **1965**, *43*, 343; Caille; Corriu *Chem. Commun.* **1967**, 1251, *Tetrahedron* **1969**, *25*, 2005; Coombes; Moodie; Schofield *J. Chem. Soc. B* **1968**, 800; Hoggett; Moodie; Schofield *J. Chem. Soc. B* **1969**, 1; Christy; Ridd; Stears *J. Chem. Soc. B* **1970**, 797; Ridd *Acc. Chem. Res.* **1971**, *4*, 248-253; Taylor; Tewson *J. Chem. Soc., Chem. Commun.* **1973**, 836; Naidenov; Guk; Golod *J. Org. Chem. USSR* **1982**, *18*, 1731. For further support for π complexes, see Olah; Overchuk *Can. J. Chem.* **1965**, *43*, 3279; Olah *Acc. Chem. Res.* **1971**, *4*, 240-248; Olah; Lin *J. Am. Chem. Soc.* **1974**, *96*, 2892; Koptiug; Rogozhnikova; Detsina *J. Org. Chem. USSR* **1983**, *19*, 1007; El-Dusouqui; Mahmud; Sulfab *Tetrahedron Lett.* **1987**, *28*, 2417; Sedaghat-Herati; Sharifi *J. Organomet. Chem.* **1989**, *363*, 39. For an excellent discussion of the whole question, see Banthorpe *Chem. Rev.* **1970**, *70*, 295-322, especially sections VI and IX.

²⁷For discussions, see Stock *Prog. Phys. Org. Chem.* **1976**, *12*, 21-47; Ridd *Adv. Phys. Org. Chem.* **1978**, *16*, 1-49.

For the reason given above and for other reasons, it is unlikely that the encounter complex is a π complex, but just what kind of attraction exists between Y^+ and ArH is not known, other than the presumption that they are together within a solvent cage (see also p. 520). There is evidence (from isomerizations occurring in the alkyl group, as well as other observations) that π complexes are present on the pathway from substrate to arenium ion in the gas phase protonation of alkylbenzenes.²⁸

The S_E1 Mechanism

The S_E1 mechanism (*substitution electrophilic unimolecular*) is rare, being found only in certain cases in which carbon is the leaving atom (see 1-38, 1-39) or when a very strong base is present (see 1-1, 1-11, and 1-42).²⁹ It consists of two steps with an intermediate carbanion. The IUPAC designation is D_E + A_E.



Reactions 2-41, 2-45, and 2-46 also take place by this mechanism when applied to aryl substrates.

ORIENTATION AND REACTIVITY

Orientation and Reactivity in Monosubstituted Benzene Rings³⁰

When an electrophilic substitution reaction is performed on a monosubstituted benzene, the new group may be directed primarily to the ortho, meta, or para position and the substitution may be slower or faster than with benzene itself. The group already on the ring determines which position the new group will take and whether the reaction will be slower or faster than with benzene. Groups that increase the reaction rate are called *activating* and those that slow it *deactivating*. Some groups are predominantly meta-directing; all of these are deactivating. Others are mostly ortho-para directing; some of these are deactivating too, but most are activating. Groups direct *predominantly*, but usually not *exclusively*. For example, nitration of nitrobenzene gave 93% *m*-dinitrobenzene, 6% of the ortho, and 1% of the para isomer.

The orientation and reactivity effects of each group are explained on the basis of resonance and field effects on the stability of the intermediate arenium ion. To understand why we can use this approach, it is necessary to know that in these reactions the product is usually kinetically and not thermodynamically controlled (see p. 214). Some of the reactions are irreversible and the others are usually stopped well before equilibrium is reached. Therefore, which of the three possible intermediates is formed is dependent not on the thermodynamic stability of the products but on the activation energy necessary to form each of the three

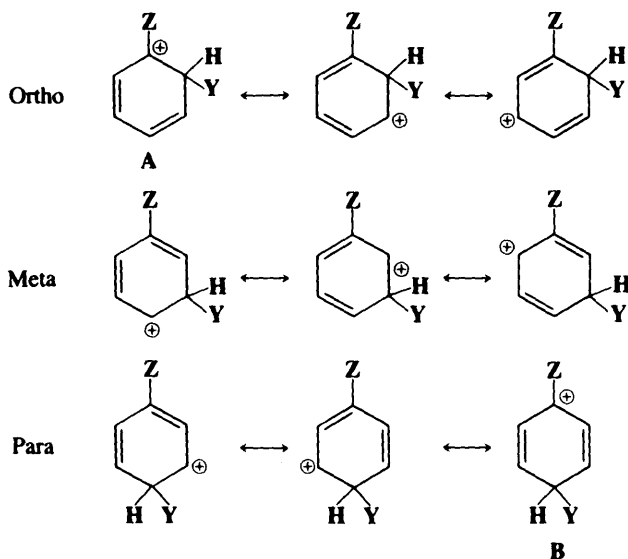
²⁸Holman; Gross *J. Am. Chem. Soc.* **1989**, *111*, 3560.

²⁹It has also been found with a metal (SnMe₃) as electrofuge: Eaborn; Hornfeld; Walton *J. Chem. Soc. B* **1967**, 1036.

³⁰For a review of orientation and reactivity in benzene and other aromatic rings, see Hoggett; Moodie; Penton; Schofield *Nitration and Aromatic Reactivity*; Cambridge University Press: Cambridge, 1971, pp. 122-145, 163-220.

intermediates. It is not easy to predict which of the three activation energies is lowest, but we make the assumption that the free-energy profile resembles either Figure 6.2(a) or (b). In either case, the transition state is closer in energy to the arenium ion intermediate than to the starting compounds. Invoking the Hammond postulate (p. 215), we can then assume that the geometry of the transition state also resembles that of the intermediate and that anything that increases the stability of the intermediate will also lower the activation energy necessary to attain it. Since the intermediate, once formed, is rapidly converted to products, we can use the relative stabilities of the three intermediates as guides to predict which products will predominantly form. Of course, if reversible reactions are allowed to proceed to equilibrium, we may get product ratios that are quite different. For example, the sulfonation of naphthalene at 80°C, where the reaction does not reach equilibrium, gives mostly α -naphthalenesulfonic acid,³¹ while at 160°C, where equilibrium is attained, the β isomer predominates³² (the α isomer is thermodynamically less stable because of steric interaction between the SO_3H group and the hydrogen at the 8 position).

These are the three possible ions:



For each ion we see that the ring has a positive charge. We can therefore predict that any group Z that has an electron-donating field effect ($+I$) should stabilize all three ions (relative to **1**), but that electron-withdrawing groups, which increase the positive charge on the ring, should destabilize them. We can also make a further prediction concerning field effects. These taper off with distance and are thus strongest at the carbon connected to the group Z. Of the three arenium ions, only the ortho and para have any positive charge at this carbon. None of the canonical forms of the meta ion has a positive charge there and so the hybrid has none either. Therefore, $+I$ groups should stabilize all three ions but mostly the ortho and para, so they should be not only activating but ortho-para-directing as well. On the other hand, $-I$ groups, by removing electron density, should destabilize all three ions but mostly the ortho and para, and should be not only deactivating but also meta-directing.

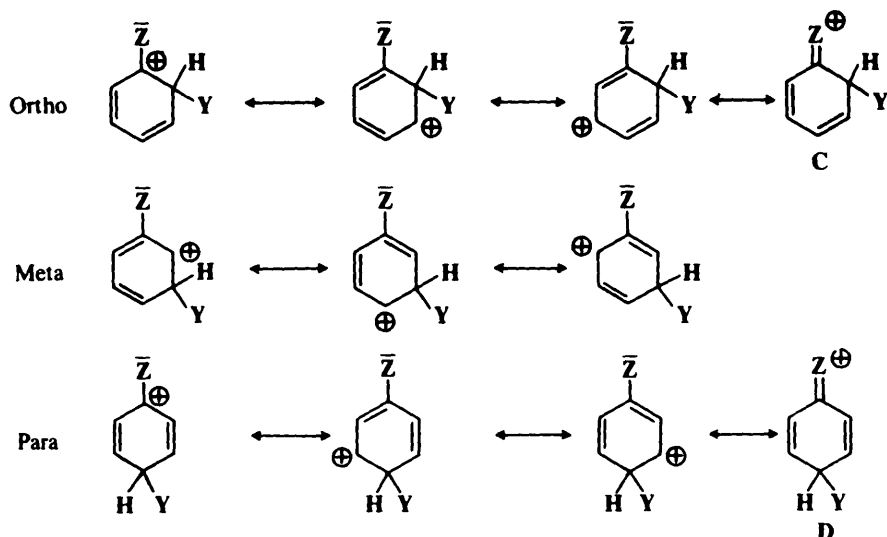
These conclusions are correct as far as they go, but they do not lead to the proper results in all cases. In many cases there is *resonance interaction* between Z and the ring; this also

³¹Fierz; Weissenbach *Helv. Chim. Acta* **1920**, 3, 312.

³²Witt, *Ber.* **1915**, 48, 743.

affects the relative stability, in some cases in the same direction as the field effect, in others differently.

Some substituents have a pair of electrons (usually unshared) that may be contributed toward the ring. The three arenium ions would then look like this:



For each ion the same three canonical forms can be drawn as before, but now we can draw an extra form for the ortho and para ions. The stability of these two ions is increased by the extra form not only because it is another canonical form, but because it is more stable than the others and makes a greater contribution to the hybrid. Every atom (except of course hydrogen) in these forms (C and D) has a complete octet, while all the other forms have one carbon atom with a sextet. No corresponding form can be drawn for the meta isomer. The inclusion of this form in the hybrid lowers the energy not only because of rule 6 (p. 35), but also because it spreads the positive charge over a larger area—out onto the group Z. Groups with a pair of electrons to contribute would be expected, then, in the absence of field effects, not only to direct ortho and para, but also to activate these positions for electrophilic attack.

On the basis of these discussions, we can distinguish three types of groups.

1. Groups that contain an unshared pair of electrons on the atom connected to the ring. In this category are O^- , NR_2 , NHR , NH_2 ,³³ OH , OR , NHCOR , OCOR , SR , and the four halogens.³⁴ The SH group would probably belong here too, except that in the case of thiophenols electrophiles usually attack the sulfur rather than the ring, and ring substitution is not feasible with these substrates.³⁵ The resonance explanation predicts that all these

³³It must be remembered that in acid solution amines are converted to their conjugate acids, which for the most part are meta-directing (type 2). Therefore in acid (which is the most common medium for electrophilic substitutions) amino groups may direct meta. However, unless the solution is highly acidic, there will be a small amount of free amine present, and since amino groups are activating and the conjugate acids deactivating, ortho-para direction is often found even under acidic conditions.

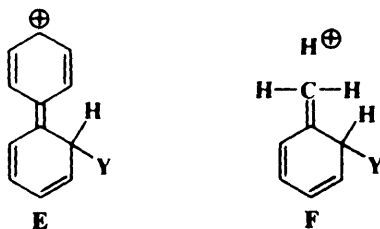
³⁴For a review of the directing and orienting effects of amino groups, see Chuchani, in Patai *The Chemistry of the Amino Group*; Wiley: New York, 1968, pp. 250-265; for other groups see Kohnstam; Williams, in Patai *The Chemistry of the Ether Linkage*; Wiley: New York, 1967, pp. 132-150.

³⁵Tarbell; Herz *J. Am. Chem. Soc.* **1953**, *75*, 4657. Ring substitution is possible if the SH group is protected. For a method of doing this, see Walker *J. Org. Chem.* **1966**, *31*, 835.

groups should be ortho-para-directing, and they are, though all except O^- are electron-withdrawing by the field effect (p. 18). Therefore, for these groups, resonance is more important than the field effect. This is especially true for NR_2 , NHR , NH_2 , and OH , which are *strongly* activating, as is O^- . The other groups are mildly activating, except for the halogens, which are deactivating. Fluorine is the least deactivating, and fluorobenzenes usually show a reactivity approximating that of benzene itself. The other three halogens deactivate about equally. In order to explain why chlorine, bromine, and iodine deactivate the ring, even though they direct ortho-para, we must assume that the canonical forms **C** and **D** make such great contributions to the respective hybrids that they make the ortho and para arenium ions more stable than the meta, even though the $-I$ effect of the halogen is withdrawing sufficient electron density from the ring to deactivate it. The three halogens make the ortho and para ions more stable than the meta, but less stable than the unsubstituted arenium ion (**1**). For the other groups that contain an unshared pair, the ortho and para ions are more stable than either the meta ion or the unsubstituted ion. For most of the groups in this category, the meta ion is more stable than **1**, so that groups such as NH_2 , OH , etc. activate the meta positions too, but not as much as the ortho and para positions (see also the discussion on pp. 516-517).

2. Groups that lack an unshared pair on the atom connected to the ring and that are $-I$. In this category are, in approximate order of decreasing deactivating ability, NR_3^+ , NO_2 , CF_3 , CN , SO_3H , CHO , COR , $COOH$, $COOR$, $CONH_2$, CCl_3 , and NH_3^+ . Also in this category are all other groups with a positive charge on the atom directly connected to the ring³⁶ (SR_2^+ , PR_3^+ , etc.) and many groups with positive charges on atoms farther away, since often these are still powerful $-I$ groups. The field-effect explanation predicts that these should all be meta-directing and deactivating, and (except for NH_3^+) this is the case. The NH_3^+ group is an anomaly, since this group directs para about as much as or a little more than it directs meta.³⁷ The NH_2Me^+ , $NHMe_2^+$, and NMe_3^+ groups all give more meta than para substitution, the percentage of para product decreasing with the increasing number of methyl groups.³⁸

3. Groups that lack an unshared pair on the atom connected to the ring and that are ortho-para-directing. In this category are alkyl groups, aryl groups, and the COO^- group,³⁹ all of which activate the ring. We shall discuss them separately. Since aryl groups are $-I$ groups, they might seem to belong to category 2. They are nevertheless ortho-para-directing and activating. This can be explained in a similar manner as in category 1, with a pair of electrons from the aromatic sextet playing the part played by the unshared pair, so that we have forms like **E**. The effect of negatively charged groups like COO^- is easily explained



³⁶For discussions, see Gastaminza; Modro; Ridd; Utley *J. Chem. Soc. B* **1968**, 534; Gastaminza; Ridd; Roy *J. Chem. Soc. B* **1969**, 684; Gilow; De Shazo; Van Cleave *J. Org. Chem.* **1971**, 36, 1745; Hoggett; Moodie; Penton; Schofield, Ref. 30, pp. 167-176.

³⁷Brickman; Ridd *J. Chem. Soc.* **1965**, 6845; Hartshorn; Ridd *J. Chem. Soc. B* **1968**, 1063. For a discussion, see Ridd, in *Aromaticity*, *Chem. Soc. Spec. Publ.* no. 21, 1967, pp. 149-162.

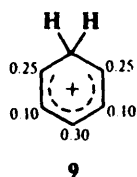
³⁸Brickman; Utley; Ridd *J. Chem. Soc.* **1965**, 6851.

³⁹Spryskov; Golubkin *J. Gen. Chem. USSR* **1961**, 31, 833. Since the COO^- group is present only in alkaline solution, where electrophilic substitution is not often done, it is seldom met with.

by the field effect (negatively charged groups are of course electron-donating), since there is no resonance interaction between the group and the ring. The effect of alkyl groups can be explained in the same way, but, in addition, we can also draw canonical forms, even though there is no unshared pair. These of course are hyperconjugation forms like **F**. This effect, like the field effect, predicts activation and ortho-para direction, so that it is not possible to say how much each effect contributes to the result. Another way of looking at the effect of alkyl groups (which sums up both field and hyperconjugation effects) is that (for $Z = R$) the ortho and para arenium ions are more stable because each contains a form (**A** and **B**) that is a tertiary carbocation, while all the canonical forms for the meta ion and for **1** are secondary carbocations. In activating ability, alkyl groups usually follow the Baker-Nathan order (p. 68), but not always.⁴⁰

The Ortho/Para Ratio⁴¹

When an ortho-para-directing group is on a ring, it is usually difficult to predict how much of the product will be the ortho isomer and how much the para isomer. Indeed, these proportions can depend greatly on the reaction conditions. For example, chlorination of toluene gives an ortho/para ratio anywhere from 62:38 to 34:66.⁴² Nevertheless, certain points can be made. On a purely statistical basis there would be 67% ortho and 33% para, since there are two ortho positions and only one para. However, the phenonium ion **9**,



which arises from protonation of benzene, has the approximate charge distribution shown.⁴³ If we accept this as a model for the arenium ion in aromatic substitution, a para substituent would have a greater stabilizing effect on the adjacent carbon than an ortho substituent. If other effects are absent, this would mean that more than 33% para and less than 67% ortho substitution would be found. In hydrogen exchange (reaction 1-1), where other effects are absent, it has been found for a number of substituents that the average ratio of the logarithms of the partial rate factors for these positions (see p. 516 for a definition of partial rate factor) was close to 0.865,⁴⁴ which is not far from the value predicted from the ratio of charge densities in **9**. This picture is further supported by the fact that meta-directing groups, which destabilize a positive charge, give ortho/para ratios greater than 67:33⁴⁵ (of course the total amount of ortho and para substitution with these groups is small, but the *ratios* are generally greater than 67:33). Another important factor is the steric effect. If either the group on the ring or the attacking group is large, steric hindrance inhibits formation of the ortho product and increases the amount of the para isomer. An example may be seen in the nitration, under the same conditions, of toluene and *t*-butylbenzene. The former gave 58% of the ortho compound and 37% of the para, while the more bulky *t*-butyl group gave 16% of the

⁴⁰For examples of situations where the Baker-Nathan order is not followed, see Eaborn; Taylor, *J. Chem. Soc.* **1961**, 247; Stock *J. Org. Chem.* **1961**, 26, 4120; Utley; Vaughan *J. Chem. Soc. B* **1968**, 196; Schubert; Gurka *J. Am. Chem. Soc.* **1969**, 91, 1443; Himoe; Stock *J. Am. Chem. Soc.* **1969**, 91, 1452.

⁴¹For a discussion, see Pearson; Buchler *Synthesis* **1971**, 455-477, pp. 455-464.

⁴²Stock; Himoe *J. Am. Chem. Soc.* **1961**, 83, 4605.

⁴³Olah *Acc. Chem. Res.* **1970**, 4, 240, p. 248.

⁴⁴Bailey; Taylor *J. Chem. Soc. B* **1971**, 1446; Ansell; Le Guen; Taylor *Tetrahedron Lett.* **1973**, 13.

⁴⁵Hoggett; Moodie; Penton; Schofield, *Ref.* 30, pp. 176-180.

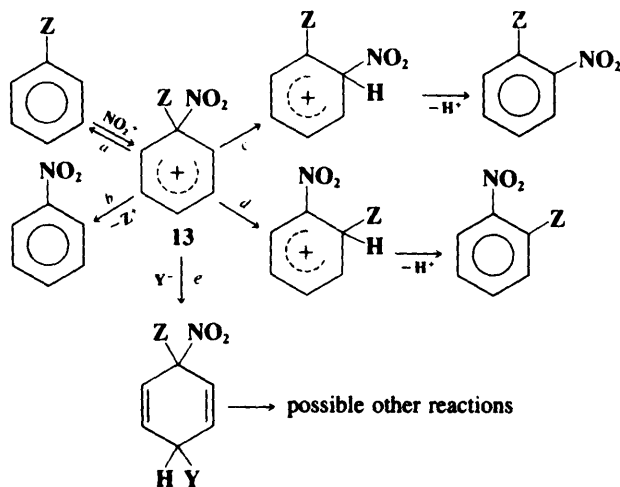
ortho product and 73% of the para.⁴⁶ Some groups are so large that they direct almost entirely para.

When the ortho-para-directing group is one with an unshared pair (this of course applies to most of them), there is another effect that increases the amount of para product at the expense of the ortho. A comparison of the intermediates involved (p. 509) shows that **C** is a canonical form with an ortho-quinonoid structure, while **D** has a para-quinonoid structure. Since we know that *para*-quinones are more stable than the ortho isomers, it seems reasonable to assume that **D** is more stable than **C** and therefore contributes more to the hybrid and increases its stability compared to the ortho intermediate.

It has been shown that it is possible to compel regiospecific para substitution by enclosing the substrate molecules in a cavity from which only the para position projects. Anisole was chlorinated in solutions containing a cyclodextrin, a molecule in which the anisole is almost entirely enclosed (see Fig. 3.4). With a high enough concentration of cyclodextrin, it was possible to achieve a para/ortho ratio of 21.6⁴⁷ (in the absence of the cyclodextrin the ratio was only 1.48). This behavior is a model for the regioselectivity found in the action of enzymes.

Ipsso Attack

We have discussed orientation in the case of monosubstituted benzenes entirely in terms of attack at the ortho, meta, and para positions, but attack at the position bearing the substituent (called the *ipso position*⁴⁸) can also be important. Ipsso attack has mostly been studied for nitration.⁴⁹ When NO_2^+ attacks at the ipso position there are at least five possible fates for the resulting arenium ion (**13**).



⁴⁶Nelson; Brown *J. Am. Chem. Soc.* **1951**, 73, 5605. For product ratios in the nitration of many monoalkylbenzenes, see Baas; Wepster *Recl. Trav. Chim. Pays-Bas* **1971**, 90, 1081, 1089, **1972**, 91, 285, 517, 831.

⁴⁷Breslow; Campbell *J. Am. Chem. Soc.* **1969**, 91, 3085, *Bioorg. Chem.* **1971**, 1, 140. See also Chen; Kaeding; Dwyer *J. Am. Chem. Soc.* **1979**, 101, 6783; Konishi; Yokota; Ichihashi; Okano; Kiji *Chem. Lett.* **1980**, 1423; Komiyama; Hirai *J. Am. Chem. Soc.* **1983**, 105, 2018, **1984**, 106, 174; Chênevert; Ampleman *Can. J. Chem.* **1987**, 65, 307; Komiyama *Polym. J. (Tokyo)* **1988**, 20, 439.

⁴⁸Perrin; Skinner *J. Am. Chem. Soc.* **1971**, 93, 3389. For a review of ipso substitution, see Traynham *J. Chem. Educ.* **1983**, 60, 937-941.

⁴⁹For a review, see Moodie; Schofield *Acc. Chem. Res.* **1976**, 9, 287-292. See also Fischer; Henderson; RayMahasay *Can. J. Chem.* **1987**, 65, 1233, and other papers in this series.

Path a. The arenium ion can lose NO_2^+ and revert to the starting compounds. This results in no net reaction and is often undetectable.

Path b. The arenium ion can lose Z^+ , in which case this is simply aromatic substitution with a leaving group other than H (see 1-37 to 1-44).

Path c. The electrophilic group (in this case NO_2^+) can undergo a 1,2-migration, followed by loss of the proton. The product in this case is the same as that obtained by direct attack of NO_2^+ at the ortho position of PhZ. It is not always easy to tell how much of the ortho product in any individual case arises from this pathway,⁵⁰ though there is evidence that it can be a considerable proportion. Because of this possibility, many of the reported conclusions about the relative reactivity of the ortho, meta, and para positions are cast into doubt, since some of the product may have arisen not from direct attack at the ortho position, but from attack at the ipso position followed by rearrangement.⁵¹

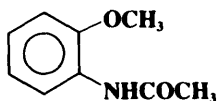
Path d. The ipso substituent (Z) can undergo 1,2-migration, which also produces the ortho product (though the rearrangement would become apparent if there were other substituents present). The evidence is that this pathway is very minor, at least when the electrophile is NO_2^+ .⁵²

Path e. Attack of a nucleophile on 13. In some cases the products of such an attack (cyclohexadienes) have been isolated⁵³ (this is 1,4-addition to the aromatic ring), but further reactions are also possible.

Orientation in Benzene Rings with More than One Substituent⁵⁴

It is often possible in these cases to predict the correct isomer. In many cases the groups already on the ring reinforce each other. Thus, 1,3-dimethylbenzene is substituted at the 4 position (ortho to one group and para to the other), but not at the 5 position (meta to both). Likewise the incoming group in *p*-chlorobenzoic acid goes to the position ortho to the chloro and meta to the carboxyl group.

When the groups oppose each other, predictions may be more difficult. In a case such as



where two groups of about equal directing ability are in competing positions, all four products can be expected, and it is not easy to predict the proportions, except that steric hindrance should probably reduce the yield of substitution ortho to the acetamido group, especially for large electrophiles. Mixtures of about equal proportions are frequent in such cases. Nevertheless, even when groups on a ring oppose each other, there are some regularities.

1. If a strong activating group competes with a weaker one or with a deactivating group, the former controls. Thus *o*-cresol gives substitution mainly ortho and para to the hydroxyl group and not to the methyl. For this purpose we can arrange the groups in the following

⁵⁰For methods of doing so, see Gibbs; Moodie; Schofield *J. Chem. Soc., Perkin Trans. 2* **1978**, 1145.

⁵¹This was first pointed out by Myhre *J. Am. Chem. Soc.* **1972**, 94, 7921.

⁵²For examples of such migration, where Z = Me, see Hartshorn; Readman; Robinson; Sies; Wright *Aust. J. Chem.* **1988**, 41, 373.

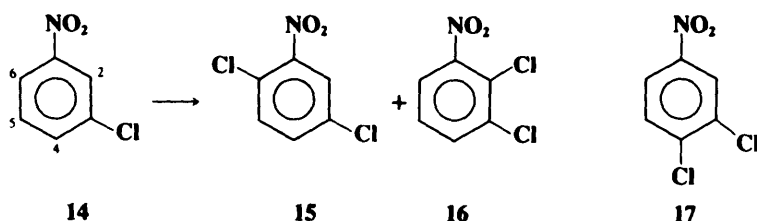
⁵³For examples, see Banwell; Morse; Myhre; Vollmar *J. Am. Chem. Soc.* **1977**, 99, 3042; Fischer; Greig *Can. J. Chem.* **1978**, 56, 1063.

⁵⁴For a quantitative discussion, see pp. 516-517.

order: NH_2 , OH , NR_2 , O^- > OR , OCOR , NHCOR > R , Ar > halogen > meta-directing groups.

2. All other things being equal, a third group is least likely to enter between two groups in the meta relationship. This is the result of steric hindrance and increases in importance with the size of the groups on the ring and with the size of the attacking species.⁵⁵

3. When a meta-directing group is meta to an ortho-para-directing group, the incoming group primarily goes ortho to the meta-directing group rather than para. For example, chlorination of **14** gives mostly **15**. The importance of this effect is underscored by the fact that **16**, which is in violation of the preceding rule, is formed in smaller amounts, but **17** is



not formed at all. This is called the *ortho effect*,⁵⁶ and many such examples are known.⁵⁷ Another is the nitration of *p*-bromotoluene, which gives 2,3-dinitro-4-bromotoluene. In this case, once the first nitro group came in, the second was directed ortho to it rather than para, even though this means that the group has to come in between two groups in the meta position. There is no good explanation yet for the ortho effect, though possibly there is intramolecular assistance from the meta-directing group.

It is interesting that chlorination of **14** illustrates all three rules. Of the four positions open to the electrophile, the 5 position violates rule 1, the 2 position rule 2, and the 4 position rule 3. The principal attack is therefore at position 6.

Orientation in Other Ring Systems⁵⁸

In fused ring systems the positions are not equivalent and there is usually a preferred orientation, even in the unsubstituted hydrocarbon. The preferred positions may often be predicted as for benzene rings. Thus it is possible to draw more canonical forms for the arenium ion when naphthalene is attacked at the α position than when it is attacked at the β position, and the α position is the preferred site of attack,⁵⁹ though, as previously mentioned (p. 508), the isomer formed by substitution at the β position is thermodynamically more stable and is the product if the reaction is reversible and equilibrium is reached. Because of the more extensive delocalization of charges in the corresponding arenium ions, naphthalene is more reactive than benzene and substitution is faster at both positions. Similarly,

⁵⁵In some cases, an electrophile preferentially attacks the position between two groups in the meta relationship. For a list of some of these cases and a theory to explain them, see Kruse; *Ch. J. Chem. Soc., Chem. Commun.* **1982**, 1333.

⁵⁶This is not the same as the ortho effect mentioned on p. 286.

⁵⁷See Hammond; Hawthorne, in *Newman Steric Effects in Organic Chemistry*; Wiley: New York, 1956, pp. 164-200, 178-182.

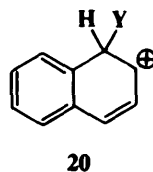
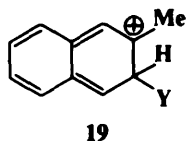
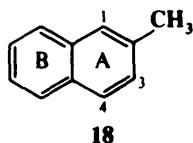
⁵⁸For a review of substitution on nonbenzenoid aromatic systems, see Hafner; Moritz, in *Olah Friedel-Crafts and Related Reactions*, vol. 4; Wiley: New York, 1965, pp. 127-183. For a review of aromatic substitution on ferrocenes, see Bublitz; Rinchart, *Org. React.* **1969**, *17*, 1-154.

⁵⁹For a discussion on the preferred site of attack for many ring systems, see de la Mare; *Ridd Aromatic Substitution—Nitration and Halogenation*; Academic Press: New York, 1959, pp. 169-209.

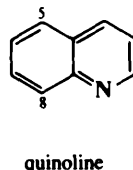
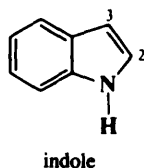
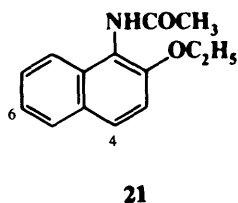
anthracene, phenanthrene, and other fused polycyclic aromatic hydrocarbons are also substituted faster than benzene.

Heterocyclic compounds, too, have nonequivalent positions, and the principles are similar.⁶⁰ Furan, thiophene, and pyrrole are chiefly substituted at the 2 position, and all are substituted faster than benzene.⁶¹ Pyrrole is particularly reactive, with a reactivity approximating that of aniline or the phenoxide ion. For pyridine⁶² it is not the free base that is attacked but the conjugate acid, pyridinium ion.⁶³ The 3 position is most reactive, but the reactivity in this case is much less than that of benzene, being similar to that of nitrobenzene. However, groups can be introduced into the 4 position of a pyridine ring indirectly, by performing the reaction on the corresponding pyridine N-oxide.⁶⁴

When fused ring systems contain substituents, successful predictions can often be made by using a combination of the above principles. Thus, ring A of 2-methylnaphthalene (**18**)



is activated by the methyl group; ring B is not (though the presence of a substituent in a fused ring system affects all the rings,⁶⁵ the effect is generally greatest on the ring to which it is attached). We therefore expect substitution in ring A. The methyl group activates positions 1 and 3, which are ortho to itself, but not position 4, which is meta to it. However, substitution at the 3 position gives rise to an arenium ion for which it is impossible to write a low-energy canonical form in which ring B has a complete sextet. All we can write are forms like **19**, in which the sextet is no longer intact. In contrast, substitution at the 1 position gives rise to a more stable arenium ion, for which two canonical forms (one of them is **20**) can be written in which ring B is benzenoid. We thus predict predominant substitution at C-1, and that is what is generally found.⁶⁶ However, in some cases predictions are much harder to make. For example, chlorination or nitration of **21** gives mainly the 4 derivative, but bromination yields chiefly the 6 compound.⁶⁷



⁶⁰For a monograph, see Katritzky; Taylor, Ref. 1.

⁶¹For a review of electrophilic substitution on five-membered aromatic heterocycles, see Marino *Adv. Heterocycl. Chem.* **1971**, 13, 235-314.

⁶²For reviews of substitution on pyridines and other six-membered nitrogen-containing aromatic rings, see Comins; O'Connor *Adv. Heterocycl. Chem.* **1988**, 44, 199-267; Aksel'rod; Berezovskii *Russ. Chem. Rev.* **1970**, 39, 627-643; Katritzky; Johnson *Angew. Chem. Int. Ed. Engl.* **1967**, 6, 608-615 [*Angew. Chem.* 79, 629-636]; Abramovitch; Saha *Adv. Heterocycl. Chem.* **1966**, 6, 229-345. For a review of methods of synthesizing 3-substituted pyrroles, see Anderson; Loader *Synthesis* **1985**, 353-364.

⁶³Olah; Olah; Overchuk *J. Org. Chem.* **1965**, 30, 3373; Katritzky; Kingsland *J. Chem. Soc. B* **1968**, 862.

⁶⁴Jaffé *J. Am. Chem.* **1954**, 76, 3527.

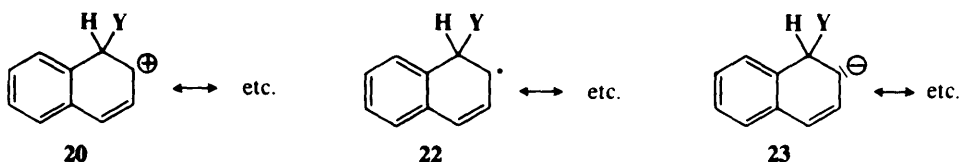
⁶⁵See, for example, Ansell; Sheppard; Simpson; Stroud; Taylor *J. Chem. Soc., Perkin Trans 2* **1979**, 381.

⁶⁶For example, see Alcorn; Wells *Aust. J. Chem.* **1965**, 18, 1377, 1391; Eaborn; Golborn; Spillett; Taylor *J. Chem. Soc. B* **1968**, 1112; Kim; Chen; Krieger; Judd; Simpson; Berliner *J. Am. Chem. Soc.* **1970**, 92, 910. For discussions, see Taylor *Chimia* **1968**, 22, 1-8; Gore; Siddiquei; Thorburn *J. Chem. Soc., Perkin Trans 1* **1972**, 1781.

⁶⁷Bell *J. Chem. Soc.* **1959**, 519.

For fused heterocyclic systems too, we can often make predictions based on the above principles, though many exceptions are known. Thus, indole is chiefly substituted in the pyrrole ring (at position 3) and reacts faster than benzene, while quinoline generally reacts in the benzene ring, at the 5 and 8 positions, and slower than benzene, though faster than pyridine.

In alternant hydrocarbons (p. 50) the reactivity at a given position is similar for electrophilic, nucleophilic, and free-radical substitution, because the same kind of resonance can be shown in all three types of intermediate (compare **20**, **22**, and **23**). Attack at the position

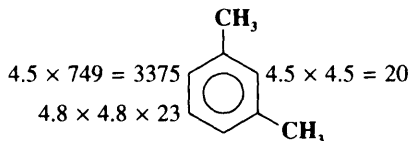


that will best delocalize a positive charge will also best delocalize a negative charge or an unpaired electron. Most results are in accord with these predictions. For example, naphthalene is attacked primarily at the 1 position by NO_2^+ , NH_2^- , and Ph^\bullet , and always more readily than benzene.

Quantitative Treatments of Reactivity in the Substrate

Quantitative rate studies of aromatic substitutions are complicated by the fact that there are usually several hydrogens that can leave, so that measurements of overall rate ratios do not give a complete picture as they do in nucleophilic substitutions, where it is easy to compare substrates that have only one possible leaving group in a molecule. What is needed is not, say, the overall rate ratio for acetylation of toluene vs. that for benzene, but the *rate ratio at each position*. These can be calculated from the overall rates and a careful determination of the proportion of isomers formed, provided that the products are kinetically controlled, as is usually the case. We may thus define the *partial rate factor* for a given group and a given reaction as the rate of substitution at a single position relative to a single position in benzene. For example, for acetylation of toluene the partial rate factors are: for the ortho position $o_f^{\text{Me}} = 4.5$, for the meta $m_f^{\text{Me}} = 4.8$, and for the para $p_f^{\text{Me}} = 749$.⁶⁸ This means that toluene is acetylated at the ortho position 4.5 times as fast as a single position in benzene, or 0.75 times as fast as the overall rate of acetylation of benzene. A partial rate factor greater than 1 for a given position indicates that the group in question activates that position for the given reaction. Partial rate factors differ from one reaction to another and are even different, though less so, for the same reaction under different conditions.

Once we know the partial rate factors, we can predict the proportions of isomers to be obtained when two or more groups are present on a ring, if we make the assumption that the effect of substituents is additive. For example, if the two methyl groups in *m*-xylene have the same effect as the methyl group in toluene, we can calculate the theoretical partial rate factors at each position by multiplying those from toluene, so they should be as indicated:

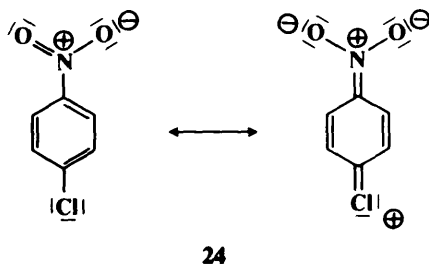


⁶⁸Brown; Marino; Stock *J. Am. Chem. Soc.* **1959**, *81*, 3310.

TABLE 11.2 Calculated and experimental isomer distributions in the acetylation of *m*-xylene⁶⁹

Position	Isomer distribution, %	
	Calculated	Observed
2	0.30	0
4	99.36	97.5
5	0.34	2.5

From this it is possible to calculate the overall theoretical rate ratio for acetylation of *m*-xylene relative to benzene, since this is one-sixth the sum of the partial rate factors (in this case 1130), and the isomer distribution if the reaction is kinetically controlled. The overall rate ratio actually is 347⁶⁹ and the calculated and observed isomer distributions are listed in Table 11.2.⁶⁹ In this case, and in many others, agreement is fairly good, but many cases are known where the effects are not additive.⁷⁰ For example, the treatment predicts that for 1,2,3-trimethylbenzene there should be 35% 5 substitution and 65% 4 substitution, but acetylation gave 79% 5 substitution and 21% of the 4 isomer. The treatment is thrown off by steric effects, such as those mentioned earlier (p. 511), by products arising from ipso attack (p. 512) and by resonance interaction *between* groups (for example, **24**), which must make the results deviate from simple additivity of the effects of the groups.



Another approach that avoids the problem created by having competing leaving groups present in the same substrate is the use of substrates that contain only one leaving group. This is most easily accomplished by the use of a leaving group other than hydrogen. By this means overall rate ratios can be measured for specific positions.⁷¹ Results obtained in this way⁷² give a reactivity order quite consistent with that for hydrogen as leaving group.

A quantitative scale of reactivity for aromatic substrates (fused, heterocyclic, and substituted rings) has been devised, based on the hard-soft concept (p. 261).⁷³ From molecular orbital theory, a quantity, called *activation hardness*, can be calculated for each position of an aromatic ring. The smaller the activation hardness, the faster the attack at that position; hence the treatment predicts the most likely orientations for incoming groups.

⁶⁹Marino; Brown *J. Am. Chem. Soc.* **1959**, 81, 5929.

⁷⁰For some examples where additivity fails, see Fischer; Vaughan; Wright *J. Chem. Soc. B* **1967**, 368; Coombes; Crout; Hoggett; Moodie; Schofield *J. Chem. Soc. B* **1970**, 347; Richards; Wilkinson; Wright *Aust. J. Chem.* **1972**, 25, 2369; Cook; Phillips; Ridd *J. Chem. Soc., Perkin Trans. 2* **1974**, 1166. For a theoretical treatment of why additivity fails, see Godfrey *J. Chem. Soc. B* **1971**, 1545.

⁷¹For a review of aryl-silicon and related cleavages, see Eaborn *J. Organomet. Chem.* **1975**, 100, 43-57.

⁷²See, for example, Deans and Eaborn *J. Chem. Soc.* **1959**, 2299; Eaborn; Jackson *J. Chem. Soc. B* **1969**, 21.

⁷³Zhou; Parr *J. Am. Chem. Soc.* **1990**, 112, 5720.

A Quantitative Treatment of Reactivity of the Electrophile. The Selectivity Relationship

Not all electrophiles are equally powerful. The nitronium ion attacks not only benzene but also aromatic rings that contain a strongly deactivating group. On the other hand, diazonium ions couple only with rings containing a powerful activating group. Attempts have been made to correlate the influence of substituents with the power of the attacking group. The most obvious way to do this is with the Hammett equation (p. 278):

$$\log \frac{k}{k_0} = \rho\sigma$$

For aromatic substitution, k_0 is divided by 6 and, for meta substitution, k is divided by 2, so that comparisons are made for only one position (consequently, k/k_0 for, say, the methyl group at a para position is identical to the partial rate factor ρ_f^{Me}). It was soon found that, while this approach worked fairly well for electron-withdrawing groups, it failed for those that are electron-donating. However, if the equation is modified by the insertion of the Brown σ^+ values instead of the Hammett σ values (because a positive charge develops during the transition state), more satisfactory correlations can be made, even for electron-donating groups (see Table 9.4 for a list of σ^+ values).⁷⁴ Groups with a negative value of σ_p^+ or σ_m^+ are activating for that position; groups with a positive value are deactivating. The ρ values correspond to the susceptibility of the reaction to stabilization or destabilization by the Z group and to the reactivity of the electrophile. The ρ values vary not only with the electrophile but also with conditions. A large negative value of ρ means an electrophile of relatively low reactivity. Of course, this approach is completely useless for ortho substitution, since the Hammett equation does not apply there.

A modification of the Hammett approach, suggested by Brown, called the *selectivity relationship*,⁷⁵ is based on the principle that reactivity of a species varies inversely with selectivity. Table 11.3 shows how electrophiles can be arranged in order of selectivity as measured by two indexes: (1) their selectivity in attacking toluene rather than benzene, and (2) their selectivity between the meta and para positions in toluene.⁷⁶ As the table shows, an electrophile more selective in one respect is also more selective in the other. In many

TABLE 11.3 Relative rates and product distributions in some electrophilic substitutions on toluene and benzene⁷⁶

Reaction	Relative rate $k_{\text{toluene}}/k_{\text{benzene}}$	Product distribution, %	
		<i>m</i>	<i>p</i>
Bromination	605	0.3	66.8
Chlorination	350	0.5	39.7
Benzoylation	110	1.5	89.3
Nitration	23	2.8	33.9
Mercuration	7.9	9.5	69.5
Isopropylation	1.8	25.9	46.2

⁷⁴For a discussion of the limitations of the Hammett equation approach, see Koptiyug; Salakhutdinov; Detsina *J. Org. Chem. USSR* **1984**, 20, 1039.

⁷⁵Stock; Brown *Adv. Phys. Org. Chem.* **1963**, 1, 35-154.

⁷⁶Ref. 75, p. 45.

cases, electrophiles known to be more stable (hence less reactive) than others show a higher selectivity, as would be expected. For example, the *t*-butyl cation is more stable and more selective than the isopropyl (p. 166), and Br₂ is more selective than Br⁺. However, deviations from the relationship are known.⁷⁷ Selectivity depends not only on the nature of the electrophile but also on the temperature. As expected, it normally decreases with increasing temperature.

Brown assumed that a good measurement of selectivity was the ratio of the para and meta partial rate factors in toluene. He defined the selectivity S_f of a reaction as

$$S_f = \log \frac{p_f^{\text{Me}}}{m_f^{\text{Me}}}$$

That is, the more reactive an attacking species, the less preference it has for the para position compared to the meta. If we combine the Hammett–Brown $\sigma^+ \rho$ relationship with the linearity between $\log S_f$ and $\log p_f^{\text{Me}}$ and between $\log S_f$ and $\log m_f^{\text{Me}}$, it is possible to derive the following expressions:

$$\log p_f^{\text{Me}} = \frac{\sigma_p^+}{\sigma_p^+ - \sigma_m^+} S_f$$

$$\log m_f^{\text{Me}} = \frac{\sigma_m^+}{\sigma_p^+ - \sigma_m^+} S_f$$

S_f is related to ρ by

$$S_f = \rho(\sigma_p^+ - \sigma_m^+)$$

The general validity of these equations is supported by a great deal of experimental data on aromatic substitution reactions of toluene. Examples of values for some reactions obtained from these equations are given in Table 11.4.⁷⁸ For other substituents, the treatment works well with groups that, like methyl, are not very polarizable. For more polarizable groups the correlations are sometimes satisfactory and sometimes not, probably because each electrophile in the transition state makes a different demand on the electrons of the substituent group.

Not only are there substrates for which the treatment is poor, but it also fails with very powerful electrophiles; this is why it is necessary to postulate the encounter complex mentioned on p. 506. For example, relative rates of nitration of *p*-xylene, 1,2,4-trimethylbenzene, and 1,2,3,5-tetramethylbenzene were 1.0, 3.7, and 6.4,⁷⁹ though the extra methyl groups

TABLE 11.4 Values of m_f^{Me} , p_f^{Me} , S_f , and ρ for three reactions of toluene⁷⁸

Reaction	m_f^{Me}	p_f^{Me}	S_f	ρ
PhMe + EtBr $\xrightarrow[\text{benzene, 25}^\circ\text{C}]{\text{GaBr}_3}$	1.56	6.02	0.587	-2.66
PhMe + HNO₃ $\xrightarrow[45^\circ\text{C}]{90\% \text{ HOAc}}$	2.5	58	1.366	-6.04
PhMe + Br₂ $\xrightarrow[25^\circ\text{C}]{85\% \text{ HOAc}}$	5.5	2420	2.644	-11.40

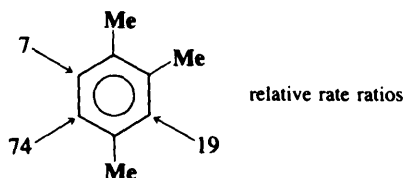
⁷⁷At least some of these may arise from migration of groups already on the ring; see Olah; Olah; Ohyama *J. Am. Chem. Soc.* **1984**, 106, 5284.

⁷⁸Stock; Brown *J. Am. Chem. Soc.* **1959**, 81, 3323. Ref. 75 presents many tables of these kinds of data. See also DeHaan; Chan; Chang; Ferrara; Wainschel *J. Org. Chem.* **1986**, 51, 1591, and other papers in this series.

⁷⁹Olah; Lin, Ref. 26.

should enhance the rates much more (*p*-xylene itself reacted 295 times faster than benzene). The explanation is that with powerful electrophiles the reaction rate is so rapid (reaction taking place at virtually every encounter⁸⁰ between an electrophile and substrate molecule)⁸¹ that the presence of additional activating groups can no longer increase the rate.⁸²

Given this behavior (little selectivity in distinguishing between different substrate molecules), the selectivity relationship would predict that positional selectivity should also be very small. However, it is not. For example, under conditions where nitration of *p*-xylene and 1,2,4-trimethylbenzene takes place at about equal rates, there was no corresponding lack of selectivity at positions *within* the latter.⁸³ Though steric effects are about the same at both positions, more than 10 times as much 5-nitro product was formed as 6-nitro product.



It is clear that the selectivity relationship has broken down and it becomes necessary to explain why such an extremely rapid reaction should occur with positional selectivity. The explanation offered is that the rate-determining step is formation of an encounter complex (12, p. 506).⁸⁴ Since the position of attack is not determined in the rate-determining step, the 5/6 ratio is not related to the reaction rate. Essentially the same idea was suggested earlier⁸⁵ and for the same reason (failure of the selectivity relationship in some cases), but the earlier explanation specifically pictured the complex as a π complex, and we have seen (p. 506) that there is evidence against this.

One interesting proposal⁸⁶ is that the encounter pair is a radical pair $\overline{\text{NO}_2} \cdot \text{ArH}^\cdot$ formed by an electron transfer (SET), which would explain why the electrophile, once in the encounter complex, can acquire the selectivity that the free NO_2^+ lacked (it is not proposed that a radical pair is present in all aromatic substitutions; only in those that do not obey the selectivity relationship). The radical pair subsequently collapses to the arenium ion. There is evidence⁸⁷ both for and against this proposal.⁸⁸

The Effect of the Leaving Group

In the vast majority of aromatic electrophilic substitutions, the leaving group is H^+ (it is certainly one of the best), and very little work has been done on the relative electrofugal

⁸⁰See Coombes; Moodie; Schofield, Ref. 29; Moodie; Schofield; Thomas *J. Chem. Soc., Perkin Trans. 2* **1978**, 318.

⁸¹For a review of diffusion control in electrophilic aromatic substitution, see Ridd, Ref. 27.

⁸²Coombes; Moodie; Schofield, Ref. 26; Hoggett; Moodie; Schofield, Ref. 26; Hartshorn; Moodie; Schofield; Thompson *J. Chem. Soc. B* **1971**, 2447; Manglik; Moodie; Schofield; Dedeglu; Dutly; Rys *J. Chem. Soc., Perkin Trans 2* **1981**, 1358.

⁸³Barnett; Moodie; Schofield; Weston *J. Chem. Soc., Perkin Trans. 2* **1975**, 648; Barnett; Moodie; Schofield; Taylor; Weston *J. Chem. Soc., Perkin Trans. 2* **1979**, 747.

⁸⁴For kinetic evidence in favor of encounter complexes, see Sheats; Strachan *Can. J. Chem.* **1978**, 56, 1280. For evidence for such complexes in the gas phase, see Attinà; Cacace; de Petris *Angew. Chem. Int. Ed. Engl.* **1987**, 26, 1177 [*Angew. Chem.* 99, 1174].

⁸⁵Olah, Ref. 26.

⁸⁶Perrin *J. Am. Chem. Soc.* **1977**, 99, 5516.

⁸⁷For evidence in favor of the proposal, see Reents; Freiser *J. Am. Chem. Soc.* **1980**, 102, 271; Morkovnik; Dobaeva; Panov; Okhlobystin *Doklad. Chem.* **1980**, 251, 116; Sankararaman; Haney; Kochi *J. Am. Chem. Soc.* **1987**, 109, 5235; Keumi; Hamanaka; Hasegawa; Minamide; Inoue; Kitajima *Chem. Lett.* **1988**, 1285; Johnston; Ridd; Sandall *J. Chem. Soc., Chem. Commun.* **1989**, 244. For evidence against it, see Barnes; Myhre *J. Am. Chem. Soc.* **1978**, 100, 975; Ebersson; Radner *Acc. Chem. Res.* **1987**, 20, 53-59; Baciocchi; Mandolini *Tetrahedron* **1987**, 43, 4035.

⁸⁸For a review, see Morkovnik *Russ. Chem. Rev.* **1988**, 57, 144-160.

ability of other leaving groups. However, the following orders of leaving-group ability have been suggested:⁸⁹ (1) for leaving groups that depart without assistance (S_N1 process with respect to the leaving group), NO₂⁺⁹⁰ < iso-Pr⁺ ~ SO₃ < *t*-Bu⁺ ~ ArN₂⁺ < ArCHOH⁺ < NO⁺ < CO₂; (2) for leaving groups that depart with assistance from an outside nucleophile (S_N2 process), Me⁺ < Cl⁺ < Br⁺ < D⁺ ~ RCO⁺ < H⁺ ~ I⁺ < Me₃Si⁺. We can use this kind of list to help predict which group, X or Y, will cleave from an arenium ion **1** once it has been formed, and so obtain an idea of which electrophilic substitutions are feasible. However, a potential leaving group can also affect a reaction in another way: by influencing the rate at which the original electrophile attacks directly at the ipso position. Partial rate factors for electrophilic attack at a position substituted by a group other than hydrogen are called ipso partial rate factors (*i*_p^X).⁴⁸ Such factors for the nitration of *p*-haloanisoles are 0.18, 0.08, and 0.06, for *p*-iodo-, *p*-bromo-, and *p*-chloroanisole, respectively.⁹¹ This means, for example, that the electrophile in this case attacks the 4 position of 4-iodoanisole 0.18 times as fast as a single position of benzene. Note that this is far slower than it attacks the 4 position of anisole itself so that the presence of the iodo group greatly slows the reaction at that position. A similar experiment on *p*-cresol showed that ipso attack at the methyl position was 6.8 times slower than attack at the para position of phenol.⁹² Thus, in these cases, both an iodo and a methyl group deactivate the ipso position.⁹³

REACTIONS

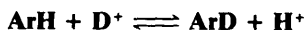
The reactions in this chapter are classified according to leaving group. Hydrogen replacements are treated first, then rearrangements in which the attacking entity is first cleaved from another part of the molecule (hydrogen is also the leaving group in these cases), and finally replacements of other leaving groups.

Hydrogen as the Leaving Group in Simple Substitution Reactions

A. Hydrogen as the Electrophile

1-1 Hydrogen Exchange

Deuterio-de-hydrogenation or Deuteriation



Aromatic compounds can exchange hydrogens when treated with acids. The reaction is used chiefly to study mechanistic questions⁹⁴ (including substituent effects), but can also be useful to deuterate or tritrate aromatic rings selectively. The usual directive effects apply and, for example, phenol treated with D₂O gives slow exchange on heating, with only ortho and para hydrogens being exchanged.⁹⁵ Strong acids, of course, exchange faster with aromatic substrates, and this exchange must be taken into account when studying the mechanism of any aromatic substitution catalyzed by acids. There is a great deal of evidence that exchange

⁸⁹Perrin *J. Org. Chem.* **1971**, 36, 420.

⁹⁰For examples where NO₂⁺ is a leaving group (in a migration), see Bullen; Ridd; Sabek *J. Chem. Soc., Perkin Trans. 2* **1990**, 1681, and other papers in this series.

⁹¹Ref. 48. See also Fischer; Zollinger *Helv. Chim. Acta* **1972**, 55, 2139.

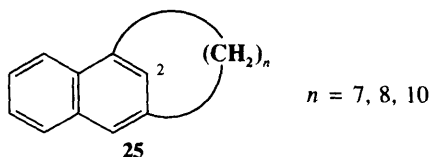
⁹²Tee; Iyengar; Bennett *J. Org. Chem.* **1986**, 51, 2585.

⁹³For other work on ipso reactivity, see Baciocchi; Illuminati *J. Am. Chem. Soc.* **1967**, 89, 4017; Berwin *J. Chem. Soc., Chem. Commun.* **1972**, 237; Galley; Hahn *J. Am. Chem. Soc.* **1974**, 96, 4337; Clemens; Hartshorn; Richards; Wright *Aust. J. Chem.* **1977**, 30, 103, 113.

⁹⁴For a review, see Taylor, in Bamford; Tipper, Ref. 1, pp. 194-277.

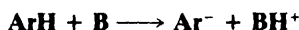
⁹⁵Small; Wolfenden *J. Chem. Soc.* **1936**, 1811.

takes place by the ordinary arenium ion mechanism. Among the evidence are the orientation effects noted above and the finding that the reaction is general-acid-catalyzed, which means that a proton is transferred in the slow step⁹⁶ (p. 259). Furthermore, many examples have been reported of stable solutions of arenium ions formed by attack of a proton on an aromatic ring.⁴ Simple aromatic compounds can be extensively deuterated in a convenient fashion by treatment with D₂O and BF₃.⁹⁷ It has been shown that tritium exchange takes place readily at the 2 position of **25**, despite the fact that this position is hindered by the bridge. The



rates were not very different from the comparison compound 1,3-dimethylnaphthalene.⁹⁸

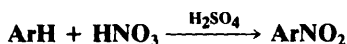
Hydrogen exchange can also be effected with strong bases,⁹⁹ such as NH₂⁻. In these cases the slow step is the proton transfer:



so the S_E1 mechanism and not the usual arenium ion mechanism is operating.¹⁰⁰ Aromatic rings can also be deuterated by treatment with D₂O and a rhodium(III) chloride¹⁰¹ or platinum¹⁰² catalyst or with C₆D₆ and an alkylaluminum dichloride catalyst,¹⁰³ though rearrangements may take place during the latter procedure. Tritium can be introduced by treatment with T₂O and an alkylaluminum dichloride catalyst.¹⁰³ Tritiation at specific sites (e.g. more than 90% para in toluene) has been achieved with T₂ gas and a microporous aluminophosphate catalyst.¹⁰⁴

B. Nitrogen Electrophiles

1-2 Nitration or Nitro-de-hydrogenation



Most aromatic compounds, whether of high or low reactivity, can be nitrated, because a wide variety of nitrating agents is available.¹⁰⁵ For benzene, the simple alkylbenzenes, and less reactive compounds, the most common reagent is a mixture of concentrated nitric and

⁹⁶For example, see Challis; Long *J. Am. Chem. Soc.* **1963**, 85, 2524; Batts; Gold *J. Chem. Soc.* **1964**, 4284; Kresge; Chiang; Sato *J. Am. Chem. Soc.* **1967**, 89, 4418; Gruen; Long *J. Am. Chem. Soc.* **1967**, 89, 1287; Butler; Hendry *J. Chem. Soc. B* **1970**, 852.

⁹⁷Larsen; Chang *J. Org. Chem.* **1978**, 43, 3602.

⁹⁸Laws; Neary; Taylor *J. Chem. Soc., Perkin Trans. 2* **1987**, 1033.

⁹⁹For a review of base-catalyzed hydrogen exchange on heterocycles, see Elvidge; Jones; O'Brien; Evans; Sheppard *Adv. Heterocycl. Chem.* **1974**, 16, 1-31.

¹⁰⁰Shatenshtein *Tetrahedron* **1962**, 18, 95.

¹⁰¹Lockley *Tetrahedron Lett.* **1982**, 23, 3819; *J. Chem. Res. (S)* **1985**, 178.

¹⁰²See, for example, Leitch *Can. J. Chem.* **1954**, 32, 813; Fraser; Renaud *J. Am. Chem. Soc.* **1966**, 88, 4365; Fischer; Puza *Synthesis* **1973**, 218; Blake; Garnett; Gregor; Hannan; Hoa; Long *J. Chem. Soc., Chem. Commun.* **1975**, 930. See also Parshall *Acc. Chem. Res.* **1975**, 8, 113-117.

¹⁰³Garnett; Long; Vining; Mole *J. Am. Chem. Soc.* **1972**, 94, 5913, 8632; Long; Garnett; West *Tetrahedron Lett.* **1978**, 4171.

¹⁰⁴Garnett; Kennedy; Long; Than; Watson *J. Chem. Soc., Chem. Commun.* **1988**, 763.

¹⁰⁵For monographs, see Olah; Malhotra; Narang *Nitration: Methods and Mechanisms*; VCH: New York, 1989; Schofield *Aromatic Nitration*; Cambridge University Press: Cambridge, 1980; Hoggett; Moodie; Penton; Schofield, Ref. 30. For reviews, see Weaver, in *Feuer Chemistry of the Nitro and Nitroso Groups*, pt. 2; Wiley: New York, 1970, pp. 1-48; de la Mare; Ridd, Ref. 59, pp. 48-93. See also Ref. 1. For a review of side reactions, see Suzuki *Synthesis* **1977**, 217-238.

sulfuric acids, but for active substrates, the reaction can be carried out with nitric acid alone, or in water, acetic acid, or acetic anhydride. In fact, these milder conditions are necessary for active compounds such as amines, phenols, and pyrroles, since reaction with mixed nitric and sulfuric acids would oxidize these substrates. If anhydrous conditions are required, nitration can be effected with N_2O_5 ¹⁰⁶ in CCl_4 in the presence of P_2O_5 , which removes the water formed in the reaction.¹⁰⁷ Nitration in alkaline media can be accomplished with esters of nitric acid such as ethyl nitrate (EtONO_2). These reagents can also be used with proton or Lewis-acid catalysts. Other nitrating agents are NaNO_2 and trifluoroacetic acid,¹⁰⁸ N_2O_4 (which gives good yields with polycyclic hydrocarbons¹⁰⁹), and nitronium salts¹¹⁰ such as $\text{NO}_2^+ \text{BF}_4^-$, $\text{NO}_2^+ \text{PF}_6^-$, and $\text{NO}_2^+ \text{CF}_3\text{SO}_3^-$. The last-mentioned salt gives a very high yield of products at low temperatures.¹¹¹ Aromatic hydrocarbons and halobenzenes are nitrated in high yields with clay-supported cupric nitrate (claycop),¹¹² with predominant para regioselectivity.¹¹³ With active substrates such as amines and phenols, nitration can be accomplished by nitrosation under oxidizing conditions with a mixture of dilute nitrous and nitric acids.¹¹⁴ Active substrates can also be nitrated, conveniently and under mild conditions, with nitrocyclohexadienones such as 2,3,5,6-tetrabromo-4-methyl-4-nitro-1,4-cyclohexadienone.¹¹⁵

When amines are nitrated under strong-acid conditions, meta orientation is generally observed, because the species undergoing nitration is actually the conjugate acid of the amine. If the conditions are less acidic, the free amine is nitrated and the orientation is ortho-para. Although the free base may be present in much smaller amounts than the conjugate acid, it is far more susceptible to aromatic substitution (see also p. 510). Because of these factors and because they are vulnerable to oxidation by nitric acid, primary aromatic amines are often protected before nitration by treatment with acetyl chloride (**0-52**) or acetic anhydride (**0-53**). Nitration of the resulting acetanilide derivative avoids all these problems. There is evidence that when the reaction takes place on the free amine, it is the nitrogen that is attacked to give an N-nitro compound $\text{Ar}-\text{NH}-\text{NO}_2$ which rapidly undergoes rearrangement (see **1-32**) to give the product.¹¹⁶

Since the nitro group is deactivating, it is usually easy to stop the reaction after one group has entered the ring, but a second and a third group can be introduced if desired, especially when an activating group is also present. Even *m*-dinitrobenzene can be nitrated if vigorous conditions are applied. This has been accomplished with $\text{NO}_2^+ \text{BF}_4^-$ in FSO_3H at 150°C .¹¹⁷

¹⁰⁶For a review of N_2O_5 see Fischer, in Feuer; Nielsen *Nitro Compounds, Recent Advances in Synthesis and Chemistry*; VCH: New York, 1990, pp. 267-365.

¹⁰⁷For another method, see Olah; Krishnamurthy; Narang *J. Org. Chem.* **1982**, 47, 596.

¹⁰⁸Uemura; Toshimitsu; Okano *J. Chem. Soc., Perkin Trans. 1* **1978**, 1076.

¹⁰⁹Radner *Acta Chem. Scand., Ser. B* **1983**, 37, 65.

¹¹⁰Olah; Kuhn *J. Am. Chem. Soc.* **1962**, 84, 3684. These have also been used together with crown ethers: Masci *J. Chem. Soc., Chem. Commun.* **1982**, 1262; *J. Org. Chem.* **1985**, 50, 4081. For a review of nitronium salts in organic chemistry, see Guk; Ilyushin; Golod; Gidasov *Russ. Chem. Rev.* **1983**, 52, 284-297.

¹¹¹Coon; Blucher; Hill *J. Org. Chem.* **1973**, 38, 4243; Effenberger; Geke *Synthesis* **1975**, 40.

¹¹²For reviews of clay-supported nitrates, see Cornélis; Laszlo *Synthesis* **1985**, 909-918; Laszlo *Acc. Chem. Res.* **1986**, 121-127; Laszlo; Cornélis *Aldrichimica Acta* **1988**, 21, 97-103.

¹¹³Laszlo; Pennetreau *J. Org. Chem.* **1987**, 52, 2407; Cornélis; Delaude; Gerstmans; Laszlo *Tetrahedron Lett.* **1988**, 29, 5657; Cornélis; Gerstmans; Laszlo *Chem. Lett.* **1988**, 1839; Laszlo; Vandormael *Chem. Lett.* **1988**, 1843. See also Smith; Fry; Butters; Nay *Tetrahedron Lett.* **1989**, 30, 5333. For similar nitrations of phenols, see Cornélis; Laszlo; Pennetreau *Bull. Soc. Chim. Belg.* **1984**, 93, 961; Poirier; Vottero *Tetrahedron* **1989**, 45, 1415. For a method of nitrating phenols in the ortho position, see Pervez; Onyiriuka; Rees; Rooney; Suckling *Tetrahedron* **1988**, 44, 4555.

¹¹⁴For discussions of the mechanism in this case, see Giffney; Ridd *J. Chem. Soc., Perkin Trans. 2* **1979**, 618; Bazanova; Stotskii *J. Org. Chem. USSR* **1980**, 16, 2070, 2075; Ross; Moran; Malhotra *J. Org. Chem.* **1983**, 48, 2118; Dix; Moodie *J. Chem. Soc., Perkin Trans. 2* **1986**, 1097; Leis; Peña; Ridd *Can. J. Chem.* **1989**, 67, 1677. For a review, see Ridd, Ref. 122a.

¹¹⁵Lemaire; Guy; Roussel; Guette *Tetrahedron* **1987**, 43, 835.

¹¹⁶Ridd; Scriven *J. Chem. Soc., Chem. Commun.* **1972**, 641. See also Helsby; Ridd *J. Chem. Soc., Perkin Trans. 2* **1983**, 1191.

¹¹⁷Olah; Lin *Synthesis* **1974**, 444.

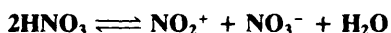
With most of the reagents mentioned, the attacking species is the nitronium ion NO_2^+ . Among the ways in which this ion is formed are:

1. In concentrated sulfuric acid, by an acid-base reaction in which nitric acid is the base:



This ionization is essentially complete.

2. In concentrated nitric acid alone,¹¹⁸ by a similar acid-base reaction in which one molecule of nitric acid is the acid and another the base:



This equilibrium lies to the left (about 4% ionization), but enough NO_2^+ is formed for nitration to occur.

3. The equilibrium just mentioned occurs to a small extent even in organic solvents.
4. With N_2O_5 in CCl_4 , there is spontaneous dissociation:



but in this case there is evidence that some nitration also takes place with undissociated N_2O_5 as the electrophile.

5. When nitronium salts are used, NO_2^+ is of course present to begin with. Esters and acyl halides of nitric acid ionize to form NO_2^+ . Nitrocyclohexadienones are converted to NO_2^+ and the corresponding phenol.¹¹⁵

There is a great deal of evidence that NO_2^+ is present in most nitrations and that it is the attacking entity,¹¹⁹ e.g.,

1. Nitric acid has a peak in the Raman spectrum. When nitric acid is dissolved in concentrated sulfuric acid, the peak disappears and two new peaks appear, one at 1400 cm^{-1} attributable to NO_2^+ and one at 1050 cm^{-1} due to HSO_4^- .¹²⁰

2. On addition of nitric acid, the freezing point of sulfuric acid is lowered about four times the amount expected if no ionization has taken place.¹²¹ This means that the addition of one molecule of nitric acid results in the production of four particles, which is strong evidence for the ionization reaction between nitric and sulfuric acids given above.

3. The fact that nitronium salts in which nitronium ion is known to be present (by x-ray studies) nitrate aromatic compounds shows that this ion does attack the ring.

4. The rate of the reaction with most reagents is proportional to the concentration of NO_2^+ , not to that of other species.¹²² When the reagent produces this ion in small amounts, the attack is slow and only active substrates can be nitrated. In concentrated and aqueous mineral acids the kinetics are second order: first order each in aromatic substrate and in nitric acid (unless pure nitric acid is used in which case there are pseudo-first-order kinetics). But in organic solvents such as nitromethane, acetic acid, and CCl_4 , the kinetics are first order in nitric acid alone and zero order in aromatic substrate, because the rate-determining step is formation of NO_2^+ and the substrate does not take part in this.

In a few cases, depending on the substrate and solvent, there is evidence that the arenium ion is not formed directly, but via the intermediacy of a radical pair (see p. 520):^{122a}

¹¹⁸See Belson; Strachan *J. Chem. Soc., Perkin Trans. 2* **1989**, 15.

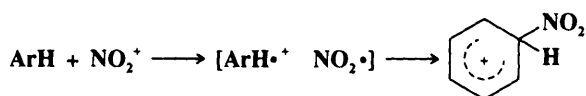
¹¹⁹For an exhaustive study of this reaction, see Hughes; Ingold; and co-workers *J. Chem. Soc.* **1950**, 2400-2684.

¹²⁰Ingold; Millen; Poole *J. Chem. Soc.* **1950**, 2576.

¹²¹Gillespie; Graham; Hughes; Ingold; Peeling *J. Chem. Soc.* **1950**, 2504.

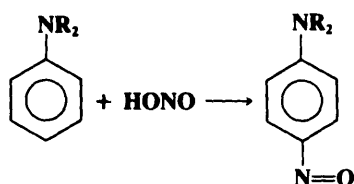
¹²²This is not always strictly true. See Ross; Kuhlmann; Malhotra *J. Am. Chem. Soc.* **1983**, 105, 4299.

^{122a}For a review of radical processes in aromatic nitration, see Ridd *Chem. Soc. Rev.* **1991**, 20, 149-165. For a review of aromatic substitutions involving radical cations, see Kochi *Adv. Free Radical Chem. (Greenwich, Conn.)* **1990**, 1, 53-119.



OS I, 372, 396, 408 (see also OS 53, 129); II, 254, 434, 438, 447, 449, 459, 466; III, 337, 644, 653, 658, 661, 837; IV, 42, 364, 654, 711, 722, 735; V, 346, 480, 829, 1029, 1067.

1-3 Nitrosation or Nitroso-de-hydrogenation



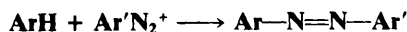
Ring nitrosation¹²³ with nitrous acid is normally carried out only with active substrates such as amines and phenols. However, primary aromatic amines give diazonium ions (2-49) when treated with nitrous acid,¹²⁴ and secondary amines tend to give N-nitroso rather than C-nitroso compounds (2-51); hence this reaction is normally limited to phenols and tertiary aromatic amines. Nevertheless secondary aromatic amines can be C-nitrosated in two ways. The N-nitroso compound first obtained can be isomerized to a C-nitroso compound (1-33), or it can be treated with another mole of nitrous acid to give an N,C-dinitroso compound. Also, a successful nitrosation of anisole has been reported, where the solvent was $\text{CF}_3\text{COOH}-\text{CH}_2\text{Cl}_2$.¹²⁵

Much less work has been done on the mechanism of this reaction than on the preceding one.¹²⁶ In some cases the attacking entity is NO^+ , but in others it is apparently NOCl , NOBr , N_2O_3 , etc., in each of which there is a carrier of NO^+ . NOCl and NOBr are formed during the normal process of making nitrous acid—the treatment of sodium nitrite with HCl or HBr . Nitrosation requires active substrates because NO^+ is much less reactive than NO_2^+ . Kinetic studies have shown that NO^+ is at least 10^{14} times less reactive than NO_2^+ .¹²⁷ A consequence of the relatively high stability of NO^+ is that this species is easily cleaved from the arenium ion, so that k_{-1} competes with k_2 (p. 503) and isotope effects are found.¹²⁸ With phenols, there is evidence that nitrosation may first take place at the OH group, after which the nitrite ester thus formed rearranges to the C-nitroso product.¹²⁹ Tertiary aromatic amines substituted in the ortho position generally do not react with HONO , probably because the ortho substituent prevents planarity of the dialkylamino group, without which the ring is no longer activated. This is an example of steric inhibition of resonance (p. 36).

OS I, 214, 411, 511; II, 223; IV, 247.

1-4 Diazonium Coupling

Arylazo-de-hydrogenation



¹²³For a review, see Williams *Nitrosation*; Cambridge University Press: Cambridge, 1988, pp. 58-76.

¹²⁴For examples of formation of C-nitroso compounds from primary and secondary amines, see Hoefnagel; Wepster *Recl. Trav. Chim. Pays-Bas* **1989**, 108, 97.

¹²⁵Radner; Wall; Loncar *Acta Chem. Scand.* **1990**, 44, 152.

¹²⁶For a review of nitrosation mechanisms at C and other atoms, see Williams *Adv. Phys. Org. Chem.* **1983**, 19, 381-428. See also Ref. 123.

¹²⁷Challis; Higgins; Lawson *J. Chem. Soc., Perkin Trans. 2*, **1972**, 1831; Challis; Higgins *J. Chem. Soc., Perkin Trans. 2* **1972**, 2365.

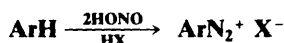
¹²⁸Challis; Lawson *J. Chem. Soc. B* **1971**, 770; Challis; Higgins *J. Chem. Soc., Perkin Trans. 2* **1973**, 1597.

¹²⁹Gosney; Page *J. Chem. Soc., Perkin Trans. 2* **1980**, 1783.

Aromatic diazonium ions normally couple only with active substrates such as amines and phenols.¹³⁰ Many of the products of this reaction are used as dyes (*azo dyes*).¹³¹ Presumably because of the size of the attacking species, substitution is mostly para to the activating group, unless that position is already occupied, in which case ortho substitution takes place. The pH of the solution is important both for phenols and amines. For amines, the solutions may be mildly acidic or neutral. The fact that amines give ortho and para products shows that even in mildly acidic solution they react in their un-ionized form. If the acidity is too high, the reaction does not occur, because the concentration of free amine becomes too small. Phenols must be coupled in slightly alkaline solution where they are converted to the more reactive phenoxide ions, because phenols themselves are not active enough for the reaction. However, neither phenols nor amines react in moderately alkaline solution, because the diazonium ion is converted to a diazo hydroxide $\text{Ar}-\text{N}=\text{N}-\text{OH}$. Primary and secondary amines face competition from attack at the nitrogen.¹³² However, the resulting N-azo compounds (aryl triazenes) can be isomerized to C-azo compounds (**1-34**). In at least some cases, even when the C-azo compound is isolated, it is the result of initial N-azo compound formation followed by isomerization. It is therefore possible to synthesize the C-azo compound directly in one laboratory step.¹³³ Acylated amines and phenolic ethers and esters are ordinarily not active enough for this reaction, though it is sometimes possible to couple them (as well as such polyalkylated benzenes as mesitylene and pentamethylbenzene) to diazonium ions containing electron-withdrawing groups in the para position, since such groups increase the concentration of the positive charge and thus the electrophilicity of the ArN_2^+ . Some coupling reactions which are otherwise very slow (in cases where the coupling site is crowded) are catalyzed by pyridine for reasons discussed on p. 504. Phase transfer catalysis has also been used.¹³⁴ Coupling of a few aliphatic diazonium compounds to aromatic rings has been reported. All the examples reported so far involve cyclopropanediazonium ions and bridgehead diazonium ions, in which loss of N_2 would lead to very unstable carbocations.¹³⁵

OS I, 49, 374; II, 35, 39, 145.

1-5 Direct Introduction of the Diazonium Group Diazonation or Diazo-de-hydrogenation



Diazonium salts can be prepared directly by replacement of an aromatic hydrogen without the necessity of going through the amino group.¹³⁶ The reaction is essentially limited to active substrates (amines and phenols), since otherwise poor yields are obtained. Since the reagents and the substrate are the same as in reaction **1-3**, the first species formed is the nitroso compound. In the presence of excess nitrous acid, this is converted to the diazonium ion.¹³⁷ The reagent (azidochloromethylene)dimethylammonium chloride $\text{Me}_2\text{N}^+=\text{C}(\text{Cl})\text{N}_3$ Cl^- can also introduce the diazonium group directly into a phenol.¹³⁸

¹³⁰For reviews, see Szele; Zollinger *Top. Curr. Chem.* **1983**, *112*, 1-66; Hegarty, in Patai *The Chemistry of Diazonium and Diazo Groups*, pt. 2; Wiley: New York, 1978, pp. 545-551.

¹³¹For reviews of azo dyes, see Zollinger *Color Chemistry*; VCH: New York, 1987, pp. 85-148; Gordon; Gregory *Organic Chemistry in Colour*; Springer: New York, 1983, pp. 95-162.

¹³²See Penton; Zollinger *Helv. Chim. Acta* **1981**, *64*, 1717, 1728.

¹³³Kelly; Penton; Zollinger *Helv. Chim. Acta* **1982**, *65*, 122.

¹³⁴Hashida; Kubota; Sekiguchi *Bull. Chem. Soc. Jpn.* **1988**, *61*, 905.

¹³⁵See Szele; Zollinger, Ref. 130, pp. 3-6.

¹³⁶Tedder *J. Chem. Soc.* **1957**, 4003.

¹³⁷Tedder; Theaker *Tetrahedron* **1959**, *5*, 288; Kamalova; Nazarova; Solodova; Yaskova *J. Org. Chem. USSR* **1988**, *24*, 1004.

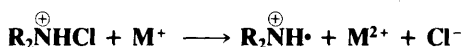
¹³⁸Kokel; Viehe *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 716 [*Angew. Chem.* **92**, 754].

1-6 Amination or Amino-de-hydrogenation¹³⁹



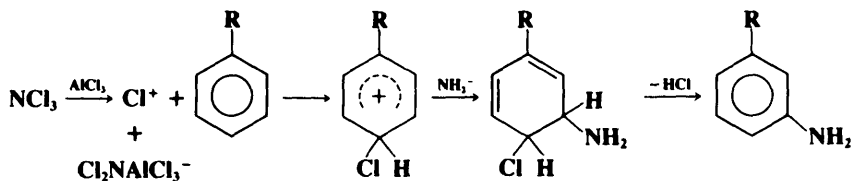
Aromatic compounds can be converted to primary aromatic amines, in 10 to 65% yields, by treatment with hydrazoic acid HN_3 in the presence of AlCl_3 or H_2SO_4 .¹⁴⁰ Higher yields (> 90%) have been reported with trimethylsilyl azide Me_3SiN_3 and triflic acid $\text{F}_3\text{CSO}_2\text{OH}$.¹⁴¹ Tertiary amines have been prepared in fairly good yields (about 50 to 90%) by treatment of aromatic hydrocarbons with N-chlorodialkylamines, by heating in 96% sulfuric acid; or with AlCl_3 or FeCl_3 in nitroalkane solvents; or by irradiation.¹⁴²

Tertiary (and to a lesser extent, secondary) aromatic amines can also be prepared in moderate to high yields by amination with an N-chlorodialkylamine (or an N-chloroalkylamine) and a metallic-ion catalyst (e.g., Fe^{2+} , Ti^{3+} , Cu^+ , Cr^{2+}) in the presence of sulfuric acid.¹⁴³ The attacking species in this case is the aminium radical ion $\text{R}_2\text{NH}^{\oplus}\cdot$ formed by¹⁴⁴



Because attack is by a positive species (even though it is a free radical), orientation is similar to that in other electrophilic substitutions (e.g., phenol and acetanilide give ortho and para substitution, mostly para). When an alkyl group is present, attack at the benzylic position competes with ring substitution. Aromatic rings containing only meta-directing groups do not give the reaction at all. Fused ring systems react well.¹⁴⁵

Unusual orientation has been reported for amination with halamines and with NCl_3 in the presence of AlCl_3 . For example, toluene gave predominately meta amination.¹⁴⁶ It has been suggested that initial attack in this case is by Cl^+ and that a nitrogen nucleophile (whose structure is not known but is represented here as NH_2^- for simplicity) adds to the resulting arenium ion, so that the initial reaction is addition to a carbon-carbon double bond followed by elimination of HCl :¹⁴⁷



According to this suggestion, the electrophilic attack is at the para position (or the ortho, which leads to the same product) and the meta orientation of the amino group arises indirectly. This mechanism is called the σ -substitution mechanism.

Aromatic compounds that do not contain meta-directing groups can be converted to diarylamines by treatment with aryl azides in the presence of phenol at -60°C : $\text{ArH} +$

¹³⁹For a review, see Kovacic, in Olah, Ref. 58, vol. 3, 1964, pp. 1493-1506.

¹⁴⁰Kovacic; Russell; Bennett *J. Am. Chem. Soc.* **1964**, 86, 1588.

¹⁴¹Olah; Ernst *J. Org. Chem.* **1989**, 54, 1203.

¹⁴²Bock; Kompa *Angew. Chem. Int. Ed. Engl.* **1965**, 4, 783 [*Angew. Chem.* 77, 807]. *Chem. Ber.* **1966**, 99, 1347, 1357, 1361.

¹⁴³For reviews, see Minisci *Top. Curr. Chem.* **1976**, 62, 1-48, pp. 6-16, *Synthesis* **1973**, 1-24, pp. 2-12, Sosnovsky; Rawlinson *Adv. Free-Radical Chem.* **1972**, 4, 203-284, pp. 213-238.

¹⁴⁴For a review of aminium radical ions, see Chow *React. Intermed. (Plenum)* **1980**, 1, 151-262.

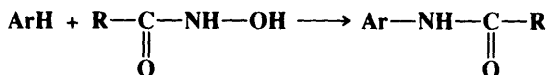
¹⁴⁵The reaction has been extended to the formation of primary aromatic amines, but the scope is narrow: Citterio; Gentile; Minisci; Navarrini; Serravalle; Ventura *J. Org. Chem.* **1984**, 49, 4479.

¹⁴⁶See Kovacic; Lange; Foot; Goralski; Hiller; Levisky *J. Am. Chem. Soc.* **1964**, 86, 1650; Strand; Kovacic *J. Am. Chem. Soc.* **1973**, 95, 2977.

¹⁴⁷Kovacic; Levisky *J. Am. Chem. Soc.* **1966**, 88, 1000.

$\text{Ar}'\text{N}_3 \rightarrow \text{Ar}'\text{NHAr}'$.¹⁴⁸ Diarylamines are also obtained by the reaction of N-arylhydroxylamines with aromatic compounds (benzene, toluene, anisole) in the presence of F_3CCOOH : $\text{ArH} + \text{Ar}'\text{NHOH} \rightarrow \text{Ar}'\text{NHAr}'$.¹⁴⁹

Direct amidation can be carried out if an aromatic compound is heated with a hydroxamic acid in polyphosphoric acid, though the scope is essentially limited to phenolic ethers.¹⁵⁰



Also see 3-18 and 3-19.

C. Sulfur Electrophiles

1-7 Sulfonation or Sulfo-de-hydrogenation



The sulfonation reaction is very broad in scope and many aromatic hydrocarbons (including fused ring systems), aryl halides, ethers, carboxylic acids, amines,¹⁵¹ acylated amines, ketones, nitro compounds, and sulfonic acids have been sulfonated.¹⁵² Phenols can also be successfully sulfonated, but attack at oxygen may compete.¹⁵³ Sulfonation is often accomplished with concentrated sulfuric acid, but it can also be done with fuming sulfuric acid, SO_3 , ClSO_2OH , or other reagents. As with nitration (1-2), reagents of a wide variety of activity are available to suit both highly active and highly inactive substrates. Since this is a reversible reaction (see 1-41), it may be necessary to drive the reaction to completion. However, at low temperatures the reverse reaction is very slow and the forward reaction is practically irreversible.¹⁵⁴ SO_3 reacts much more rapidly than sulfuric acid—with benzene it is nearly instantaneous. Sulfones are often side products. When sulfonation is carried out on a benzene ring containing four or five alkyl and/or halogen groups, rearrangements usually occur (see 1-40).

A great deal of work has been done on the mechanism,¹⁵⁵ chiefly by Cerfontain and co-workers. Mechanistic study is made difficult by the complicated nature of the solutions. Indications are that the electrophile varies with the reagent, though SO_3 is involved in all cases, either free or combined with a carrier. In aqueous H_2SO_4 solutions the electrophile is thought to be H_3SO_4^+ (or a combination of H_2SO_4 and H_3O^+) at concentrations below about 80 to 85% H_2SO_4 , and $\text{H}_2\text{S}_2\text{O}_7$ (or a combination of H_2SO_4 and SO_3) at concentrations higher than this¹⁵⁶ (the changeover point varies with the substrate¹⁵⁷). Evidence for a change

¹⁴⁸Nakamura; Ohno; Oka *Synthesis* **1974**, 882. See also Takeuchi; Takano *J. Chem. Soc., Perkin Trans. 1* **1986**, 611.

¹⁴⁹Shudo; Ohta; Okamoto *J. Am. Chem. Soc.* **1981**, 103, 645.

¹⁵⁰Wassmundt; Padegimas *J. Am. Chem. Soc.* **1967**, 89, 7131; March; Engenito *J. Org. Chem.* **1981**, 46, 4304.

¹⁵¹See Khelevin *J. Org. Chem. USSR* **1984**, 20, 339, 1173, 1723, **1987**, 23, 1709, **1988**, 24, 535.

¹⁵²For reviews, see Nelson, in Olah, Ref. 58, vol. 3, 1964, pp. 1355-1392; Gilbert, *Sulfonation and Related Reactions*; Wiley: New York, 1965, pp. 62-83, 87-124.

¹⁵³See, for example de Wit; Woldhuis; Cerfontain *Recl. Trav. Chim. Pays-Bas* **1988**, 107, 668.

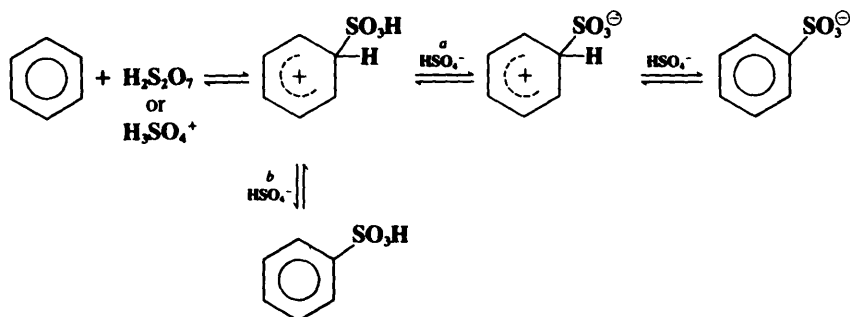
¹⁵⁴Spryskov *J. Gen. Chem. USSR* **1960**, 30, 2433.

¹⁵⁵For a monograph, see Cerfontain *Mechanistic Aspects in Aromatic Sulfonation and Desulfonation*; Wiley: New York, 1968. For reviews, see Cerfontain *Recl. Trav. Chim. Pays-Bas* **1985**, 104, 153-165; Cerfontain; Kort *Int. J. Sulfur Chem. C* **1971**, 6, 123-136; Taylor, in Bamford; Tipper, Ref. 1, pp. 56-77.

¹⁵⁶Kort; Cerfontain *Recl. Trav. Chim. Pays-Bas* **1968**, 87, 24, **1969**, 88, 860; Maarsen; Cerfontain *J. Chem. Soc., Perkin Trans. 2* **1977**, 1003; Cerfontain; Lambrechts; Schaasberg-Nienhuis; Coombes; Hadjigeorgiou; Tucker *J. Chem. Soc., Perkin Trans. 2* **1985**, 659.

¹⁵⁷See, for example, Kaandorp; Cerfontain *Recl. Trav. Chim. Pays-Bas* **1969**, 88, 725.

in electrophile is that in the dilute and in the concentrated solutions the rate of the reaction was proportional to the activity of H_3SO_4^+ and $\text{H}_2\text{S}_2\text{O}_7$, respectively. Further evidence is that with toluene as substrate the two types of solution gave very different ortho/para ratios. The mechanism is essentially the same for both electrophiles and may be shown as:¹⁵⁶



The other product of the first step is HSO_4^- or H_2O from $\text{H}_2\text{S}_2\text{O}_7$ or H_3SO_4^+ , respectively. Path *a* is the principal route, except at very high H_2SO_4 concentrations, when path *b* becomes important. With H_3SO_4^+ the first step is rate-determining under all conditions, but with $\text{H}_2\text{S}_2\text{O}_7$ the first step is the slow step only up to about 96% H_2SO_4 , when a subsequent proton transfer becomes partially rate-determining.¹⁵⁸ $\text{H}_2\text{S}_2\text{O}_7$ is more reactive than H_3SO_4^+ . In fuming sulfuric acid (H_2SO_4 containing excess SO_3), the electrophile is thought to be $\text{H}_3\text{S}_2\text{O}_7^+$ (protonated $\text{H}_2\text{S}_2\text{O}_7$) up to about 104% H_2SO_4 and $\text{H}_2\text{S}_4\text{O}_{13}$ ($\text{H}_2\text{SO}_4 + 3\text{SO}_3$) beyond this concentration.¹⁵⁹ Finally, when pure SO_3 is the reagent in aprotic solvents, SO_3 itself is the actual electrophile.¹⁶⁰ Free SO_3 is the most reactive of all these species, so that attack here is generally fast and a subsequent step is usually rate-determining, at least in some solvents.

OS II, 42, 97, 482, 539; III, 288, 824; IV, 364; VI, 976.

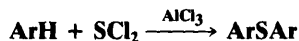
1-8 Halosulfonation or Halosulfo-de-hydrogenation



Aromatic sulfonyl chlorides can be prepared directly, by treatment of aromatic rings with chlorosulfuric acid.¹⁶¹ Since sulfonic acids can also be prepared by the same reagent (1-7), it is likely that they are intermediates, being converted to the halides by excess chlorosulfuric acid.¹⁶² The reaction has also been effected with bromo- and fluorosulfuric acids.

OS I, 8, 85.

1-9 Sulfurization



¹⁵⁸Kort; Cerfontain *Recl. Trav. Chim. Pays-Bas* **1967**, 86, 865.

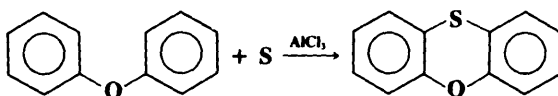
¹⁵⁹Kort; Cerfontain *Recl. Trav. Chim. Pays-Bas* **1969**, 88, 1298; Koeberg-Telder; Cerfontain *J. Chem. Soc., Perkin Trans. 2* **1973**, 633.

¹⁶⁰Koeberg-Telder; Cerfontain *Recl. Trav. Chim. Pays-Bas* **1971**, 90, 193, **1972**, 91, 22; Lammertsma; Cerfontain *J. Chem. Soc., Perkin Trans. 2* **1980**, 28.

¹⁶¹For a review, see Gilbert, *Ref. 152*, pp. 84-87.

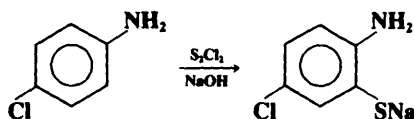
¹⁶²For a discussion of the mechanism with this reagent, see van Albada; Cerfontain *J. Chem. Soc., Perkin Trans. 2* **1977**, 1548, 1557.

Diaryl sulfides can be prepared by treating aromatic compounds with SCl_2 and a Friedel-Crafts catalyst. Other reagents that can bring about the same result are S_2Cl_2 , thionyl chloride, and even sulfur itself. A catalyst is not always necessary. The reaction has been used for ring closure:



When thionyl chloride is used, diaryl sulfoxides are usually the main products.¹⁶³ Unsymmetrical diaryl sulfides can be obtained by treatment of an aromatic compound with an aryl sulfonyl chloride (ArSO_2Cl) in the presence of a trace amount of iron powder.¹⁶⁴ Aromatic amines and phenols can be alkylthiolated (giving mostly ortho product) by treatment with an alkyl disulfide and a Lewis acid catalyst.¹⁶⁵

With certain substrates (primary amines with a chloro group, or a group not replaceable by chloro, in the para position), treatment with S_2Cl_2 and NaOH gives thiophenolate salts:



This is called the *Herz reaction*.¹⁶⁶

OS II, 242, 485. Also see OS I, 574; III, 76.

1-10 Sulfonylation

Alkylsulfonylation or Alkylsulfo-de-hydrogenation



Diaryl sulfones can be formed by treatment of aromatic compounds with aryl sulfonyl chlorides and a Friedel-Crafts catalyst.¹⁶⁷ This reaction is analogous to Friedel-Crafts acylation with carboxylic acid halides (1-14). In a better procedure, the aromatic compound is treated with an aryl sulfonic acid and P_2O_5 in polyphosphoric acid.¹⁶⁸ Still another method uses an arylsulfonic trifluoromethanesulfonic anhydride $\text{ArSO}_2\text{OSO}_2\text{CF}_3$ (generated in situ from ArSO_2Br and $\text{CF}_3\text{SO}_3\text{Ag}$) without a catalyst.¹⁶⁹

The reaction can be extended to the preparation of alkyl aryl sulfones by the use of a sulfonyl fluoride.¹⁷⁰

¹⁶³Nikolenko; Krizhechkovskaya *J. Gen. Chem. USSR* **1963**, 33, 3664; Oae; Zalut *J. Am. Chem. Soc.* **1960**, 82, 5359.

¹⁶⁴Fujisawa; Kabori; Ohtsuka; Tsuchihashi *Tetrahedron Lett.* **1968**, 5071.

¹⁶⁵Ranken; McKinnie *Synthesis* **1984**, 117, *J. Org. Chem.* **1989**, 54, 2985.

¹⁶⁶For a review, see Warburton *Chem. Rev.* **1957**, 57, 1011-1020.

¹⁶⁷For reviews, see Taylor, in Bamford; Tipper, Ref. 1, pp. 77-83; Jensen; Goldman, in Olah, Ref. 58, vol. 3, 1964, pp. 1319-1347.

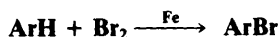
¹⁶⁸Graybill *J. Org. Chem.* **1967**, 32, 2931; Sipe; Clary; White *Synthesis* **1984**, 283. See also Ueda; Uchiyama; Kano *Synthesis* **1984**, 323.

¹⁶⁹Effenberger; Huthmacher *Chem. Ber.* **1976**, 109, 2315. For similar methods, see Hancock; Tyobeka; Weigel *J. Chem. Res., (S)* **1980**, 270; Ono; Nakamura; Sato; Itoh *Chem. Lett.* **1988**, 395.

¹⁷⁰Hyatt; White *Synthesis* **1984**, 214.

D. Halogen Electrophiles

1-11 Halogenation¹⁷¹ or Halo-de-hydrogenation



1. Chlorine and bromine. Aromatic compounds can be brominated or chlorinated by treatment with bromine or chlorine in the presence of a catalyst, most often iron. However, the real catalyst is not the iron itself, but the ferric bromide or ferric chloride formed in small amounts from the reaction between iron and the reagent. Ferric chloride and other Lewis acids are often directly used as catalysts, as is iodine. When thallium(III) acetate is the catalyst, many substrates are brominated with high regioselectivity para to an ortho-para-directing group.¹⁷² For active substrates, including amines, phenols, naphthalene, and polyalkylbenzenes¹⁷³ such as mesitylene and isodurene, no catalyst is needed. Indeed, for amines and phenols the reaction is so rapid that it is carried out with a dilute solution of Br₂ or Cl₂ in water at room temperature. Even so, with amines it is not possible to stop the reaction before all the available ortho and para positions are substituted, because the initially formed haloamines are weaker bases than the original amines and are less likely to be protonated by the liberated HX.¹⁷⁴ For this reason, primary amines are often converted to the corresponding anilides if monosubstitution is desired. With phenols it is possible to stop after one group has entered.¹⁷⁵ The rapid room-temperature reaction with amines and phenols is often used as a test for these compounds. Chlorine is a more active reagent than bromine. Phenols can be brominated exclusively in the ortho position (disubstitution of phenol gives 2,6-dibromophenol) by treatment about -70°C with Br₂ in the presence of *t*-butylamine or triethylenediamine, which precipitates out the liberated HBr.¹⁷⁶ Predominant ortho chlorination¹⁷⁷ of phenols has been achieved with chlorinated cyclohexadienes,¹⁷⁸ while para chlorination of phenols, phenolic ethers, and amines can be accomplished with *N*-chloroamines¹⁷⁹ and with *N*-chlorodimethylsulfonium chloride Me₂S⁺Cl⁻ Cl⁻.¹⁸⁰ The last method is also successful for bromination. On the other hand, certain alkylated phenols can be brominated in the meta positions with Br₂ in the super-acid solution SbF₅-HF.¹⁸¹ It is likely that the meta orientation is the result of conversion by the super acid of the OH group

¹⁷¹For a monograph, see de la Mare *Electrophilic Halogenation*; Cambridge University Press: Cambridge, 1976. For reviews, see Buchler; Pearson *Survey of Organic Synthesis*; Wiley: New York, 1970, pp. 392-404; Braendlin; McBee, in Olah, Ref. 58, vol. 3, 1964, pp. 1517-1593. For a review of the halogenation of heterocyclic compounds, see Eisch *Adv. Heterocycl. Chem.* **1966**, 7, 1-37. For a list of reagents, with references, see Larock *Comprehensive Organic Transformations*; VCH: New York, 1989, pp. 315-318.

¹⁷²McKillop; Bromley; Taylor *J. Org. Chem.* **1972**, 37, 88.

¹⁷³For a review of aromatic substitution on polyalkylbenzenes, see Baciocchi; Illuminati *Prog. Phys. Org. Chem.* **1967**, 5, 1-79.

¹⁷⁴Monobromination (para) of aromatic amines has been achieved with tetrabutylammonium tribromide: Berthelot; Guette; Desbène; Basselier; Chaquin; Masure *Can. J. Chem.* **1989**, 67, 2061. For another procedure, see Onaka; Izumi *Chem. Lett.* **1984**, 2007.

¹⁷⁵For a review of the halogenation of phenols, see Brittain; de la Mare, in Patai; Rappoport *The Chemistry of Functional Groups, Supplement D*, pt. 1; Wiley: New York, 1983, pp. 522-532.

¹⁷⁶Pearson; Wysong; Breder *J. Org. Chem.* **1967**, 32, 2358.

¹⁷⁷For other methods of regioselective chlorination or bromination, see Schmitz; Pagenkopf *J. Prakt. Chem.* **1985**, 327, 998; Watson *J. Org. Chem.* **1985**, 50, 2145; Smith; Butters; Paget; Nay *Synthesis* **1985**, 1157, *Tetrahedron Lett.* **1988**, 29, 1319; Kodomari; Takahashi; Yoshitomi *Chem. Lett.* **1987**, 1901; Kamigata; Satoh; Yoshida; Matsuyama; Kameyama *Bull. Chem. Soc. Jpn.* **1988**, 61, 2226; de la Vega; Sasson *J. Chem. Soc., Chem. Commun.* **1989**, 653.

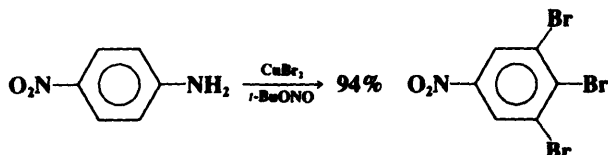
¹⁷⁸Guy; Lemaire; Guette *Tetrahedron* **1982**, 38, 2339, 2347; Lemaire; Guy; Guette *Bull. Soc. Chim. Fr.* **1985**, 477.

¹⁷⁹Lindsay Smith; McKeer; Taylor *J. Chem. Soc., Perkin Trans. 2* **1987**, 1533, **1988**, 385, **1989**, 1529, 1537. See also Minisci; Vismara; Fontana; Platone; Faraci *J. Chem. Soc., Perkin Trans. 2* **1989**, 123.

¹⁸⁰Olah; Ohannesian; Arvanaghi *Synthesis* **1986**, 868.

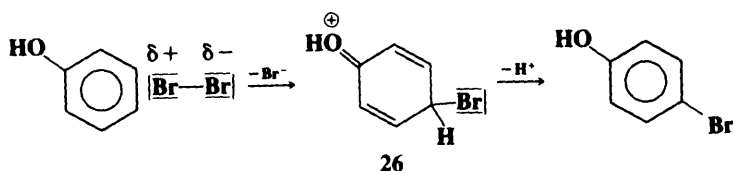
¹⁸¹Jacquesy; Jouannetaud; Makani *J. Chem. Soc., Chem. Commun.* **1980**, 110.

to the OH_2^+ group, which should be meta-directing because of its positive charge. Bromination and the Sandmeyer reaction (4-25) can be carried out in one laboratory step by treatment of an aromatic primary amine with CuBr_2 and *t*-butyl nitrite, e.g.,¹⁸²



Other reagents have been used, among them HOCl ,¹⁸³ HOBr , and N-chloro and N-bromo amides (especially N-bromosuccinimide and tetraalkylammonium polyhalides¹⁸⁴). In all but the last of these cases the reaction is catalyzed by the addition of acids. Dibromo-isocyanuric acid in H_2SO_4 is a very good brominating agent¹⁸⁵ for substrates with strongly deactivating substituents.¹⁸⁶ Two particularly powerful reagents consist of (1) S_2Cl_2 and AlCl_3 in sulfuryl chloride (SO_2Cl_2) (the *BMC reagent*)¹⁸⁷ and (2) dichlorine oxide Cl_2O and a strong acid such as sulfuric.¹⁸⁸ If the substrate contains alkyl groups, side-chain halogenation (4-1) is possible with most of the reagents mentioned, including chlorine and bromine. Since side-chain halogenation is catalyzed by light, the reactions should be run in the absence of light wherever possible.

For reactions in the absence of a catalyst, the attacking entity is simply Br_2 or Cl_2 that has been polarized by the ring.¹⁸⁹



Evidence for molecular chlorine or bromine as the attacking species in these cases is that acids, bases, and other ions, especially chloride ion, accelerate the rate about equally, though if chlorine dissociated into Cl^+ and Cl^- , the addition of chloride should decrease the rate and the addition of acids should increase it. The conjugate base of **26** (4-bromo-2,5-cyclohexadienone) has been detected spectrally in the aqueous bromination of phenol.¹⁹⁰

When a Lewis-acid catalyst is used with chlorine or bromine, the attacking entity may be Cl^+ or Br^+ , formed by $\text{FeCl}_3 + \text{Br}_2 \rightarrow \text{FeCl}_3\text{Br}^- + \text{Br}^+$, or it may be Cl_2 or Br_2 , polarized by the catalyst. With other reagents, the attacking entity in brominations may be Br^+ or a species such as H_2OBr^+ (the conjugate acid of HOBr), in which H_2O is a carrier of Br^+ .¹⁹¹

¹⁸²Doyle; Van Lente; Mowat; Fobare *J. Org. Chem.* **1980**, 45, 2570.

¹⁸³For the use of calcium hypochlorite, see Nwaukwa; Keehn *Synth. Commun.* **1989**, 19, 799.

¹⁸⁴See Kajigaeshi; Moriwaki; Tanaka; Fujisaki; Kakinami; Okamoto *J. Chem. Soc., Perkin Trans. 1* **1990**, 897, and other papers in this series.

¹⁸⁵Nitrobenzene is pentabrominated in 1 min with this reagent in 15% oleum at room temperature.

¹⁸⁶Gottardi *Monatsh. Chem.* **1968**, 99, 815, **1969**, 100, 42.

¹⁸⁷Ballester; Molinet; Castañer *J. Am. Chem. Soc.* **1960**, 82, 4254; Andrews, Glidewell; Walton *J. Chem. Res. (S)* **1978**, 294.

¹⁸⁸Marsh; Farnham; Sam; Smart *J. Am. Chem. Soc.* **1982**, 104, 4680.

¹⁸⁹For reviews of the mechanism of halogenation, see de la Mare, Ref. 171; de la Mare; Swedlund, in Patai *The Chemistry of the Carbon-Halogen Bond*, pt. 1; Wiley: New York, 1973; pp. 490-536; Taylor, in Bamford; Tipper, Ref. 1, pp. 83-139; Berliner *J. Chem. Educ.* **1966**, 43, 124-133. See also Schubert; Dial *J. Am. Chem. Soc.* **1975**, 97, 3877; Keefer; Andrews *J. Am. Chem. Soc.* **1977**, 99, 5693; Briggs; de la Mare; Hall *J. Chem. Soc., Perkin Trans. 2* **1977**, 106; Tee; Paventi; Bennett *J. Am. Chem. Soc.* **1989**, 111, 2233.

¹⁹⁰Tee; Iyengar; Paventi *J. Org. Chem.* **1983**, 48, 759. See also Tee; Iyengar *J. Am. Chem. Soc.* **1985**, 107, 455, *Can. J. Chem.* **1990**, 68, 1769.

¹⁹¹For discussions, see Gilow; Ridd *J. Chem. Soc., Perkin Trans. 2* **1973**, 1321; Rao; Mali; Dangat *Tetrahedron* **1978**, 34, 205.

With HOCl in water the electrophile may be Cl_2O , Cl_2 , or H_2OCl^+ ; in acetic acid it is generally AcOCl . All these species are more reactive than HOCl itself.¹⁹² It is extremely doubtful that Cl^+ is a significant electrophile in chlorinations by HOCl.¹⁹² It has been demonstrated in the reaction between N-methylaniline and calcium hypochlorite that the chlorine attacking entity attacks the *nitrogen* to give N-chloro-N-methylaniline, which rearranges (as in 1-35) to give a mixture of ring-chlorinated N-methylanilines in which the ortho isomer predominates.¹⁹³

FeCl_3 itself, and also CuCl_2 , SbCl_5 , etc.,¹⁹⁴ can give moderate yields of aryl chlorides.¹⁹⁵ The electrophile might be a species such as FeCl_2^+ , but the reactions can also take place by a free-radical mechanism.¹⁹⁶

When chlorination or bromination is carried out at high temperatures (e.g., 300 to 400°C), ortho-para-directing groups direct meta and vice versa.¹⁹⁷ A different mechanism operates here, which is not completely understood. It is also possible for bromination to take place by the SEI mechanism, e.g., in the *t*-BuOK-catalyzed bromination of 1,3,5-tribromobenzene.¹⁹⁸

2. Iodine. Iodine is the least reactive of the halogens in aromatic substitution.¹⁹⁹ Except for active substrates, an oxidizing agent must normally be present to oxidize I_2 to a better electrophile.²⁰⁰ Examples of such oxidizing agents are HNO_3 , HIO_3 , SO_3 , peracetic acid, and H_2O_2 .²⁰¹ ICl is a better iodinating agent than iodine itself.²⁰² Among other reagents used have been IF (prepared directly from the elements),²⁰³ benzyltrimethylammonium dichloroiodate (which iodates phenols, aromatic amines, and N-acylated aromatic amines),²⁰⁴ and the combination of iodine cyanide ICN and a Lewis acid, which is a good reagent for active substrates.²⁰⁵ Iodination can also be accomplished by treatment of the substrate with I_2 in the presence of copper salts,²⁰⁶ SbCl_5 ,²⁰⁷ silver trifluoromethanesulfonate $\text{CF}_3\text{SO}_3\text{Ag}$,²⁰⁸ HgO-BF_4 ,²⁰⁹ Al_2O_3 ,²¹⁰ AgNO_3 ,²¹¹ Ag_2SO_4 ,²¹² or thallium(I) acetate.²¹³ The TIOAc method is regioselective for ortho iodination.

The actual attacking species is less clear than with bromine or chlorine. Iodine itself is too unreactive, except for active species such as phenols, where there is good evidence that

¹⁹²Swain; Crist *J. Am. Chem. Soc.* **1972**, 94, 3195.

¹⁹³Haberfield; Paul *J. Am. Chem. Soc.* **1965**, 87, 5502; Gassman; Campbell *J. Am. Chem. Soc.* **1972**, 94, 3891; Paul; Haberfield *J. Org. Chem.* **1976**, 41, 3170.

¹⁹⁴Kovacic; Wu; Stewart *J. Am. Chem. Soc.* **1960**, 82, 1917; Ware; Borchert *J. Org. Chem.* **1961**, 26, 2267; Commandeur; Mathais; Raynier; Waegell *Nouv. J. Chim.* **1979**, 3, 385; Makhon'kov; Cheprakov; Rodkin; Beletskaya *J. Org. Chem. USSR* **1988**, 24, 211; Kodomari; Satoh; Yoshitomi *J. Org. Chem.* **1988**, 53, 2093.

¹⁹⁵For a review of halogenations with metal halides, see Kovacic, in Olah, Ref. 58, vol. 4, 1965, pp. 111-126.

¹⁹⁶Nonhebel *J. Chem. Soc.* **1963**, 1216; Nonhebel; Russell *Tetrahedron* **1969**, 25, 3493.

¹⁹⁷For a review of this type of reaction, see Kooyman *Pure. Appl. Chem.* **1963**, 7, 193-202.

¹⁹⁸Mach; Bunnett *J. Am. Chem. Soc.* **1974**, 96, 936.

¹⁹⁹For reviews of I_2 as an electrophilic reagent, see Pizey, in Pizey *Synthetic Reagents*, vol. 3; Wiley: New York, 1977, pp. 227-276. For reviews of aromatic iodination, see Merkushev *Synthesis* **1988**, 923-937. *Russ. Chem. Rev.* **1984**, 53, 343-350.

²⁰⁰Butler *J. Chem. Educ.* **1971**, 48, 508.

²⁰¹For a discussion, see Makhon'kov; Cheprakov; Beletskaya *J. Org. Chem. USSR* **1989**, 24, 2029.

²⁰²For a review of ICl , see McClelland, in Pizey, Ref. 199, vol. 5, 1983, pp. 85-164.

²⁰³Rozen; Zamir *J. Org. Chem.* **1990**, 55, 3552.

²⁰⁴See Kajigaeshi; Kakinami; Watanabe; Okamoto *Bull. Chem. Soc. Jpn.* **1989**, 62, 1349, and references cited therein.

²⁰⁵Radner *Acta Chem. Scand.* **1989**, 43, 481. For another method, see Edgar; Falling *J. Org. Chem.* **1990**, 55, 5287.

²⁰⁶Baird; Surridge *J. Org. Chem.* **1970**, 35, 3436; Horiuchi; Satoh *Bull. Chem. Soc. Jpn.* **1984**, 57, 2691; Makhon'kov; Cheprakov; Rodkin; Beletskaya *J. Org. Chem. USSR* **1986**, 22, 1003.

²⁰⁷Uemura; Onoe; Okano *Bull. Chem. Soc. Jpn.* **1974**, 47, 147.

²⁰⁸Kobayashi; Kumadaki; Yoshida *J. Chem. Res. (S)* **1977**, 215. For a similar procedure, see Merkushev; Simakhina; Koveshnikova *Synthesis* **1980**, 486.

²⁰⁹Barluenga; Campos; González; Asensio *J. Chem. Soc., Perkin Trans. 1* **1984**, 2623.

²¹⁰Pagni; Kabalka; Boothe; Gaetano; Stewart; Conaway; Dial; Gray; Larson; Luidhart *J. Org. Chem.* **1988**, 53, 4477.

²¹¹Sy; Lodge *Tetrahedron Lett.* **1989**, 30, 3769.

²¹²Sy; Lodge; By *Synth. Commun.* **1990**, 20, 877.

²¹³Cambie; Rutledge; Smith-Palmer; Woodgate *J. Chem. Soc., Perkin Trans. 1* **1976**, 1161.

I_2 is the attacking entity.²¹⁴ There is evidence that AcOI may be the attacking entity when peroxyacetic acid is the oxidizing agent,²¹⁵ and I_3^+ when SO_3 or HIO_3 is the oxidizing agent.²¹⁶ I^+ has been implicated in several procedures.^{216a} For an indirect method for accomplishing aromatic iodination, see 2-30.

3. Fluorine. Direct fluorination of aromatic rings with F_2 is not feasible at room temperature, because of the extreme reactivity of F_2 .²¹⁷ It has been accomplished at low temperatures (e.g., -70 to $-20^\circ C$, depending on the substrate),²¹⁸ but the reaction is not yet of preparative significance. Fluorination has also been reported with silver difluoride AgF_2 ,²¹⁹ with cesium fluoroxysulfate $CsSO_4F$,²²⁰ with acetyl hypofluorite CH_3COOF (generated from F_2 and sodium acetate),²²¹ with XeF_2 ,²²² with an N-fluoroperfluoroalkyl sulfonamide, e.g., $(CF_3SO_2)_2NF$,²²³ and with fluoroxytrifluoromethane CF_3OF ²²⁴ under various conditions and with various yields, in some cases by electrophilic and in other cases by free-radical mechanisms. However, none of these methods seems likely to displace the Schiemann reaction (3-24) as the most common method for introducing fluorine into aromatic rings.

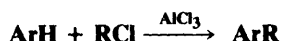
The overall effectiveness of reagents in aromatic substitution is $Cl_2 > BrCl > Br_2 > ICl > I_2$.

OS I, 111, 121, 123, 128, 207, 323; II, 95, 97, 100, 173, 196, 343, 347, 349, 357, 592; III, 132, 134, 138, 262, 267, 575, 796; IV, 114, 166, 256, 545, 547, 872, 947; V, 117, 147, 206, 346; VI, 181, 700; 67, 222. Also see OS II, 128.

E. Carbon Electrophiles In the reactions in this section, a new carbon-carbon bond is formed. With respect to the aromatic ring, they are electrophilic substitutions, because a positive species attacks the ring. We treat them in this manner because it is customary. However, with respect to the electrophile, most of these reactions are nucleophilic substitutions, and what was said in Chapter 10 is pertinent to them.

1-12 Friedel-Crafts Alkylation

Alkylation or Alkyl-de-hydrogenation



²¹⁴Grovenstein; Aprahamian; Bryan; Gnanapragasam; Kilby; McKelvey; Sullivan *J. Am. Chem. Soc.* **1973**, 95, 4261.

²¹⁵Ogata; Urasaki *J. Chem. Soc. C* **1970**, 1689.

²¹⁶Arotzky; Butler; Darby *J. Chem. Soc. C* **1970**, 1480.

^{216a}Galli *J. Org. Chem.* **1991**, 56, 3238.

²¹⁷For a monograph on fluorinating agents, see German; Zemskov *New Fluorinating Agents in Organic Synthesis*; Springer: New York, 1989. For reviews of F_2 in organic synthesis, see Purrington; Kagen; Patrick *Chem. Rev.* **1986**, 86, 997-1018; Grakauskas, *Intra-Sci. Chem. Rep.* **1971**, 5, 85-104. For a review of fluoroaromatic compounds, see Hewitt; Silvester *Aldrichimica Acta* **1988**, 21, 3-10.

²¹⁸Grakauskas *J. Org. Chem.* **1970**, 35, 723; Cacace; Giacomello; Wolf *J. Am. Chem. Soc.* **1980**, 102, 3511; Stavber; Zupan *J. Org. Chem.* **1983**, 48, 2223. See also Purrington; Woodward *J. Org. Chem.* **1991**, 56, 142.

²¹⁹Zweig; Fischer; Lancaster *J. Org. Chem.* **1980**, 45, 3597.

²²⁰Ip; Arthur; Winans; Appelman *J. Am. Chem. Soc.* **1981**, 103, 1964; Stavber; Zupan *J. Org. Chem.* **1985**, 50, 3609; Appelman; Basile; Hayatsu *Tetrahedron* **1984**, 40, 189; Patrick; Darling *J. Org. Chem.* **1986**, 51, 3242.

²²¹See Hebel; Lerman; Rozen *Bull. Soc. Chim. Fr.* **1986**, 861; Visser; Bakker; van Halteren; Herscheid; Brinkman; Hockstra *J. Org. Chem.* **1986**, 51, 1886.

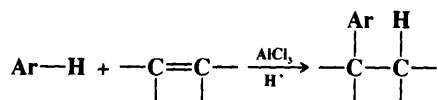
²²²Shaw; Hyman; Filler *J. Am. Chem. Soc.* **1969**, 91, 1563, **1970**, 92, 6498, *J. Org. Chem.* **1971**, 36, 2917; Mackenzie; Fajer *J. Am. Chem. Soc.* **1970**, 92, 4994; Filler *Isr. J. Chem.* **1978**, 17, 71.

²²³Singh; DesMarteau; Zuberi; Witz; Huang *J. Am. Chem. Soc.* **1987**, 109, 7194.

²²⁴Barton; Ganguly; Hesse; Loo; Pechet *Chem. Commun.* **1968**, 806; Kollonitsch; Barash; Doldouras *J. Am. Chem. Soc.* **1970**, 92, 7494; Patrick; Cantrell; Chang *J. Am. Chem. Soc.* **1979**, 101, 7434; Fifolt; Olczak; Mundhenke; Bieron *J. Org. Chem.* **1985**, 50, 4576. For a review of this reagent, see Barton *Pure. Appl. Chem.* **1977**, 49, 1241-1249.

The alkylation of aromatic rings, called *Friedel–Crafts alkylation*, is a reaction of very broad scope.²²⁵ The most important reagents are alkyl halides, olefins, and alcohols, but many other types of reagent have also been employed.²²⁵ When alkyl halides are used, the reactivity order is $F > Cl > Br > I$ ²²⁶; e.g., $FCH_2CH_2CH_2Cl$ reacts with benzene to give $PhCH_2CH_2CH_2Cl$ ²²⁷ when the catalyst is BCl_3 . By the use of this catalyst, it is therefore possible to place a haloalkyl group on a ring (see also 1-24).²²⁸ Di- and trihalides, when all the halogens are the same, usually react with more than one molecule of aromatic compound; it is usually not possible to stop the reaction earlier.²²⁹ Thus, benzene with CH_2Cl_2 gives not $PhCH_2Cl$, but Ph_2CH_2 ; benzene with $CHCl_3$ gives Ph_3CH . With CCl_4 , however, the reaction stops when only three rings have been substituted to give Ph_3CCl .

Olefins are especially good alkylating agents. With respect to them the reaction is addition of ArH to a $C=C$ double bond:



Acetylene reacts with 2 moles of aromatic compound to give 1,1-diarylethanes, but other alkynes react poorly, if at all. Alcohols are more active than alkyl halides, though if a Lewis-acid catalyst is used, more catalyst is required, since the catalyst complexes with the OH group. However, proton acids, especially H_2SO_4 , are often used to catalyze alkylation with alcohols. When carboxylic esters are the reagents, there is competition between alkylation and acylation (1-14). Though this competition can often be controlled by choice of catalyst, and alkylation is usually favored, carboxylic esters are not often employed in Friedel–Crafts reactions. Other alkylating agents are ethers, thiols, sulfates, sulfonates, alkyl nitro compounds,²³⁰ and even alkanes and cycloalkanes, under conditions where these are converted to carbocations. Notable here are ethylene oxide, which puts the CH_2CH_2OH group onto the ring, and cyclopropane. For all types of reagent the reactivity order is allylic \sim benzylic $>$ tertiary $>$ secondary $>$ primary.

Regardless of which reagent is used, a catalyst is nearly always required.²³¹ Aluminum chloride and boron trifluoride are the most common, but many other Lewis acids have been used, and also proton acids such as HF and H_2SO_4 .²³² For active halides a trace of a less

²²⁵For a monograph, see Roberts; Khalaf *Friedel–Crafts Alkylation Chemistry*; Marcel Dekker: New York, 1984. For a treatise on Friedel–Crafts reactions in general, see Olah *Friedel–Crafts and Related Reactions*; Wiley: New York, 1963-1965. Volume 1 covers general aspects, such as catalyst activity, intermediate complexes, etc. Volume 2 covers alkylation and related reactions. In this volume the various reagents are treated by the indicated authors as follows: alkenes and alkanes, Patinkin; Friedman, pp. 1-288; dienes and substituted alkenes, Koncos; Friedman, pp. 289-412; alkynes, Franzen, pp. 413-416; alkyl halides, Drahowzal, pp. 417-475; alcohols and ethers, Schriesheim, pp. 477-595; sulfonates and inorganic esters, Drahowzal, pp. 641-658. For a monograph in which five chapters of the above treatise are reprinted and more recent material added, see Olah *Friedel–Crafts Chemistry*; Wiley: New York, 1973.

²²⁶For example, see Calloway *J. Am. Chem. Soc.* **1937**, 59, 1474; Brown; Jungk *J. Am. Chem. Soc.* **1955**, 77, 5584.

²²⁷Olah; Kuhn *J. Org. Chem.* **1964**, 29, 2317.

²²⁸For a review of selectivity in this reaction, i.e., which group preferentially attacks when the reagent contains two or more, see Olah, in Olah, Ref. 225, vol. 1, pp. 881-905. This review also covers the case of alkylation vs. acylation.

²²⁹It has proven possible in some cases. Thus, arenes ArH have been converted to $ArCCl_3$ with CCl_4 and excess $AlCl_3$; Raabe; Hörhold *J. Prakt. Chem.* **1987**, 329, 1131; Belen'kii; Brokhovetsky; Krayushkin *Chem. Scr.* **1989**, 29, 81.

²³⁰Bonvino; Casini; Ferappi; Cingolani; Pietroni *Tetrahedron* **1981**, 37, 615.

²³¹There are a few exceptions. Certain alkyl and vinylic triflates alkylate aromatic rings without a catalyst; see Gramstad; Haszeldine *J. Chem. Soc.* **1957**, 4069; Olah; Nishimura *J. Am. Chem. Soc.* **1974**, 96, 2214; Stang; Anderson *Tetrahedron Lett.* **1977**, 1485, *J. Am. Chem. Soc.* **1978**, 100, 1520.

²³²For a review of catalysts and solvents in Friedel–Crafts reactions, see Olah, in Olah, Ref. 225, vol. 1, pp. 201-366, 853-881.

active catalyst, e.g., ZnCl_2 , may be enough. For an unreactive halide, such as chloromethane, a more powerful catalyst is needed, for example, AlCl_3 , and in larger amounts. In some cases, especially with olefins, a Lewis-acid catalyst causes reaction only if a small amount of proton-donating cocatalyst is present. Catalysts have been arranged in the following order of overall reactivity: $\text{AlBr}_3 > \text{AlCl}_3 > \text{GaCl}_3 > \text{FeCl}_3 > \text{SbCl}_5^{233} > \text{ZrCl}_4, \text{SnCl}_4 > \text{BCl}_3, \text{BF}_3, \text{SbCl}_3^{234}$ but the reactivity order in each case depends on the substrate, reagent, and conditions. Nafion-H, a superacidic perfluorinated resinsulfonic acid, is a very good catalyst for gas phase alkylations with alkyl halides, alcohols, or olefins.²³⁵

Friedel-Crafts alkylation is unusual among the principal aromatic substitutions in that the entering group is activating so that di- and polyalkylation are frequently observed. However, the activating effect of simple alkyl groups (e.g., ethyl, isopropyl) is such that compounds with these groups as substituents are attacked in Friedel-Crafts alkylations only about 1.5 to 3 times as fast as benzene,²³⁶ so it is often possible to obtain high yields of monoalkyl product. Actually, the fact that di- and polyalkyl derivatives are frequently obtained is not due to the small difference in reactivity but to the circumstance that alkylbenzenes are preferentially soluble in the catalyst layer, where the reaction actually takes place.²³⁷ This factor can be removed by the use of a suitable solvent, by high temperatures, or by high-speed stirring.

Also unusual is the fact that the OH, OR, NH_2 , etc., groups do not facilitate the reaction, since the catalyst coordinates with these basic groups. Although phenols give the usual Friedel-Crafts reactions, orienting ortho and para, the reaction is very poor for amines. However, amines can undergo the reaction if olefins are used as reagents and aluminum anilides as catalysts.²³⁸ In this method the catalyst is prepared by treating the amine to be alkylated with $\frac{1}{2}$ mole of AlCl_3 . A similar reaction can be performed with phenols, though here the catalyst is $\text{Al}(\text{OAr})_3$.²³⁹ Primary aromatic amines (and phenols) can be methylated regioselectively in the ortho position by an indirect method (see 1-26). For an indirect method for regioselective ortho methylation of phenols, see p. 872.

Naphthalene and other fused ring compounds generally give poor yields in Friedel-Crafts alkylation, because they are so reactive that they react with the catalyst. Heterocyclic rings are usually also poor substrates for the reaction. Although some furans and thiophenes have been alkylated, a true alkylation of a pyridine or a quinoline has never been described.²⁴⁰ However, alkylation of pyridine and other nitrogen heterocycles can be accomplished by a free radical (4-23) and by a nucleophilic method (3-17).

In most cases, meta-directing groups make the ring too inactive for alkylation. Nitrobenzene cannot be alkylated, and there are only a few reports of successful Friedel-Crafts alkylations when electron-withdrawing groups are present.²⁴¹ This is not because the attacking species is not powerful enough; indeed we have seen (p. 518) that alkyl cations are among the most powerful of electrophiles. The difficulty is caused by the fact that, with inactive substrates, degradation and polymerization of the electrophile occurs before it can attack the ring. However, if an activating and a deactivating group are both present on a

²³³For a review of SbCl_5 as a Friedel-Crafts catalyst, see Yakobson; *Furin Synthesis* **1980**, 345-364.

²³⁴Russell *J. Am. Chem. Soc.* **1959**, *81*, 4834.

²³⁵For a review of Nafion-H in organic synthesis, see Olah; *Prakash Synthesis* **1986**, 513-531.

²³⁶Condon *J. Am. Chem. Soc.* **1948**, *70*, 2265; Olah; Kuhn; Flood *J. Am. Chem. Soc.* **1962**, *84*, 1688.

²³⁷Francis *Chem. Rev.* **1948**, *43*, 257.

²³⁸For a review, see Stroh; Ebersberger; Haberland; Hahn *Newer Methods Prep. Org. Chem.* **1963**, *2*, 227-252.

This article also appeared in *Angew. Chem.* **1957**, *69*, 124-131.

²³⁹Koshchii; Kozlikovskii; Matyusha *J. Org. Chem. USSR* **1988**, *24*, 1358; Laan; Giesen; Ward *Chem. Ind. (London)* **1989**, 354. For a review, see Stroh; Seydel; Hahn *Newer Methods Prep. Org. Chem.* **1963**, *2*, 337-359. This article also appeared in *Angew. Chem.* **1957**, *69*, 669-706.

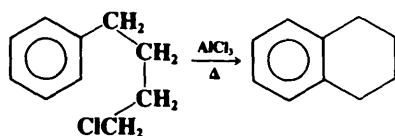
²⁴⁰Drahowzal, in Olah, Ref. 225, vol. 2, p. 433.

²⁴¹Campbell; Spaeth *J. Am. Chem. Soc.* **1959**, *81*, 5933; Yoneda; Fukuhara; Takahashi; Suzuki *Chem. Lett.* **1979**, 1003; Shen; Liu; Chen *J. Org. Chem.* **1990**, *55*, 3961.

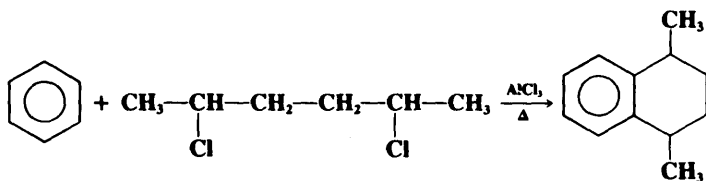
ring, Friedel-Crafts alkylation can be accomplished.²⁴² Aromatic nitro compounds can be methylated by a nucleophilic mechanism (3-17).

An important synthetic limitation of Friedel-Crafts alkylation is that rearrangement frequently takes place in the reagent. For example, benzene treated with *n*-propyl bromide gives mostly isopropylbenzene (cumene) and much less *n*-propylbenzene. Rearrangement is usually in the order primary \rightarrow secondary \rightarrow tertiary and occurs mostly by migration of H^- but also of R^- (see discussion of rearrangement mechanisms in Chapter 18). It is therefore not usually possible to put a primary alkyl group (other than methyl and ethyl) onto an aromatic ring by Friedel-Crafts alkylation. Because of these rearrangements, *n*-alkylbenzenes are often prepared by *acylation* (1-14), followed by reduction (9-37).

An important use of the Friedel-Crafts alkylation reaction is to effect ring closure.²⁴³ The most common method is to heat with aluminum chloride an aromatic compound having a halogen, hydroxy, or olefinic group in the proper position, as, for example, in the preparation of tetralin:



Another way of effecting ring closure through Friedel-Crafts alkylation is to use a reagent containing two groups, e.g.,



These reactions are most successful for the preparation of 6-membered rings,²⁴⁴ though 5- and 7-membered rings have also been closed in this manner. For other Friedel-Crafts ring-closure reactions, see 1-13, 1-14, and 1-23.

From what has been said thus far it is evident that the electrophile in Friedel-Crafts alkylation is a carbocation, at least in most cases.²⁴⁵ This is in accord with the knowledge that carbocations rearrange in the direction primary \rightarrow secondary \rightarrow tertiary (see Chapter 18). In each case the cation is formed from the attacking reagent and the catalyst. For the three most important types of reagent these reactions are:



From alcohols and Lewis acids:



From alcohols and proton acids:



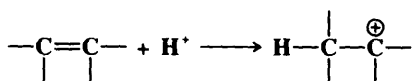
²⁴²Olah, in Olah, Ref. 225, vol. 1, p. 34.

²⁴³For a review, see Barclay, in Olah, Ref. 225, vol. 2, pp. 785-977.

²⁴⁴See Khalaf; Roberts J. Org. Chem. 1966, 31, 89.

²⁴⁵For a discussion of the mechanism see Taylor *Electrophilic Aromatic Substitution*, Ref. 1, pp. 188-213.

From olefins (a supply of protons is always required):



There is direct evidence, from ir and nmr spectra, that the *t*-butyl cation is quantitatively formed when *t*-butyl chloride reacts with AlCl_3 in anhydrous liquid HCl .²⁴⁶ In the case of olefins, Markovnikov's rule (p. 750) is followed. Carbocation formation is particularly easy from some reagents, because of the stability of the cations. Triphenylmethyl chloride²⁴⁷ and 1-chloroadamantane²⁴⁸ alkylate activated aromatic rings (e.g., phenols, amines) with no catalyst or solvent. Ions as stable as this are less reactive than other carbocations and often attack only active substrates. The tropylium ion, for example, alkylates anisole but not benzene.²⁴⁹ It was noted on p. 337 that relatively stable vinylic cations can be generated from certain vinylic compounds. These have been used to introduce vinylic groups into aryl substrates.²⁵⁰

However, there is much evidence that many Friedel-Crafts alkylations, especially with primary reagents, do not go through a completely free carbocation. The ion may exist as a tight ion pair with, say, AlCl_4^- as the counterion or as a complex. Among the evidence is that methylation of toluene by methyl bromide and methyl iodide gave different ortho/para/meta ratios,²⁵¹ though if the same species attacked in each case we would expect the same ratios. Other evidence is that, in some cases, the reaction kinetics are third order; first order each in aromatic substrate, attacking reagent, and catalyst.²⁵² In these instances a mechanism in which the carbocation is slowly formed and then rapidly attacks the ring is ruled out since, in such a mechanism, the substrate would not appear in the rate expression. Since it is known that free carbocations, once formed, rapidly attack the ring, there are no free carbocations here. Another possibility (with alkyl halides) is that some alkylations take place by an $\text{S}_\text{N}2$ mechanism (with respect to the halide), in which case no carbocations would be involved at all. However, a completely $\text{S}_\text{N}2$ mechanism requires inversion of configuration. Most investigations of Friedel-Crafts stereochemistry, even where an $\text{S}_\text{N}2$ mechanism might most be expected, have resulted in total racemization, or at best a few percent inversion. A few exceptions have been found,²⁵³ most notably where the reagent was optically active propylene oxide, in which case 100% inversion was reported.²⁵⁴

Rearrangement is possible even with a noncarbocation mechanism. The rearrangement could occur *before* the attack on the ring takes place. It has been shown that treatment of $\text{CH}_3^{14}\text{CH}_2\text{Br}$ with AlBr_3 in the absence of any aromatic compound gave a mixture of the starting material and $^{14}\text{CH}_3\text{CH}_2\text{Br}$.²⁵⁵ Similar results were obtained with $\text{PhCH}_2^{14}\text{CH}_2\text{Br}$, in which case the rearrangement was so fast that the rate could be measured only below

²⁴⁶Kalchschmid; Mayer *Angew. Chem. Int. Ed. Engl.* **1976**, 15, 773 [*Angew. Chem.* **88**, 849].

²⁴⁷See, for example, Chuchani *J. Chem. Soc.* **1960**, 325; Hart; Cassis *J. Am. Chem. Soc.* **1954**, 76, 1634; Hickinbottom *J. Chem. Soc.* **1934**, 1700; Chuchani and Zabicky *J. Chem. Soc. C* **1966**, 297.

²⁴⁸Takaku; Taniguchi; Inamoto *Synth. Commun.* **1971**, 1, 141.

²⁴⁹Bryce-Smith; Perkins *J. Chem. Soc.* **1962**, 5295.

²⁵⁰Kitamura; Kobayashi; Taniguchi; Rappoport *J. Org. Chem.* **1982**, 47, 5503.

²⁵¹Brown; Jungk *J. Am. Chem. Soc.* **1956**, 78, 2182.

²⁵²For examples, see Brown; Grayson *J. Am. Chem. Soc.* **1953**, 75, 6285; Jungk; Smoot; Brown *J. Am. Chem. Soc.* **1956**, 78, 2185; Choi; Brown *J. Am. Chem. Soc.* **1963**, 85, 2596.

²⁵³Some instances of retention of configuration have been reported; a neighboring-group mechanism is likely in these cases: see Masuda; Nakajima; Suga *Bull. Chem. Soc. Jpn.* **1983**, 56, 1089; Effenberger; Weber *Angew. Chem. Int. Ed. Engl.* **1987**, 26, 142 [*Angew. Chem.* **99**, 146].

²⁵⁴Nakajima; Suga; Sugita; Ichikawa *Tetrahedron* **1969**, 25, 1807. For cases of almost complete inversion, with acyclic reagents, see Piccolo; Spreafico; Visentin; Valoti *J. Org. Chem.* **1985**, 50, 3945; Piccolo; Azzena; Melloni; Delogu; Valoti *J. Org. Chem.* **1991**, 56, 183.

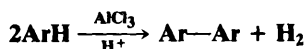
²⁵⁵Sixma; Hendriks *Recl. Trav. Chim. Pays-Bas* **1956**, 75, 169; Adema; Sixma *Recl. Trav. Chim. Pays-Bas* **1962**, 81, 323, 336.

– 70°C.²⁵⁶ Rearrangement could also occur *after* formation of the product, since alkylation is reversible (see 1-37).²⁵⁷

See 4-21 and 4-23 for free-radical alkylation.

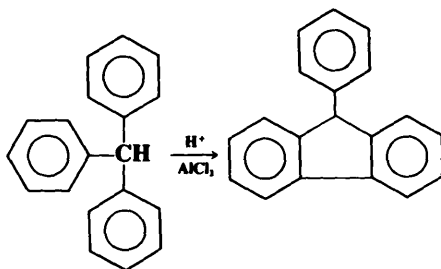
OS I, 95, 548; II, 151, 229, 232, 236, 248; III, 343, 347, 504, 842; IV, 47, 520, 620, 665, 702, 898, 960; V, 130, 654; VI, 109, 744.

1-13 Friedel-Crafts Arylation. The Scholl Reaction De-hydrogen-coupling



The coupling of two aromatic molecules by treatment with a Lewis acid and a proton acid is called the *Scholl reaction*.²⁵⁸ Yields are low and the synthesis is seldom useful. High temperatures and strong-acid catalysts are required, and the reaction fails for substrates that are destroyed by these conditions. Because the reaction becomes important with large fused-ring systems, ordinary Friedel-Crafts reactions (1-12) on these systems are rare. For example, naphthalene gives binaphthyl under Friedel-Crafts conditions. Yields can be increased by the addition of a salt such as CuCl_2 or FeCl_3 , which acts as an oxidant.²⁵⁹

Intramolecular Scholl reactions, e.g.,



are much more successful than the intermolecular kind. The mechanism is not clear, but it may involve attack by a proton to give an arenium ion of the type 9 (p. 504), which would be the electrophile that attacks the other ring.²⁶⁰ Sometimes arylations have been accomplished by treating aromatic substrates with particularly active aryl halides, especially fluorides. For free-radical arylations, see reactions 4-18 to 4-22.

OS IV, 482. Also see OS V, 102, 952.

1-14 Friedel-Crafts Acylation Acylation or Acyl-de-hydrogenation



The most important method for the preparation of aryl ketones is known as *Friedel-Crafts acylation*.²⁶¹ The reaction is of wide scope. Reagents used²⁶² are not only acyl halides but

²⁵⁶For a review of the use of isotopic labeling to study Friedel-Crafts reactions, see Roberts; Gibson *Isot. Org. Chem.* **1980**, 5, 103-145.

²⁵⁷For an example, see Lee; Hamblin; Uthe *Can. J. Chem.* **1964**, 42, 1771.

²⁵⁸For reviews, see Kovacic; Jones *Chem. Rev.* **1987**, 87, 357-79; Balaban; Nenitzescu, in Olah, Ref. 225, vol. 2, pp. 979-1047.

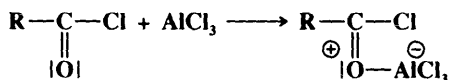
²⁵⁹Kovacic; Koch *J. Org. Chem.* **1963**, 28, 1864, **1965**, 30, 3176; Kovacic; Wu *J. Org. Chem.* **1961**, 26, 759, 762. For examples, with references, see Larock, Ref. 171, pp. 45-46.

²⁶⁰For a discussion, see Clowes *J. Chem. Soc. C* **1968**, 2519.

²⁶¹For reviews of Friedel-Crafts acylation, see Olah *Friedel-Crafts and Related Reactions*; Wiley: New York, 1963-1964, as follows: vol. 1, Olah, pp. 91-115; vol. 3, Gore, pp. 1-381; Peto, pp. 535-910; Sethna, pp. 911-1002; Jensen; Goldman, pp. 1003-1032. For another review, see Gore *Chem. Ind. (London)* **1974**, 727-731.

²⁶²For a list of reagents, with references, see Larock, Ref. 171, pp. 703-704.

also carboxylic acids, anhydrides, and ketenes. Carboxylic esters usually give predominant alkylation (see 1-12). R may be aryl as well as alkyl. The major disadvantages of Friedel-Crafts alkylation are not present here. Rearrangement of R is never found, and, because the RCO group is deactivating, the reaction stops cleanly after one group is introduced. All four acyl halides can be used, though chlorides are most commonly employed. The order of activity is usually, but not always, $I > Br > Cl > F$.²⁶³ Catalysts are Lewis acids, similar to those in reaction 1-12, but in acylation a little more than 1 mole of catalyst is required per mole of reagent, because the first mole coordinates with the oxygen of the reagent.²⁶⁴

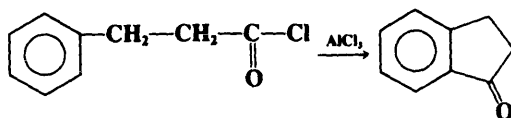


Proton acids can be used as catalysts when the reagent is a carboxylic acid. The mixed carboxylic sulfonic anhydrides $\text{RCOOSO}_2\text{CF}_3$ are extremely reactive acylating agents and can smoothly acylate benzene without a catalyst.²⁶⁵ With active substrates (e.g., aryl ethers, fused-ring systems, thiophenes), Friedel-Crafts acylation can be carried out with very small amounts of catalyst, often just a trace, or even sometimes with no catalyst at all. Ferric chloride, iodine, zinc chloride, and iron are the most common catalysts when the reactions is carried out in this manner.²⁶⁶

The reaction is quite successful for many types of substrate, including fused ring systems, which give poor results in 1-12. Compounds containing ortho-para-directing groups, including alkyl, hydroxy, alkoxy, halogen, and acetamido groups, are easily acylated and give mainly or exclusively the para products, because of the relatively large size of the acyl group. However, aromatic amines give poor results. With amines and phenols there may be competition from N- or O-acylation; however, O-acylated phenols can be converted to C-acylated phenols by the Fries rearrangement (1-30). Friedel-Crafts acylation is usually prevented by meta-directing groups. Indeed, nitrobenzene is often used as a solvent for the reaction. Many heterocyclic systems, including furans, thiophenes, pyrans, and pyrroles but not pyridines or quinolines, can be acylated in good yield (however, pyridines and quinolines can be acylated by a free-radical mechanism, reaction 4-23). Gore, in Ref. 261 (pp. 36-100; with tables, pp. 105-321), presents an exhaustive summary of the substrates to which this reaction has been applied.

When a mixed anhydride $\text{RCOOCOR}'$ is the reagent, two products are possible— ArCOR and ArCOR' . Which product predominates depends on two factors. If R contains electron-withdrawing groups, then ArCOR' is chiefly formed, but if this factor is approximately constant in R and R', the ketone with the larger R group predominantly forms.²⁶⁷ This means that *formylations* of the ring do not occur with mixed anhydrides of formic acid HCOOCOR .

An important use of the Friedel-Crafts acylation is to effect ring closure.²⁶⁸ This can be done if an acyl halide, anhydride, or acid group is in the proper position. An example is



²⁶³Yamase *Bull. Chem. Soc. Jpn.* **1961**, 34, 480; Corriu *Bull. Soc. Chim. Fr.* **1965**, 821.

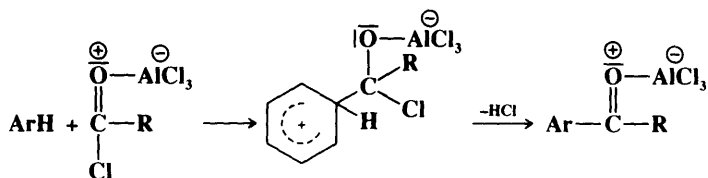
²⁶⁴The crystal structures of several of these complexes have been reported: Rasmussen; Broch *Acta Chem. Scand.* **1966**, 20, 1351; Chevrier; Le Carpentier; Weiss *J. Am. Chem. Soc.* **1972**, 94, 5718. For a review of these complexes, see Chevrier; Weiss *Angew. Chem. Int. Ed. Engl.* **1974**, 13, 1-10 [*Angew. Chem.* 86, 12-21].

²⁶⁵Effenberger; Sohn; Eppe *Chem. Ber.* **1983**, 116, 1195. See also Keumi; Yoshimura; Shimada; Kitajima *Bull. Chem. Soc. Jpn.* **1988**, 44, 455.

²⁶⁶For a review, see Pearson; Buehler *Synthesis* **1972**, 533-542.

²⁶⁷Edwards; Sibelle *J. Org. Chem.* **1963**, 28, 674.

²⁶⁸For a review, see Sethna, Ref. 261. For examples, with references, see Larock, Ref. 171, pp. 704-708.

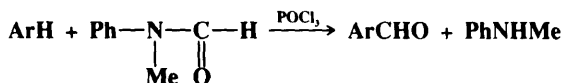


Free-ion attack is more likely for sterically hindered R.²⁷⁷ The ion CH_3CO^+ has been detected (by ir spectroscopy) in the liquid complex between acetyl chloride and aluminum chloride, and in polar solvents such as nitrobenzene; but in nonpolar solvents such as chloroform, only the complex and not the free ion is present.²⁷⁸ In any event, 1 mole of catalyst certainly remains complexed to the product at the end of the reaction. When the reaction is performed with $\text{RCO}^+ \text{SbF}_6^-$, no catalyst is required and the free ion²⁷⁹ (or ion pair) is undoubtedly the attacking entity.²⁸⁰

OS I, 109, 353, 476, 517; II, 3, 8, 15, 81, 156, 169, 304, 520, 569; III, 6, 14, 23, 53, 109, 183, 248, 272, 593, 637, 761, 798; IV, 8, 34, 88, 898, 900; V, 111; VI, 34, 618, 625.

Reactions 1-15 through 1-18 are direct formylations of the ring.²⁸¹ Reaction 1-14 has not been used for formylation, since neither formic anhydride nor formyl chloride is stable at ordinary temperatures. Formyl chloride has been shown to be stable in chloroform solution for 1 hr at -60°C ,²⁸² but it is not useful for formylating aromatic rings under these conditions. Formic anhydride has been prepared in solution, but has not been isolated.²⁸³ Mixed anhydrides of formic and other acids are known²⁸⁴ and can be used to formylate amines (see 0-53) and alcohols, but no formylation takes place when they are applied to aromatic rings. See 3-17 for a nucleophilic method for the formylation of aromatic rings.

1-15 Formylation with Disubstituted Formamides Formylation or Formyl-de-hydrogenation



The reaction with disubstituted formamides and phosphorus oxychloride, called the *Vilsmeier* or the *Vilsmeier-Haack reaction*, is the most common method for the formylation of aromatic rings.²⁸⁵ However, it is applicable only to active substrates, such as amines and phenols. Aromatic hydrocarbons and heterocycles can also be formylated, but only if they are much more active than benzene (e.g., azulenes, ferrocenes). Though N-phenyl-N-methylform-

²⁷⁷Yamase *Bull. Chem. Soc. Jpn.* **1961**, 34, 484; Gore *Bull. Chem. Soc. Jpn.* **1962**, 35, 1627; Satchell *J. Chem. Soc.* **1961**, 5404.

²⁷⁸Cook *Can. J. Chem.* **1959**, 37, 48; Cassimatis; Bonnin; Theophanides *Can. J. Chem.* **1970**, 48, 3860.

²⁷⁹Crystal structures of solid $\text{RCO}^+ \text{SbF}_6^-$ salts have been reported: Boer *J. Am. Chem. Soc.* **1968**, 90, 6706; Chevrier; Le Carpentier; Weiss *Acta Crystallogr., Sect. B* **1972**, 28, 2673; *J. Am. Chem. Soc.* **1972**, 94, 5718.

²⁸⁰Olah; Kuhn; Flood; Hardie *J. Am. Chem. Soc.* **1964**, 86, 2203; Olah; Lin; Germain *Synthesis* **1974**, 895. For a review of acylium salts in organic synthesis, see Al-Talib; Tashtoush *Org. Prep. Proced. Int.* **1990**, 22, 1-36.

²⁸¹For a review, see Olah; Kuhn, in Olah, Ref. 261, vol. 3, 1964, pp. 1153-1256. For a review of formylating agents, see Olah; Ohannesian; Arvanaghi *Chem. Rev.* **1987**, 87, 671-686. For a list of reagents, with references, see Larock, Ref. 171, pp. 702-703.

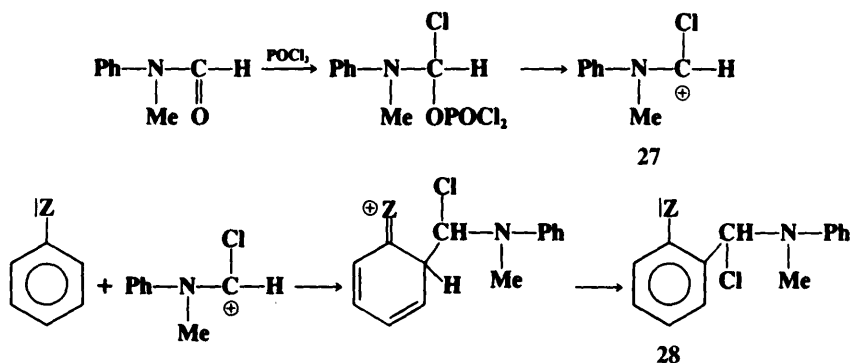
²⁸²Staab; Datta *Angew. Chem. Int. Ed. Engl.* **1964**, 3, 132 [*Angew. Chem.* **1963**, 75, 1203].

²⁸³Olah; Vankar; Arvanaghi; Sommer *Angew. Chem. Int. Ed. Engl.* **1979**, 18, 614 [*Angew. Chem.* 91, 649]; Schijf; Scheeren; van Es; Stevens *Recl. Trav. Chim. Pays-Bas* **1965**, 84, 594.

²⁸⁴Stevens; van Es *Recl. Trav. Chim. Pays-Bas* **1964**, 83, 863.

²⁸⁵For a review, see Jutz *Adv. Org. Chem.* **1976**, 9, pt. 1, 225-342.

amide is a common reagent, other arylalkyl amides and dialkyl amides are also used.²⁸⁶ Phosgene COCl_2 has been used in place of POCl_3 . The reaction has also been carried out with other amides to give ketones (actually an example of 1-14), but not often. The attacking species²⁸⁷ is **27**,²⁸⁸ and the mechanism is probably:



28 is unstable and easily hydrolyzes to the product. Either formation of **27** or the reaction of **27** with the substrate can be rate-determining, depending on the reactivity of the substrate.²⁸⁹

When $(\text{CF}_3\text{SO}_2)_2\text{O}$ was used instead of POCl_3 , the reaction was extended to some less-active compounds, including naphthalene and phenanthrene.²⁹⁰

OS I, 217; III, 98, IV, 331, 539, 831, 915.

1-16 Formylation with Zinc Cyanide and HCl. The Gatterman Reaction Formylation or Formyl-de-hydrogenation



Formylation with $\text{Zn}(\text{CN})_2$ and HCl is called the *Gatterman reaction*.²⁹¹ It can be applied to alkylbenzenes, phenols and their ethers, and many heterocyclic compounds. However, it cannot be applied to aromatic amines. In the original version of this reaction the substrate was treated with HCN, HCl, and ZnCl_2 , but the use of $\text{Zn}(\text{CN})_2$ and HCl (HCN and ZnCl_2 are generated in situ) makes the reaction more convenient to carry out and does not reduce yields. The mechanism of the Gatterman reaction has not been investigated very much, but there is an initial nitrogen-containing product that is normally not isolated but is hydrolyzed to aldehyde. The above structure is presumed for this product. When benzene was treated with NaCN under super acidic conditions ($\text{F}_3\text{CSO}_2\text{OH}-\text{SbF}_5$), a good yield of product was obtained, leading to the conclusion that the electrophile in this case was $\text{HC}^+=\text{NH}_2^+$.²⁹² The Gatterman reaction may be regarded as a special case of 1-27.

²⁸⁶For a review of dimethylformamide, see Pizey, Ref. 199, vol. 1, 1974, pp. 1-99.

²⁸⁷For a review of such species, see Kantelehnner Adv. Org. Chem. 1979, 9, pt. 2, 5-172.

²⁸⁸See Arnold; Holý Collect. Czech. Chem. Commun. 1962, 27, 2886; Martin; Martin Bull. Soc. Chim. Fr. 1963, 1637; Fritz; Oehl Liebigs Ann. Chem. 1971, 749, 159; Jugie; Smith; Martin J. Chem. Soc., Perkin Trans. 2 1975, 925.

²⁸⁹Alunni; Linda; Marino; Santini; Savelli J. Chem. Soc., Perkin Trans. 2 1972, 2070.

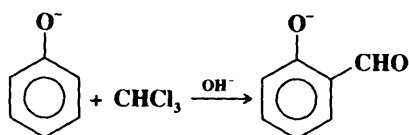
²⁹⁰Martínez; Alvarez; Barcina; Cerero; Vilar; Fraile; Hanack; Subramanian J. Chem. Soc., Chem. Commun. 1990, 1571.

²⁹¹For a review, see Truce Org. React. 1957, 9, 37-72.

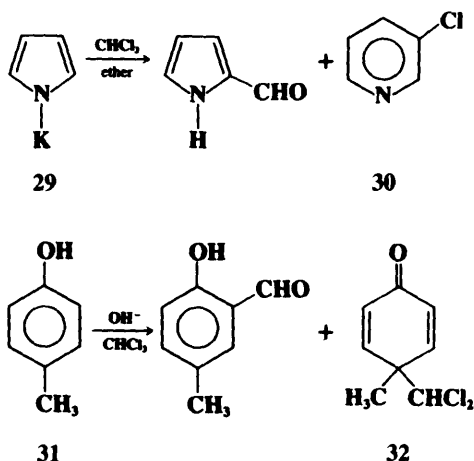
²⁹²Yato; Ohwada; Shudo J. Am. Chem. Soc. 1991, 113, 691.

Another method, formylation with CO and HCl in the presence of AlCl_3 and CuCl ²⁹³ (the *Gatterman-Koch reaction*), is limited to benzene and alkylbenzenes.²⁹⁴
OS II, 583; III, 549.

1-17 Formylation with Chloroform. The Reimer-Tiemann Reaction
Formylation or Formyl-de-hydrogenation



In the *Reimer-Tiemann reaction* chloroform and hydroxide ion are used to formylate aromatic rings.²⁹⁵ The method is useful only for phenols and certain heterocyclic compounds such as pyrroles and indoles. Unlike the previous formylation methods (1-15 and 1-16), this one is conducted in basic solution. Yields are generally low, seldom rising above 50%.²⁹⁶ The incoming group is directed ortho, unless both ortho positions are filled, in which case the attack is para.²⁹⁷ Certain substrates have been shown to give abnormal products instead of or in addition to the normal ones. For example, **29** and **31** gave, respectively, **30** and **32** as well as the normal aldehyde products. From the nature of the reagents and from the kind



of abnormal products obtained, it is clear that the attacking entity in this reaction is dichlorocarbene CCl_2 .²⁹⁸ This is known to be produced by treatment of chloroform with bases (p. 371); it is an electrophilic reagent and is known to give ring expansion of aromatic rings

²⁹³The CuCl is not always necessary: see Toniolo; Graziani *J. Organomet. Chem.* **1980**, 194, 221.

²⁹⁴For a review, see Crounse *Org. React.* **1949**, 5, 290-300.

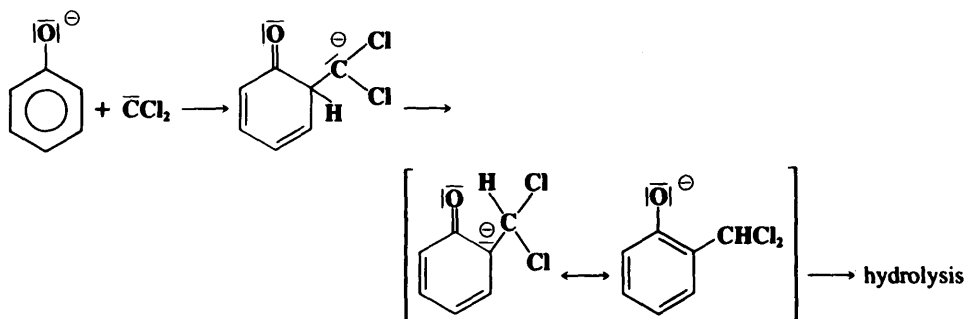
²⁹⁵For a review, see Wynberg; Meijer *Org. React.* **1982**, 28, 1-36.

²⁹⁶For improved procedures, see Thøer; Denis; Delmas; Gaset *Synth. Commun.* **1988**, 18, 2095; Cochran; Melville *Synth. Commun.* **1990**, 20, 609.

²⁹⁷Increased para selectivity has been achieved by the use of polyethylene glycol: Neumann; Sasson *Synthesis* **1986**, 569.

²⁹⁸For a review of carbene methods for introducing formyl and acyl groups into organic molecules, see Kulinkovich *Russ. Chem. Rev.* **1989**, 58, 711-719.

(see 5-50), accounting for products like **30**. The mechanism of the normal reaction is thus something like this.²⁹⁹



The formation of **32** in the case of **31** can be explained by attack of some of the CCl_2 ipso to the CH_3 group. Since this position does not contain a hydrogen, normal proton loss cannot take place and the reaction ends when the CCl_2^- moiety acquires a proton.

A method closely related to the Reimer-Tiemann reaction is the *Duff reaction*, in which hexamethylenetetramine $(\text{CH}_2)_6\text{N}_4$ is used instead of chloroform. This reaction can be applied only to phenols and amines; ortho substitution is generally observed and yields are low. A mechanism³⁰⁰ has been proposed that involves initial aminoalkylation(**1-25**) to give ArCH_2NH_2 , followed by dehydrogenation to $\text{ArCH}=\text{NH}$ and hydrolysis of this to the aldehyde product. When $(\text{CH}_2)_6\text{N}_4$ is used in conjunction with F_3CCOOH , the reaction can be applied to simple alkylbenzenes; yields are much higher and a high degree of regioselectively para substitution is found.³⁰¹ In this case too an imine seems to be an intermediate.

OS III, 463; IV, 866

1-18 Other Formylations

Formylation or Formyl-de-hydrogenation



Besides **1-15** to **1-17**, several other formylation methods are known.³⁰² In one of these, dichloromethyl methyl ether formylates aromatic rings with Friedel-Crafts catalysts.³⁰³ ArCHClOMe is probably an intermediate. Orthoformates have also been used.³⁰⁴ In another method, aromatic rings are formylated with formyl fluoride HCOF and BF_3 .³⁰⁵ Unlike formyl chloride, formyl fluoride is stable enough for this purpose. This reaction was successful for benzene, alkylbenzenes, PhCl , PhBr , and naphthalene. Phenols can be regioselectively formylated in the ortho position in high yields by treatment with two equivalents of para-formaldehyde in aprotic solvents in the presence of SnCl_4 and a tertiary amine.³⁰⁶ Phenols

²⁹⁹Robinson *J. Chem. Soc.* **1961**, 1663; Hine; van der Veen *J. Am. Chem. Soc.* **1959**, *81*, 6446. See also Langlois *Tetrahedron Lett.* **1991**, 32, 3691.

³⁰⁰Ogata; Kawasaki; Sugiura *Tetrahedron* **1968**, *24*, 5001.

³⁰¹Smith *J. Org. Chem.* **1972**, *37*, 3972.

³⁰²For methods other than those described here, see Smith; Manas *Synthesis* **1984**, 166; Olah; Laali; Farooq *J. Org. Chem.* **1985**, *50*, 1483; Nishino; Tsunoda; Kurosawa *Bull. Chem. Soc. Jpn.* **1989**, *62*, 545.

³⁰³Rieche; Gross; Höft *Chem. Ber.* **1960**, *93*, 88; Lewin; Parker; Fleming; Carroll *Org. Prep. Preced. Int.* **1978**, *10*, 201.

³⁰⁴Gross; Rieche; Matthey *Chem. Ber.* **1963**, *96*, 308.

³⁰⁵Olah; Kuhn *J. Am. Chem. Soc.* **1960**, *82*, 2380.

³⁰⁶Casiraghi; Casnati; Puglia; Sartori; Terenghi *J. Chem. Soc., Perkin Trans. I* **1980**, 1862.

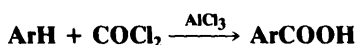
have also been formylated indirectly with 2-ethoxy-1,3-dithiolane.³⁰⁷ See also the indirect method mentioned at 1-26.

OS V, 49; VII, 162.

Reactions 1-19 and 1-20 are direct carboxylations³⁰⁸ of aromatic rings.³⁰⁹

1-19 Carboxylation with Carbonyl Halides

Carboxylation or Carboxy-de-hydrogenation

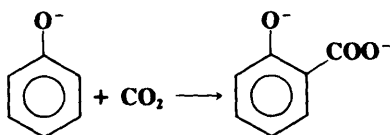


Phosgene, in the presence of Friedel–Crafts catalysts, can carboxylate the ring. This process is analogous to 1-14, but the ArCOCl initially produced hydrolyzes to the carboxylic acid. However, in most cases the reaction does not take this course, but instead the ArCOCl attacks another ring to give a ketone ArCOAr . A number of other reagents have been used to get around this difficulty, among them oxalyl chloride, urea hydrochloride, chloral Cl_3CCHO ,³¹⁰ carbamoyl chloride H_2NCOCl , and N,N -diethylcarbamoyl chloride.³¹¹ With carbamoyl chloride the reaction is called the *Gatterman amide synthesis* and the product is an amide. Among compounds carboxylated by one or another of these reagents are benzene, alkylbenzenes, and fused ring systems.³¹²

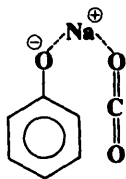
OS V, 706; VII, 420.

1-20 Carboxylation with Carbon Dioxide. The Kolbe–Schmitt Reaction

Carboxylation or Carboxy-de-hydrogenation



Sodium phenoxides can be carboxylated, mostly in the ortho position, by carbon dioxide (*the Kolbe–Schmitt reaction*). The mechanism is not clearly understood, but apparently some kind of a complex is formed between the reactants,³¹³ making the carbon of the CO_2 more



³⁰⁷Jo; Tanimoto; Sugimoto; Okano *Bull. Chem. Soc. Jpn.* **1981**, 54, 2120.

³⁰⁸For other carboxylation methods, one of which leads to the anhydride, see Sakakibara; Odaira *J. Org. Chem.* **1976**, 41, 2049; Fujiwara; Kawata; Kawauchi; Taniguchi *J. Chem. Soc., Chem. Commun.* **1982**, 132.

³⁰⁹For a review, see Olah; Olah, in Olah, Ref. 261, vol. 3, 1964, pp. 1257-1273.

³¹⁰Menegheli; Rezende; Zucco *Synth. Commun.* **1987**, 17, 457.

³¹¹Naumov; Isakova; Kost; Zakharov; Zvolinskii; Moiseikina; Nikeryasova *J. Org. Chem. USSR* **1975**, 11, 362.

³¹²For the use of phosgene to carboxylate phenols, see Sartori; Casnati; Bigi; Bonini *Synthesis* **1988**, 763.

³¹³Hales; Jones; Lindsey *J. Chem. Soc.* **1954**, 3145.

positive and putting it in a good position to attack the ring. Potassium phenoxide, which is less likely to form such a complex,³¹⁴ is chiefly attacked in the para position.³¹⁵ Carbon tetrachloride can be used instead of CO₂ under Reimer-Tiemann (1-17) conditions.

Sodium or potassium phenoxide can be carboxylated regioselectively in the para position in high yield by treatment with sodium or potassium carbonate and carbon monoxide.³¹⁶ ¹⁴C labeling showed that it is the carbonate carbon that appears in the *p*-hydroxybenzoic acid product.³¹⁷ The CO is converted to sodium or potassium formate. Carbon monoxide has also been used to carboxylate aromatic rings with palladium compounds as catalysts.³¹⁸ In addition, a palladium-catalyzed reaction has been used directly to prepare acyl fluorides $\text{ArH} \rightarrow \text{ArCOF}$.³¹⁹

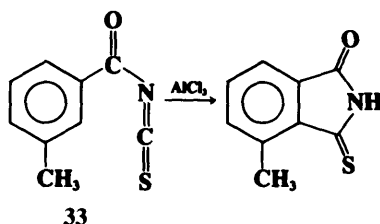
OS II, 557.

1-21 Amidation with Isocyanates

N-Alkylcarbamoyl-de-hydrogenation



N-Substituted amides can be prepared by direct attack of isocyanates on aromatic rings.³²⁰ *R* may be alkyl or aryl, but if the latter, dimers and trimers are also obtained. Isothiocyanates similarly give thioamides.³²¹ The reaction has been carried out intramolecularly both with aralkyl isothiocyanates and acyl isothiocyanates.³²² In the latter case, the product is easily hydrolyzable to a dicarboxylic acid; this is a way of putting a carboxyl group on a ring ortho



to one already there (**33** is prepared by treatment of the acyl halide with lead thiocyanate). The reaction gives better yields with substrates of the type $\text{ArCH}_2\text{CONCS}$, where six-membered rings are formed. Ethyl carbamate NH_2COOEt (with P_2O_5 in xylene)³²³ and biscarbamoyl diselenides $\text{R}_2\text{NCOSeSeCONR}_2$ ³²⁴ (with HgBr_2 or SnCl_4) have also been used to amidate aromatic rings.

OS V, 1051; VI, 465.

³¹⁴There is evidence that, in the complex formed from potassium salts, the bonding is between the aromatic compound and the carbon atom of CO₂: Hirao; Kito *Bull. Chem. Soc. Jpn.* **1973**, 46, 3470.

³¹⁵Actually, the reaction seems to be more complicated than this. At least part of the potassium *p*-hydroxybenzoate that forms comes from a rearrangement of initially formed potassium salicylate. Sodium salicylate does not rearrange. See Shine, Ref. 375, pp. 344-348. See also Ota *Bull. Chem. Soc. Jpn.* **1974**, 47, 2343.

³¹⁶Yasuhara; Nogi *J. Org. Chem.* **1968**, 33, 4512, *Chem. Ind. (London)* **1967**, 229, **1969**, 77.

³¹⁷Yasuhara; Nogi; Saishō *Bull. Chem. Soc. Jpn.* **1969**, 42, 2070.

³¹⁸See Sakakibara; Odaira, Ref. 308; Jintoku; Taniguchi; Fujiwara *Chem. Lett.* **1987**, 1159; Ugo; Chiesa *J. Chem. Soc., Perkin Trans. I* **1987**, 2625.

³¹⁹Sakakura; Chaisupakitsin; Hayashi; Tanaka *J. Organomet. Chem.* **1987**, 334, 205.

³²⁰Effenberger; Gleiter *Chem. Ber.* **1964**, 97, 472; Effenberger; Gleiter; Heider; Niess *Chem. Ber.* **1968**, 101, 502; Piccolo; Filippini; Tinucci; Valoti; Citterio *Tetrahedron* **1986**, 42, 885.

³²¹Jagodziński *Synthesis* **1988**, 717.

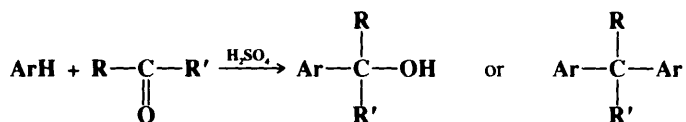
³²²Smith; Kan *J. Am. Chem. Soc.* **1960**, 82, 4753, *J. Org. Chem.* **1964**, 29, 2261.

³²³Chakraborty; Mandal; Roy *Synthesis* **1981**, 977.

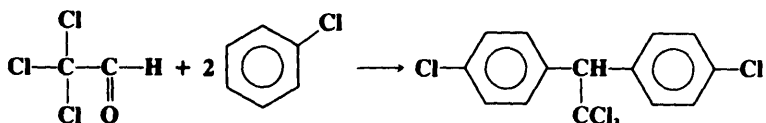
³²⁴Fujiwara; Ogawa; Kambe; Ryu; Sonoda *Tetrahedron Lett.* **1988**, 29, 6121.

Reactions 1-22 to 1-26 involve the introduction of a CH_2Z group, where Z is halogen, hydroxyl, amino, or alkylthio. They are all Friedel–Crafts reactions of aldehydes and ketones and, with respect to the carbonyl compound, additions to the $\text{C}=\text{O}$ double bond. They follow mechanisms discussed in Chapter 16.

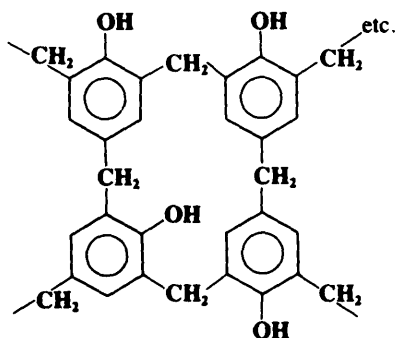
1-22 Hydroxyalkylation or Hydroxyalkyl-de-hydrogenation



The condensation of aromatic rings with aldehydes or ketones is called *hydroxyalkylation*.³²⁵ The reaction can be used to prepare alcohols,³²⁶ though more often the alcohol initially produced reacts with another molecule of aromatic compound (1-12) to give diarylation. For this the reaction is quite useful, an example being the preparation of DDT:



The diarylation reaction is especially common with phenols (the diaryl product here is called a *bisphenol*). The reaction is normally carried out in alkaline solution on the phenolate ion.³²⁷ The hydroxymethylation of phenols with formaldehyde is called the *Lederer–Manasse reaction*. This reaction must be carefully controlled,³²⁸ since it is possible for the para and both ortho positions to be substituted and for each of these to be rearylated, so that a polymeric structure is produced:



However, such polymers, which are of the Bakelite type (phenol–formaldehyde resins), are of considerable commercial importance.

The attacking species is the carbocation, $\text{R}-\overset{\oplus}{\text{C}}-\text{R}'$, formed from the aldehyde or ketone



and the acid catalyst, except when the reaction is carried out in basic solution

³²⁵For a review, see Hofmann; Schriesheim, in Olah, Ref. 261, vol. 2, pp. 597-640.

³²⁶See, for example, Casiraghi; Casnati; Puglia; Sartori *Synthesis* **1980**, 124.

³²⁷For a review, see Schnell; Krimm *Angew. Chem. Int. Ed. Engl.* **1963**, 2, 373-379 [*Angew. Chem.* 75, 662-668].

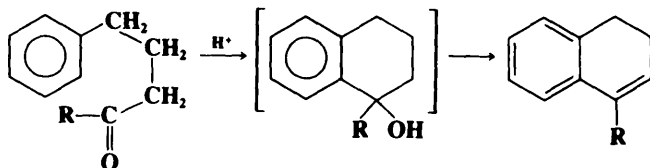
³²⁸See, for example, Casiraghi; Casnati; Pochini; Puglia; Ungaro; Sartori *Synthesis* **1981**, 143.

When an aromatic ring is treated with diethyl oxomalonate $(\text{EtOOC})_2\text{C}=\text{O}$, the product is an arylmalonic acid derivative $\text{ArC}(\text{OH})(\text{COOEt})_2$, which can be converted to an arylmalonic acid $\text{ArCH}(\text{COOEt})_2$.³²⁹ This is therefore a way of applying the malonic ester synthesis (**0-94**) to an aryl group (see also **3-14**). Of course, the opposite mechanism applies here: the aryl species is the nucleophile.

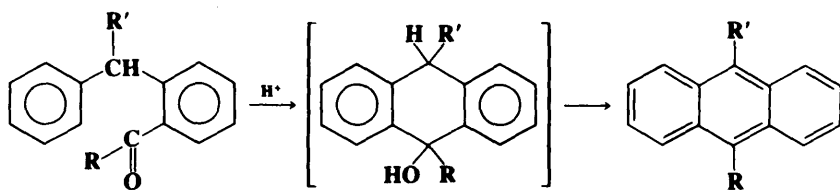
Two methods, both involving boron-containing reagents, have been devised for the regioselective ortho hydroxymethylation of phenols or aromatic amines.³³⁰

OS **III**, 326; **V**, 422; **VI**, 471, 856; **68**, 234, 238, 243. Also see OS **I**, 214.

1-23 Cyclodehydration of Aldehydes and Ketones

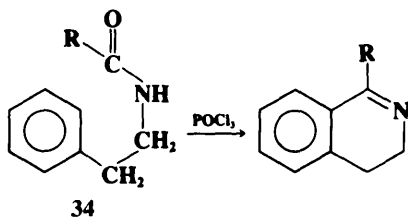


When an aromatic compound contains an aldehyde or ketone function in a position suitable for closing a six-membered ring, treatment with acid results in cyclodehydration. The reaction is a special case of **1-22**, but in this case dehydration almost always takes place to give a double bond conjugated with the aromatic ring.³³¹ The method is very general and is widely used to close both carbocyclic and heterocyclic rings.³³² Polyphosphoric acid is a common reagent, but other acids have also been used. In a variation known as the *Bradsher reaction*,³³³



diarylmethanes containing a carbonyl group in the ortho position can be cyclized to anthracene derivatives. In this case 1,4-dehydration takes place, at least formally.

Among the many applications of cyclodehydration to the formation of heterocyclic systems is the *Bischler-Napieralski reaction*.³³⁴ In this reaction amides of the type **34** are cyclized with phosphorous oxychloride:



³²⁹Ghosh; Pardo; Salomon *J. Org. Chem.* **1982**, 47, 4692.

³³⁰Sugasawa; Toyoda; Adachi; Sasakura *J. Am. Chem. Soc.* **1978**, 100, 4842; Nagata; Okada; Aoki *Synthesis* **1979**, 365.

³³¹For examples where the hydroxy compound was the principal product (with $\text{R} = \text{CF}_3$), see Fung; Abraham; Bellini; Sestan *Can. J. Chem.* **1983**, 61, 368; Bonnet-Delpon; Charpentier-Morize; Jacquot *J. Org. Chem.* **1988**, 53, 759.

³³²For a review, see Bradsher *Chem. Rev.* **1987**, 87, 1277-1297.

³³³For examples, see Bradsher *J. Am. Chem. Soc.* **1940**, 62, 486; Saraf; Vingiello *Synthesis* **1970**, 655; Ref. 332, pp. 1287-1294.

³³⁴For a review of the mechanism, see Fodor; Nagubandi *Tetrahedron* **1980**, 36, 1279-1300.

If the starting compound contains a hydroxyl group in the α position, an additional dehydration takes place and the product is an isoquinoline. Higher yields can be obtained if the amide is treated with PCl_5 to give an imino chloride $\text{ArCH}_2\text{CH}_2\text{N}=\text{CR}-\text{Cl}$, which is isolated and then cyclized by heating.³³⁵ The nitrilium ion $\text{ArCH}_2\text{CH}_2\text{N}^+\equiv\text{CR}$ is an intermediate.

OS I, 360, 478; II, 62, 194; III, 281, 300, 329, 568, 580, 581; IV, 590; V, 550; VI, 1. Also see OS I, 54.

1-24 Haloalkylation or Haloalkyl-de-hydrogenation



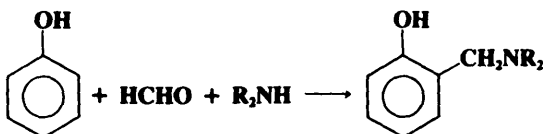
When certain aromatic compounds are treated with formaldehyde and HCl, the CH_2Cl group is introduced into the ring in a reaction called *chloromethylation*. The reaction has also been carried out with other aldehydes and with HBr and HI. The more general term *haloalkylation* covers these cases.³³⁶ The reaction is successful for benzene, and alkyl-, alkoxy-, and halobenzenes. It is greatly hindered by meta-directing groups, which reduce yields or completely prevent the reactions. Amines and phenols are too reactive and usually give polymers unless deactivating groups are also present, but phenolic ethers and esters successfully undergo the reaction. Compounds of lesser reactivity can often be chloromethylated with chloromethyl methyl ether ClCH_2OMe , bis(chloromethyl) ether $(\text{ClCH}_2)_2\text{O}$,³³⁷ methoxyacetyl chloride $\text{MeOCH}_2\text{COCl}$,³³⁸ or 1-chloro-4-(chloromethoxy)butane.³³⁹ Zinc chloride is the most common catalyst, but other Friedel-Crafts catalysts are also employed. As with reaction 1-22 and for the same reason, an important side product is the diaryl compound Ar_2CH_2 (from formaldehyde).

Apparently, the initial step involves reaction of the aromatic compound with the aldehyde to form the hydroxyalkyl compound, exactly as in 1-22, and then the HCl converts this to the chloroalkyl compound.³⁴⁰ The acceleration of the reaction by ZnCl_2 has been attributed³⁴¹ to the raising of the acidity of the medium, causing an increase in the concentration of HOCH_2^+ ions.

OS III, 195, 197, 468, 557; IV, 980.

1-25 Aminoalkylation and Amidoalkylation

Dialkylaminoalkylation or Dialkylamino-de-hydrogenation



Phenols, secondary and tertiary aromatic amines,³⁴² pyrroles, and indoles can be amino-methylated by treatment with formaldehyde and a secondary amine. Other aldehydes have

³³⁵Fodor; Gal; Phillips *Angew. Chem. Int. Ed. Engl.* **1972**, 11, 919 [*Angew. Chem.* 84, 947].

³³⁶For reviews, see Belen'kii; Vol'kenshtein; Karmanova *Russ. Chem. Rev.* **1977**, 46, 891-903; Olah; Tolgyesi, in Olah, Ref. 261, vol. 2, pp. 659-784.

³³⁷Suzuki *Bull. Chem. Soc. Jpn.* **1970**, 43, 3299; Kuimova; Mikhailov *J. Org. Chem. USSR* **1971**, 7, 1485.

³³⁸McKillop; Madjdabadi; Long *Tetrahedron Lett.* **1983**, 24, 1933.

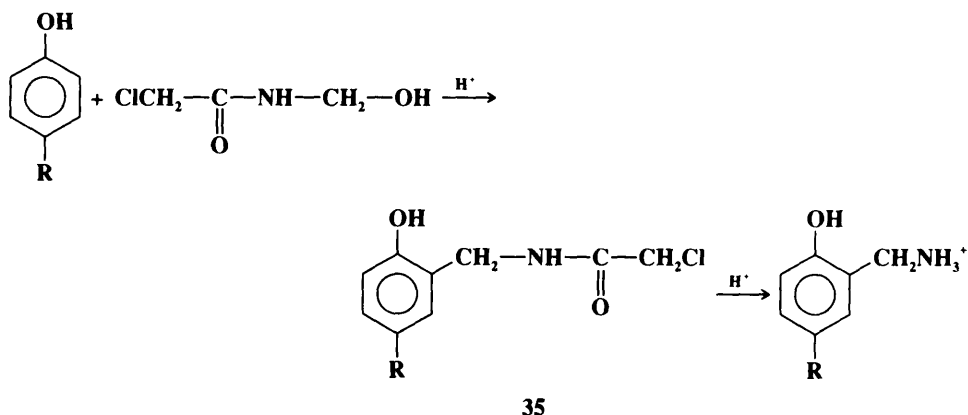
³³⁹Olah; Beal; Olah *J. Org. Chem.* **1976**, 41, 1627.

³⁴⁰Ziegler; Hontschik; Milowiz *Monatsh. Chem.* **1948**, 79, 142; Ogata; Okano *J. Am. Chem. Soc.* **1956**, 78, 5423. See also Olah; Yu *J. Am. Chem. Soc.* **1975**, 97, 2293.

³⁴¹Lyushin; Mekhtiev; Guseinova *J. Org. Chem. USSR* **1970**, 6, 1445.

³⁴²Miocque; Vierfond *Bull. Soc. Chim. Fr.* **1970**, 1896, 1901, 1907.

sometimes been employed. Aminoalkylation is a special case of the Mannich reaction (6-16). When phenols and other activated aromatic compounds are treated with N-hydroxymethylchloroacetamide, *amidomethylation* takes place³⁴³ to give **35**, which is often hydro-

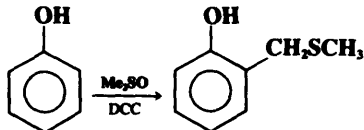


lyzed in situ to the aminoalkylated product. Other N-hydroxyalkyl and N-chlorinated compounds have also been used.³⁴³

OS I, 381; IV, 626; V, 434; VI, 965; VII, 162.

1-26 Thioalkylation

Alkylthioalkylation or Alkylthioalkyl-de-hydrogenation



A methylthiomethyl group can be inserted into the ortho position of phenols by heating with dimethyl sulfoxide and dicyclohexylcarbodiimide (DCC).³⁴⁴ Other reagents can be used instead of DCC, among them pyridine-SO₃,³⁴⁵ SOCl₂,³⁴⁶ and acetic anhydride.³⁴⁷ Alternatively, the phenol can be treated with dimethyl sulfide and N-chlorosuccinimide, followed by triethylamine.³⁴⁸ The reaction can be applied to amines (to give *o*-NH₂C₆H₄CH₂SMe) by treatment with *t*-BuOCl, Me₂S, and NaOMe in CH₂Cl₂.³⁴⁹ It is possible to convert the CH₂SMe group to the CHO group,³⁵⁰ so that this becomes an indirect method for the preparation of ortho-amino and ortho-hydroxy aromatic aldehydes; or to the CH₃ group (with Raney nickel—reaction 4-36), which makes this an indirect method³⁵¹ for the intro-

³⁴³For a review, see Zaugg *Synthesis* **1984**, 85-110.

³⁴⁴Burdon; Moffatt *J. Am. Chem. Soc.* **1966**, 88, 5855, **1967**, 89, 4725; Olofson; Marino *Tetrahedron* **1971**, 27, 4195.

³⁴⁵Claus *Monatsh. Chem.* **1971**, 102, 913.

³⁴⁶Sato; Inoue; Ozawa; Tazaki *J. Chem. Soc., Perkin Trans. 1* **1984**, 2715.

³⁴⁷Hayashi; Oda *J. Org. Chem.* **1967**, 32, 457; Pettit; Brown *Can. J. Chem.* **1967**, 45, 1306; Claus *Monatsh. Chem.* **1968**, 99, 1034.

³⁴⁸Gassman; Amick *J. Am. Chem. Soc.* **1978**, 100, 7611.

³⁴⁹Gassman; Gruetzmacher *J. Am. Chem. Soc.* **1973**, 95, 588; Gassman; van Bergen *J. Am. Chem. Soc.* **1973**, 95, 590, 591.

³⁵⁰Gassman; Drewes *J. Am. Chem. Soc.* **1978**, 100, 7600; Ref. 348.

³⁵¹For another indirect method, in this case for alkylation ortho to an amino group, see Gassman; Parton *Tetrahedron Lett.* **1977**, 2055.

duction of a CH_3 group ortho to an OH or NH_2 group.³⁴⁹ Aromatic hydrocarbons have been thioalkylated with ethyl α -(chloromethylthio)acetate $\text{ClCH}_2\text{SCH}_2\text{COOEt}$ (to give $\text{ArCH}_2\text{SCH}_2\text{COOEt}$)³⁵² and with methyl methylsulfynylmethyl sulfide $\text{MeSCH}_2\text{SOMe}$ or methylthiomethyl *p*-tolyl sulfone $\text{MeSCH}_2\text{SO}_2\text{C}_6\text{H}_4\text{Me}$ (to give ArCH_2SMe),³⁵³ in each case with a Lewis acid catalyst.

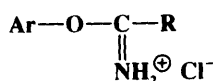
OS VI, 581, 601.

1-27 Acylation with Nitriles. The Hoesch Reaction

Acylation or Acyl-de-hydrogenation



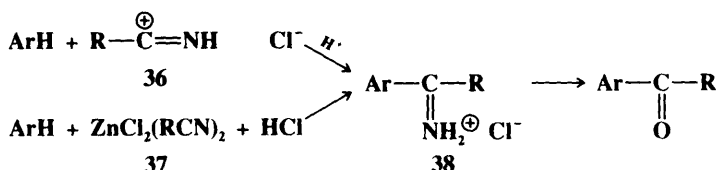
Friedel-Crafts acylation with nitriles and HCl is called the *Hoesch* or the *Houben-Hoesch reaction*.³⁵⁴ In most cases, a Lewis acid is necessary; zinc chloride is the most common. The reaction is generally useful only with phenols, phenolic ethers, and some reactive heterocyclic compounds, e.g., pyrrole, but it can be extended to aromatic amines by the use of BCl_3 .³⁵⁵ Acylation in the case of amines is regioselectively ortho. Monohydric phenols, however, generally do not give ketones³⁵⁶ but are attacked at the oxygen to produce imino esters.



An imino ester

Many nitriles have been used. Even aryl nitriles give good yields if they are first treated with HCl and ZnCl_2 and then the substrate added at 0°C .³⁵⁷ In fact, this procedure increases yields with any nitrile. If thiocyanates RSCN are used, thiol esters ArCOSR can be obtained. The Gatterman reaction (1-16) is a special case of the Hoesch synthesis.

The reaction mechanism is complex and not completely settled.³⁵⁸ The first stage consists of an attack on the substrate by a species containing the nitrile and HCl (and the Lewis acid, if present) to give an imine salt (38). Among the possible attacking species are 36 and 37. In the second stage, the salts are hydrolyzed to the products:



Ketones can also be obtained by treating phenols or phenolic ethers with a nitrile in the presence of $\text{F}_3\text{CSO}_2\text{OH}$.³⁵⁹ The mechanism in this case is different.

OS II, 522.

³⁵²Tamura; Tsugoshi; Annoura; Ishibashi *Synthesis* **1984**, 326.

³⁵³Torisawa; Satoh; Ikegami *Tetrahedron Lett.* **1988**, 29, 1729.

³⁵⁴For a review, see Ruske, in Olah, Ref. 261, vol. 3, 1964, pp. 383-497.

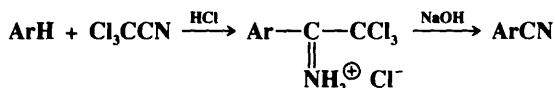
³⁵⁵Sugasawa et al., Ref. 330; Sugasawa; Adachi; Sasakura; Kitagawa *J. Org. Chem.* **1979**, 44, 578.

³⁵⁶For an exception, see Toyoda; Sasakura; Sugasawa *J. Org. Chem.* **1981**, 46, 189.

³⁵⁷Zil'berman; Rybakova *J. Gen. Chem. USSR* **1960**, 30, 1972.

³⁵⁸For discussions, see Ref. 354 and Jeffery; Satchell *J. Chem. Soc. B.* **1966**, 579.

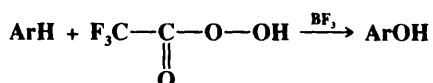
³⁵⁹Booth; Noori *J. Chem. Soc., Perkin Trans. I* **1980**, 2894; Amer; Booth; Noori; Proença *J. Chem. Soc., Perkin Trans. I* **1983**, 1075.

1-28 Cyanation or Cyano-de-hydrogenation

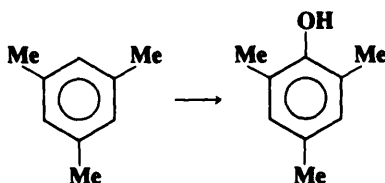
Aromatic hydrocarbons (including benzene), phenols, and phenolic ethers can be cyanated with trichloroacetonitrile, BrCN, or mercury fulminate $\text{Hg}(\text{ONC})_2$.³⁶⁰ In the case of Cl_3CCN , the actual attacking entity is probably $\text{Cl}_3\text{C}-\overset{+}{\text{C}}=\text{NH}$, formed by addition of a proton to the cyano nitrogen. Secondary aromatic amines ArNHR , as well as phenols, can be cyanated in the ortho position with Cl_3CCN and BCl_3 .³⁶¹

OS III, 293.

F. Oxygen Electrophiles Oxygen electrophiles are very uncommon, since oxygen does not bear a positive charge very well. However, there is one reaction that can be mentioned.

1-29 Hydroxylation or Hydroxy-de-hydrogenation

There have been only a few reports of direct hydroxylation³⁶² by an electrophilic process (see, however, 2-26 and 4-5).³⁶³ In general, poor results are obtained, partly because the introduction of an OH group activates the ring to further attack. Quinone formation is common. However, alkyl-substituted benzenes such as mesitylene or durene can be hydroxylated in good yield with trifluoroperacetic acid and boron trifluoride.³⁶⁴ In the case of mesitylene, the product is not subject to further attack:



In a related procedure, even benzene and substituted benzenes (e.g., PhMe; PhCl; xylenes) can be converted to phenols in good yields with sodium perborate- $\text{F}_3\text{CSO}_2\text{OH}$.³⁶⁵ Low to moderate yields of phenols can be obtained by treatment of simple alkylbenzenes with H_2O_2

³⁶⁰Olah, in Olah, Ref. 225, vol. 1, 1963, pp. 119-120.

³⁶¹Adachi; Sugawara *Synth. Commun.* **1990**, 20, 71.

³⁶²For a list of hydroxylation reagents, with references, see Larock, Ref. 171, pp. 485-486.

³⁶³For reviews of electrophilic hydroxylation, see Jacquesy; Gesson; Jouannetaud *Rev. Chem. Intermed.* **1988**, 9, 1-26, pp. 5-10; Haines *Methods for the Oxidation of Organic Compounds*; Academic Press: New York, 1985, pp. 173-176, 347-350.

³⁶⁴Hart; Buchler *J. Org. Chem.* **1964**, 29, 2397. See also Hart *Acc. Chem. Res.* **1971**, 4, 337-343.

³⁶⁵Prakash; Krass; Wang; Olah *Synlett* **1991**, 39.