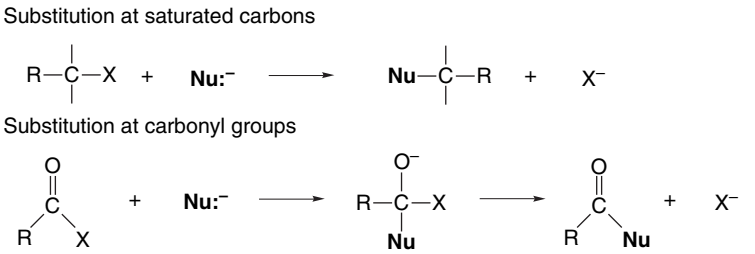
# 3

# Functional Group Interconversion by Substitution, Including Protection and Deprotection

## Introduction

Chapters 1 and 2 dealt with formation of new carbon-carbon bonds by reactions in which one carbon acts as the nucleophile and another as the electrophile. In this chapter we turn our attention to noncarbon nucleophiles. Nucleophilic substitution is used in a variety of interconversions of functional groups. We discuss substitution at both $sp^3$ carbon and carbonyl groups. Substitution at saturated carbon usually involves the $S_N2$ mechanism, whereas substitution at carbonyl groups usually occurs by addition-elimination.



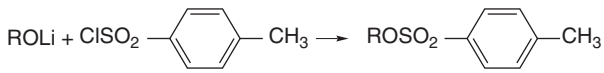

The mechanistic aspects of nucleophilic substitutions at saturated carbon and carbonyl centers were considered in Part A, Chapters 4 and 7, respectively. In this chapter we discuss some of the important synthetic transformations that involve these types of

reactions. Section 3.1 considers conversion of alcohols to reactive alkylating agents and Section 3.2 discusses the use of $S_N2$ reactions for various functional group transformations. Substitution reactions can also be used to *break* bonds for synthetic purposes, and Section 3.3 deals with cleavage of C−O bonds in ethers and esters by $S_N2$ and $S_N1$ reactions. The carbonyl substitution reactions that interconvert the acyl halides, acid anhydrides, esters, and carboxamides are discussed in Section 3.4. Often, manipulation of protecting groups also involves nucleophilic substitution and carbonyl exchange reactions. We discuss protection and deprotection of the most common functional groups in Section 3.5.

## 3.1. Conversion of Alcohols to Alkylating Agents

### 3.1.1. Sulfonate Esters

Alcohols are a very important compounds for synthesis. However, because the hydroxide ion is a very poor leaving group, alcohols are not reactive as alkylating agents. They can be activated to substitution by O-protonation, but the acidity that is required is incompatible with most nucleophiles except those, such as the halides, that are anions of strong acids. The preparation of sulfonate esters from alcohols is an effective way of installing a reactive leaving group on an alkyl chain. The reaction is very general and complications arise only if the resulting sulfonate ester is sufficiently reactive to require special precautions. *p*-Toluenesulfonate (*tosylate*) and methanesulfonate (*mesylate*) esters are used most frequently for preparative work, but the very reactive trifluoromethanesulfonates (*triflates*) are useful when an especially good leaving group is required. The usual method for introducing tosyl or mesyl groups is to allow the alcohol to react with the sulfonyl chloride in pyridine at 0°–25° C.[1] An alternative method is to convert the alcohol to a lithium salt, which is then allowed to react with the sulfonyl chloride.[2]



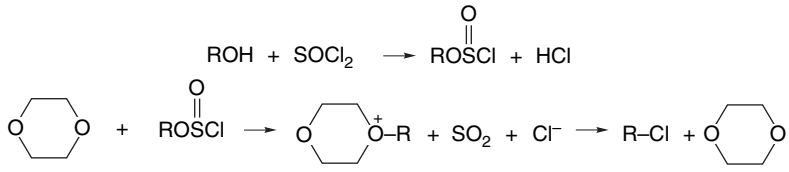

Trifluoromethanesulfonates of alkyl and allylic alcohols can be prepared by reaction with trifluoromethanesulfonic anhydride in halogenated solvents in the presence of pyridine.[3] Since the preparation of sulfonate esters does not disturb the C−O bond, problems of rearrangement or racemization do not arise in the ester formation step. However, sensitive sulfonate esters, such as allylic systems, may be subject to reversible ionization reactions, so appropriate precautions must be taken to ensure structural and stereochemical integrity. Tertiary alkyl sulfonates are neither as easily prepared nor as stable as those from primary and secondary alcohols. Under the standard preparative conditions, tertiary alcohols are likely to be converted to the corresponding alkene.

[1] R. S. Tipson, *J. Org. Chem.*, **9**, 235 (1944); G. W. Kabalka, M. Varma, R. S. Varma, P. C. Srivastava, and F. F. Knapp, Jr., *J. Org. Chem.*, **51**, 2386 (1986).
[2] H. C. Brown, R. Bernheimer, C. J. Kim, and S. E. Scheppele, *J. Am. Chem. Soc.*, **89**, 370 (1967).
[3] C. D. Beard, K. Baum, and V. Grakauskas, *J. Org. Chem.*, **38**, 3673 (1973).

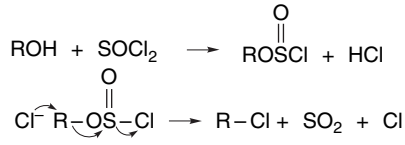
### 3.1.2. Halides

The prominent role of alkyl halides in the formation of carbon-carbon bonds by enolate alkylation was evident in Chapter 1. The most common precursors for alkyl halides are the corresponding alcohols and a variety of procedures have been developed for this transformation. The choice of an appropriate reagent is usually dictated by the sensitivity of the alcohol and any other functional groups present in the molecule. In some cases, the hydrogen halides can be used. Unsubstituted primary alcohols can be converted to bromides with hot concentrated hydrobromic acid.[4] Alkyl chlorides can be prepared by reaction of primary alcohols with hydrochloric acid–zinc chloride.[5] Owing to the harsh conditions, these procedures are only applicable to very acid-stable molecules. These reactions proceed by the $S_N2$ mechanism and elimination, and rearrangements are not a problem for primary alcohols. Reactions of hydrogen halides with tertiary alcohols proceed by the $S_N1$ mechanism, so these reactions are preparatively useful only when the carbocation intermediate is unlikely to give rise to rearranged product.[6] In general, these methods are suitable only for simple, unfunctionalized alcohols.

Another general method for converting alcohols to halides involves reactions with halides of certain nonmetallic elements. Thionyl chloride, phosphorus trichloride, and phosphorus tribromide are the most common examples of this group of reagents. These reagents are suitable for alcohols that are neither acid sensitive nor prone to structural rearrangement. The reaction of alcohols with thionyl chloride initially results in the formation of a chlorosulfite ester. There are two mechanisms by which the chlorosulfite can be converted to a chloride. In aprotic nucleophilic solvents, such as dioxane, solvent participation can lead to overall retention of configuration.[7]

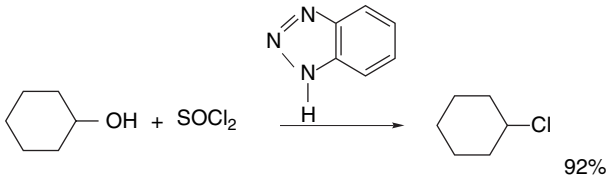



In the absence of solvent participation, chloride attack on the chlorosulfite ester leads to product with inversion of configuration.

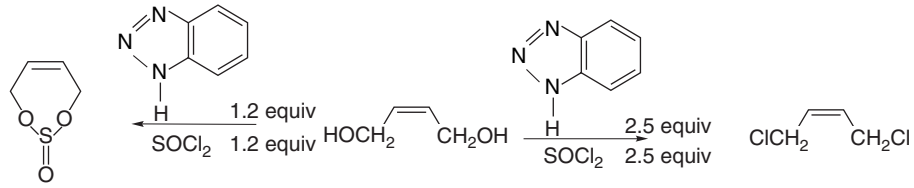



Primary and secondary alcohols are rapidly converted to chlorides by a 1:1 mixture of $SOCl_2$ and benzotriazole in an inert solvent such as $CH_2Cl_2$.[8]

4. E. E. Reid, J. R. Ruhoff, and R. E. Burnett, *Org. Synth.*, **II**, 246 (1943).
5. J. E. Copenhaver and A. M. Wharley, *Org. Synth.*, **I**, 142 (1941).
6. J. F. Norris and A. W. Olmsted, *Org. Synth.*, **I**, 144 (1941); H. C. Brown and M. H. Rei, *J. Org. Chem.*, **31**, 1090 (1966).
7. E. S. Lewis and C. E. Boozer, *J. Am. Chem. Soc.*, **74**, 308 (1952).
8. S. S. Chaudhari and K. G. Akamanchi, *Synlett*, 1763 (1999).

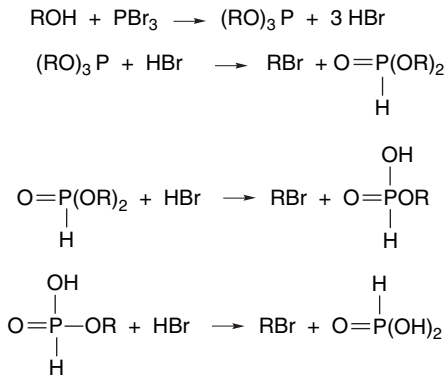



This reagent combination also converts carboxylic acids to acyl chlorides (see Section 3.4.1). The mechanistic basis for the special effectiveness of benzotriazole has not yet been determined, but it seems likely that nucleophilic catalysis is involved. Sulfinyl ester intermediates may be involved, because *Z*-2-butene-1,4-diol gives a cyclic sulfite ester with one equivalent of reagent but the dichloride with two equivalents.




Reaction with the hindered secondary alcohol menthol stops at the dialkyl sulfite ester. The examples reported do not establish the stereochemistry of the reaction.

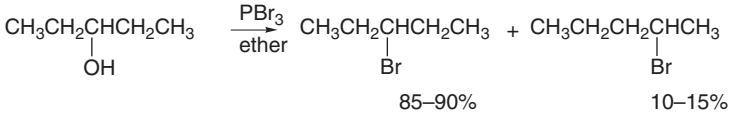
The mechanism for the reactions of alcohols with phosphorus halides can be illustrated using phosphorus tribromide. Initial reaction between the alcohol and phosphorus tribromide leads to a trialkyl phosphite ester by successive displacements of bromide. The reaction stops at this stage if it is run in the presence of an amine, which neutralizes the hydrogen bromide that is formed.[9] If the hydrogen bromide is not neutralized, the phosphite ester is protonated and each alkyl group is converted to the halide by nucleophilic substitution by bromide ion. The driving force for cleavage of the C−O bond is the formation of a strong phosphoryl double bond.



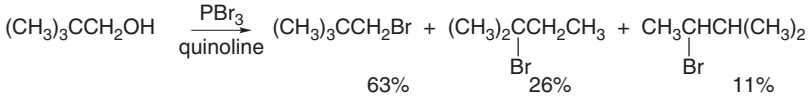

As C−Br bond formation occurs by back-side attack, inversion of the configuration at carbon is anticipated. However, both racemization and rearrangement are observed as competing processes.[10] For example, conversion of 2-butanol to 2-butyl bromide with $PBr_3$ is accompanied by 10–13% racemization and a small

[9] A. H. Ford-Moore and B. J. Perry, *Org. Synth.*, **IV**, 955 (1963).
[10] H. R. Hudson, *Synthesis*, 112 (1969).

amount of *t*-butyl bromide is also formed.[11] The extent of rearrangement increases with increasing chain length and branching.

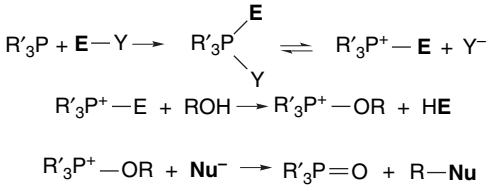



Ref. 12

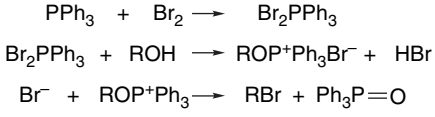



Ref. 13

Owing to the acidic conditions, these methods are limited to acid-stable molecules. Milder reagents are necessary for many functionally substituted alcohols. A very general and important method for activating alcohols toward nucleophiles is by converting them to *alkoxyphosphonium ions*.[14] The trivalent phosphorus reagents are activated by reaction with a halogen or related electrophile, and the alkoxyphosphonium ions are very reactive toward nucleophilic attack, with the driving force for substitution being formation of the strong phosphoryl bond.

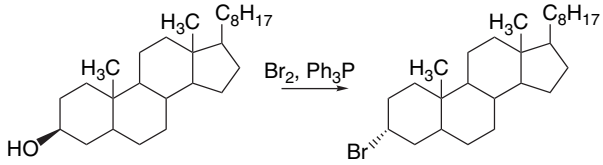



A variety of reagents can function as the electrophile $\mathbf{E}^+$ in the general mechanism. The most useful synthetic procedures for preparation of halides are based on the halogens, positive halogens sources, and diethyl azodicarboxylate. A 1:1 adduct formed from triphenylphosphine and bromine converts alcohols to bromides.[15] The alcohol displaces bromide ion from the pentavalent adduct, giving an alkoxyphosphonium intermediate. The phosphonium ion intermediate then undergoes nucleophilic attack by bromide ion, forming triphenylphosphine oxide.



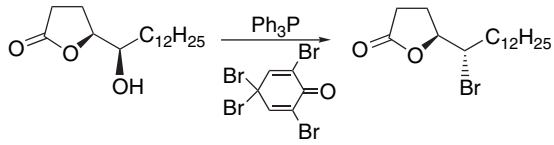

The alkoxy phosphonium intermediate is formed by a reaction that does not break the C−O bond and the second step proceeds by back-side displacement on carbon, so the stereochemistry of the overall process is inversion.

11. D. G. Goodwin and H. R. Hudson, *J. Chem. Soc. B*, 1333 (1968); E. J. Coulson, W. Gerrard, and H. R. Hudson, *J. Chem. Soc.*, 2364 (1965).
12. J. Cason and J. S. Correia, *J. Org. Chem.*, **26**, 3645 (1961).
13. H. R. Hudson, *J. Chem. Soc.*, 664 (1968).
14. B. P. Castro, *Org. React.*, **29**, 1 (1983).
15. G. A. Wiley, R. L. Hershkowitz, B. M. Rein, and B. C. Chung, *J. Am. Chem. Soc.*, **86**, 964 (1964).




Ref. 16

2,4,4,6-Tetrabromocyclohexa-2,5-dienone is also a useful bromine source.




Ref. 17

Triphenylphosphine dichloride exhibits similar reactivity and can be used to prepare chlorides.[18] The most convenient methods for converting alcohols to chlorides are based on in situ generation of chlorophosphonium ions[19] by reaction of triphenylphosphine with various chlorine compounds such as carbon tetrachloride[20] or hexachloroacetone.[21] These reactions involve formation of chlorophosphonium ions.

$$Ph_3P + CCl_4 \longrightarrow Ph_3P^+—Cl + {}^-CCl_3$$

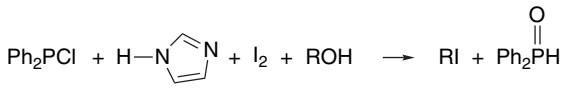
$$Ph_3P + Cl_3CCCCl_3 \longrightarrow Ph_3P^+—Cl + {}^-CCl_2CCCl_3$$

The chlorophosphonium ion then reacts with the alcohol to give an alkoxyphosphonium ion that is converted to the chloride.

$$Ph_3P^+—Cl + ROH \longrightarrow Ph_3P^+—OR + HCl$$

$$Ph_3P^+—OR + Cl^- \longrightarrow Ph_3P{=}O + R—Cl$$

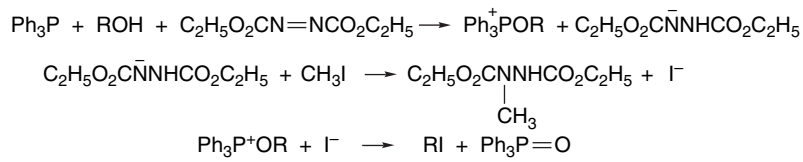
Several modifications of procedures based on halophosphonium ion have been developed. Triphenylphosphine and imidazole in combination with iodine or bromine gives good conversion of alcohols to iodides or bromides.[22] An even more reactive system consists of chlorodiphenylphosphine, imidazole, and the halogen,[23] and has the further advantage that the resulting phosphorus by-product diphenylphosphinic acid, can be extracted with base during product workup.




A very mild procedure for converting alcohols to iodides uses triphenylphosphine, diethyl azodicarboxylate (DEAD), and methyl iodide.[24] This reaction occurs

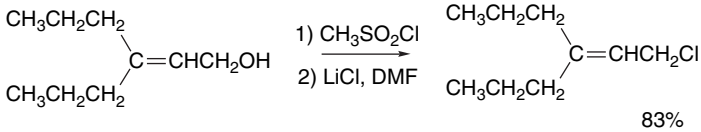
16. D. Levy and R. Stevenson, *J. Org. Chem.*, **30**, 2635 (1965).
17. A. Tanaka and T. Oritani, *Tetrahedron Lett.*, **38**, 1955 (1997).
18. L. Horner, H. Oediger, and H. Hoffmann, *Justus Liebigs Ann. Chem.*, **626**, 26 (1959).
19. R. Appel, *Angew. Chem. Int. Ed. Engl.*, **14**, 801 (1975).
20. J. B. Lee and T. J. Nolan, *Can. J. Chem.*, **44**, 1331 (1966).
21. R. M. Magid, O. S. Fruchey, W. L. Johnson, and T. G. Allen, *J. Org. Chem.*, **44**, 359 (1979).
22. P. J. Garegg, R. Johansson, C. Ortega, and B. Samuelsson, *J. Chem. Soc., Perkin Trans.*, **1**, 681 (1982).
23. B. Classon, Z. Liu, and B. Samuelsson, *J. Org. Chem.*, **53**, 6126 (1988).
24. O. Mitsunobu, *Synthesis*, 1 (1981).

with clean inversion of stereochemistry.[25] The key intermediate is again an alkoxyphosphonium ion.



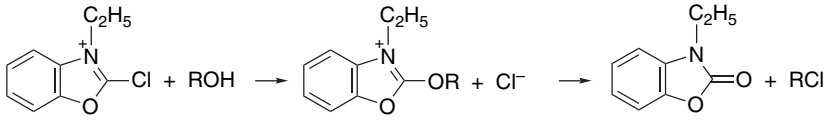
The role of the DEAD is to activate the triphenylphosphine toward nucleophilic attack by the alcohol. In the course of the reaction the N=N double bond is reduced. As is discussed later, this method is applicable for activation of alcohols to substitution by other nucleophiles in addition to halide ions. The activation of alcohols to nucleophilic attack by the triphenylphosphine-DEAD combination is called the *Mitsunobu reaction*.[26]

A very mild method that is useful for compounds that are prone to allylic rearrangement involves prior conversion of the alcohol to a sulfonate, followed by nucleophilic displacement with halide ion.



83% Ref. 27

Another very mild procedure involves reaction of the alcohol with the heterocyclic 2-chloro-3-ethylbenzoxazolium cation.[28] The alcohol adds to the electrophilic heterocyclic ring, displacing chloride. The alkoxy group is thereby activated toward a nucleophilic substitution that forms a stable product, 3-ethylbenzoxazolinone.



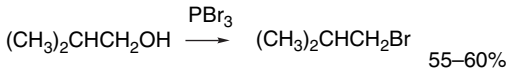
The reaction can be used for making either chlorides or bromides by using the appropriate tetraalkylammonium salt as a halide source.

Scheme 3.1 gives some examples of the various alcohol to halide conversions that have been discussed. Entries 1 and 2 are examples of synthesis of primary bromides using $PBr_3$. Entry 3 is an example of synthesis of a chloride using $Ph_3P–Cl_2$. The reactant, neopentyl alcohol, is often resistant to nucleophilic substitution and prone to rearrangement, but reacts well under these conditions. Entries 4 and 5 illustrate the use of halogenated solvents as chlorine sources in $Ph_3P$-mediated reactions. The reactions in Entries 6 and 7 involve synthesis of bromides by nucleophilic substitution on tosylates. The reactant in Entry 7 is prone to rearrangement via ring expansion,

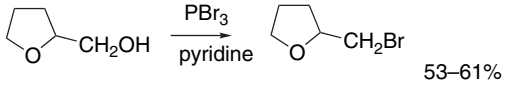
[25] H. Loibner and E. Zbiral, *Helv. Chim. Acta*, **59**, 2100 (1976).
[26] D. L. Hughes, *Org. React.*, **42**, 335 (1992).
[27] E. W. Collington and A. I. Meyers, *J. Org. Chem.*, **36**, 3044 (1971).
[28] T. Mukaiyama, S. Shoda, and Y. Watanabe, *Chem. Lett.*, 383 (1977); T. Mukaiyama, *Angew. Chem. Int. Ed. Engl.*, **18**, 707 (1979).

## Scheme 3.1. Preparation of Alkyl Halides

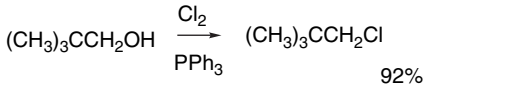
1[a]



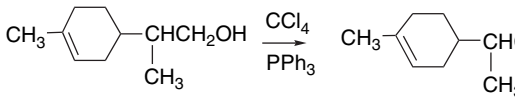

2[b]



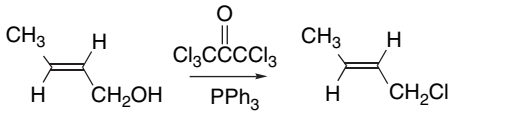

3[c]



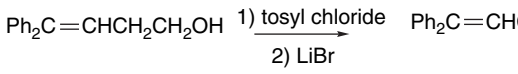

4[d]



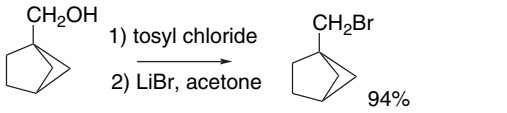

5[e]



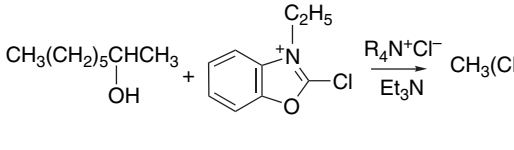

6[f]



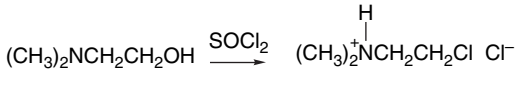

7[g]



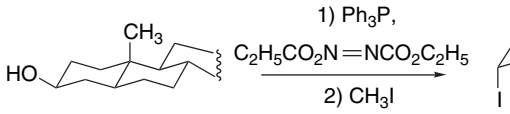

8[h]



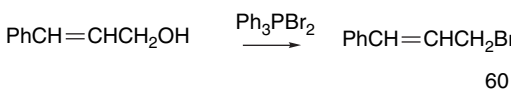

9[i]




10[j]



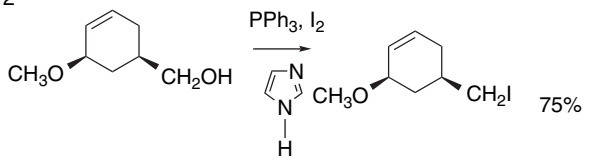

11[k]




(*Continued*)

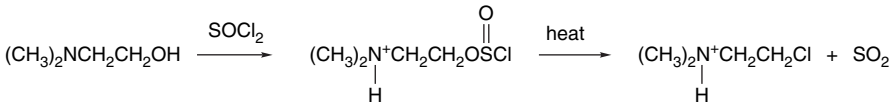
**Scheme 3.1.** (***Continued***)

12[l]




a. C. R. Noller and R. Dinsomore, *Org. Synth.*, **II**, 358 (1943).
b. L. H. Smith, *Org. Synth.*, **III**, 793 (1955).
c. G. A. Wiley, R. L. Hershkowitz, B. M. Rein, and B. C. Chung, *J. Am. Chem. Soc.*, **86**, 964 (1964).
d. D. B. MacKenzie, M. M. Angelo, and J. Wolinsky, *J. Org. Chem.*, **44**, 4042 (1979).
e. R. M. Magid, O. S. Fruchy, W. L. Johnson, and T. G. Allen, *J. Org. Chem.*, **44**, 359 (1979).
f. M. E. H. Howden, A. Maerker, J. Burdon, and J. D. Roberts, *J. Am. Chem. Soc.*, **88**, 1732 (1966).
g. K. B. Wiberg and B. R. Lowry, *J. Am. Chem. Soc.*, **85**, 3188 (1963).
h. T. Mukaiyama, S. Shoda, and Y. Watanabe, *Chem. Lett.*, 383 (1977).
i. L. A. R. Hall, V. C. Stephens, and J. H. Burkhalter, *Org. Synth.*, **IV**, 333 (1963).
j. H. Loibner and E. Zviral, *Helv. Chim. Acta*, **59**, 2100 (1976).
k. J. P. Schaefer, J. G. Higgins, and P. K. Shenoy, *Org. Synth.*, **V**, 249 (1973).
l. R. G. Linde II, M. Egbertson, R. S. Coleman, A. B. Jones, and S. J. Danishefsky, *J. Org. Chem.*, **55**, 2771 (1990).

but no rearrangement was observed under these conditions. Entry 8 illustrates the use of a chlorobenzoxazolium cation for conversion of a secondary alcohol to a chloride. This reaction was shown to proceed with inversion of configuration. Entry 9 involves conversion of a primary alcohol to a chloride using $SOCl_2$. In this particular example, the tertiary amino group captures the HCl that is formed by the reaction of the alcohol with $SOCl_2$. There is also some suggestion from the procedure that much of the reaction proceeds through a chlorosulfite intermediate. After the reactants are mixed (exothermic reaction), the material is heated in ethanol, during which time gas evolution occurs. This suggests that much of the chlorosulfite ester survives until the heating stage.




Entry 10 illustrates the application of the Mitsunobu reaction to synthesis of a steroidal iodide and demonstrates that inversion occurs. Entry 11 shows the use of the isolated $Ph_3P–Br_2$ complex. The reaction in Entry 12 involves the preparation of a primary iodide using the $Ph_3P–I_2$-imidazole reagent combination.

## 3.2. Introduction of Functional Groups by Nucleophilic Substitution at Saturated Carbon

The mechanistic aspects of nucleophilic substitution reactions were treated in detail in Chapter 4 of Part A. That mechanistic understanding has contributed to the development of nucleophilic substitution reactions as important synthetic processes. Owing to its stereospecificity and avoidance of carbocation intermediates, the $S_N2$ mechanism is advantageous from a synthetic point of view. In this section we discuss

the role of $S_N2$ reactions in the preparation of several classes of compounds. First, however, it is desirable to review the important role that solvent plays in $S_N2$ reactions. The knowledgeable manipulation of solvent and related medium effects has led to significant improvement of many synthetic procedures that proceed by the $S_N2$ mechanism.

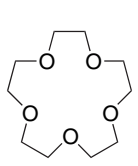
### 3.2.1. General Solvent Effects

The objective in selecting the reaction conditions for a preparative nucleophilic substitution is to enhance the mutual reactivity of the leaving group and nucleophile so that the desired substitution occurs at a convenient rate and with minimal competition from other possible reactions. The generalized order of leaving-group reactivity $RSO_3^- \sim I^- > Br^- > Cl^-$ pertains for most $S_N2$ processes. (See Section 4.2.3 of Part A for more complete data.) Mesylates, tosylates, iodides, and bromides are all widely used in synthesis. Chlorides usually react rather slowly, except in especially reactive systems, such as allyl and benzyl.

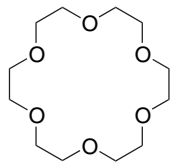
The overall synthetic objective normally governs the choice of the nucleophile. Optimization of reactivity therefore must be achieved by selection of the reaction conditions, particularly the solvent. Several generalizations about solvents can be made. Hydrocarbons, halogenated hydrocarbons, and ethers are usually unsuitable solvents for reactions involving ionic metal salts. Acetone and acetonitrile are somewhat more polar, but the solubility of most ionic compounds in these solvents is low. Solubility can be considerably improved by use of salts of cations having substantial hydrophobic character, such as those containing tetraalkylammonium ions. Alcohols are reasonably good solvents for salts, but the nucleophilicity of hard anions is relatively low in alcohols because of extensive solvation. The polar aprotic solvents, particularly dimethylformamide (DMF) and dimethylsulfoxide (DMSO), are good solvents for salts and, by virtue of selective cation solvation, anions usually show enhanced nucleophilicity in these solvents. Hexamethylphosphoric triamide (HMPA), *N*, *N*-dimethylacetamide, and *N*-methylpyrrolidinone are other examples of polar aprotic solvents.[29] The high water solubility of these solvents and their high boiling points can sometimes cause problems in product separation and purification. Furthermore, HMPA is toxic. In addition to enhancing reactivity, polar aprotic solvents also affect the order of reactivity of nucleophilic anions. In DMF the halides are all of comparable nucleophilicity,[30] whereas in hydroxylic solvents the order is $I^- > Br^- > Cl^-$ and the differences in reactivity are much greater.[31]

There are two other approaches to enhancing reactivity in nucleophilic substitutions by exploiting solvation effects on reactivity: the use of *crown ethers* as catalysts and the utilization of *phase transfer conditions*. The crown ethers are a family of cyclic polyethers, three examples of which are shown below.

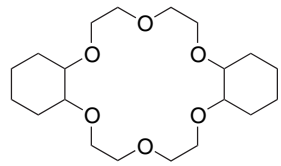
[29] A. F. Sowinski and G. M. Whitesides, *J. Org. Chem.*, **44**, 2369 (1979).
[30] W. M. Weaver and J. D. Hutchinson, *J. Am. Chem. Soc.*, **86**, 261 (1964).
[31] R. G. Pearson and J. Songstad, *J. Org. Chem.*, **32**, 2899 (1967).



15-crown-5



18-crown-6



dicyclohexano-18-crown-6

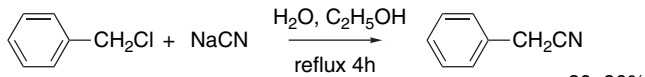
The first number designates the ring size and the second the number of oxygen atoms in the ring. By complexing the cation in the cavity of the crown ether, these compounds can solubilize salts in nonpolar solvents. In solution, the anions are more reactive as nucleophiles because they are weakly solvated. Tight ion pairing is also precluded by the complexation of the cation by the nonpolar crown ether. As a result, nucleophilicity approaches or exceeds that observed in aprotic polar solvents,[32] but the crown ethers do present some hazards. They are toxic and also have the potential to transport toxic anions, such as cyanide, through the skin.

Another method of accelerating nucleophilic substitution is to use phase transfer catalysts,[33] which are ionic substances, usually quaternary ammonium or phosphonium salts, in which the hydrocarbon groups in the cation are large enough to convey good solubility in nonpolar solvents. In other words, the cations are highly *lipophilic*. Phase transfer catalysis usually is done in a two-phase system. The reagent is dissolved in a water-insoluble solvent such as a hydrocarbon or halogenated hydrocarbon. The salt of the nucleophile is dissolved in water. Even with vigorous mixing, such systems show little tendency to react, because the nucleophile and reactant remain separated in the water and organic phases, respectively. When a phase transfer catalyst is added, the lipophilic cations are transferred to the nonpolar phase and anions are attracted from the water to the organic phase to maintain electrical neutrality. The anions are weakly solvated in the organic phase and therefore exhibit enhanced nucleophilicity. As a result, the substitution reactions proceed under relatively mild conditions. The salts of the nucleophile are often used in high concentration in the aqueous solution and in some procedures the solid salts are used.

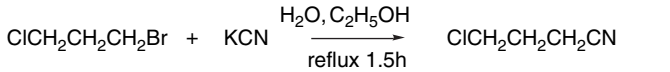
### 3.2.2. Nitriles

The replacement of a halide or sulfonate by cyanide ion, extending the carbon chain by one atom and providing an entry to carboxylic acid derivatives, has been a reaction of synthetic importance since the early days of organic chemistry. The classical conditions for preparing nitriles involve heating a halide with a cyanide salt in aqueous alcohol solution.

32. M. Hiraoka, *Crown Compounds: Their Characteristics and Application*, Elsevier, Amsterdam, 1982.
33. E. V. Dehmlow and S. S. Dehmlow, *Phase Transfer Catalysis*, 3rd Edition, Verlag Chemie, Weinheim 1992; W. P. Weber and G. W. Gokel, *Phase Transfer Catalysis in Organic Synthesis*, Springer Verlag, New York, 1977; C. M. Stark, C. Liotta, and M. Halpern, *Phase Transfer Catalysis: Fundamentals, Applications and Industrial Perspective*, Chapman and Hall, New York, 1994.

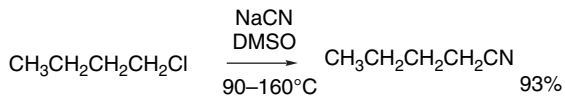


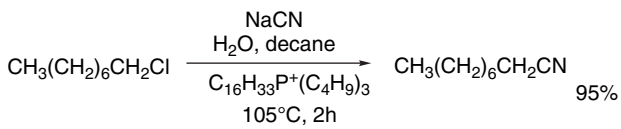

Ref. 34




Ref. 35

These reactions proceed more rapidly in polar aprotic solvents. In DMSO, for example, primary alkyl chlorides are converted to nitriles in 1 h or less at temperatures of 120°–140° C.[36] Phase transfer catalysis by hexadecyltributylphosphonium bromide permits conversion of 1-chlorooctane to octyl cyanide in 95% yield in 2 h at 105° C.[37]



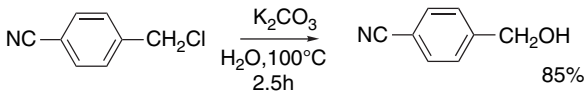




Catalysis by 18-crown-6 of the reaction of solid potassium cyanide with a variety of chlorides and bromides has been demonstrated.[38] With primary bromides, yields are high and reaction times are 15–30 h at reflux in acetonitrile (83° C). Interestingly, the chlorides are more reactive and require reaction times of only about 2 h. Secondary halides react more slowly and yields drop because of competing elimination. Tertiary halides do not react satisfactorily because elimination dominates.

### 3.2.3. Oxygen Nucleophiles

The oxygen nucleophiles that are of primary interest in synthesis are the hydroxide ion (or water), alkoxide ions, and carboxylate anions, which lead, respectively, to alcohols, ethers, and esters. Since each of these nucleophiles can also act as a base, reaction conditions are selected to favor substitution over elimination. Usually, a given alcohol is more easily obtained than the corresponding halide so the halide-to-alcohol transformation is not used extensively for synthesis. The hydrolysis of benzyl halides to the corresponding alcohols proceeds in good yield. This can be a useful synthetic transformation because benzyl halides are available either by side chain halogenation or by the chloromethylation reaction (Section 11.1.3).

34. R. Adams and A. F. Thal, *Org. Synth.*, **I**, 101 (1932).
35. C. F. H. Allen, *Org. Synth.*, **I**, 150 (1932).
36. L. Friedman and H. Shechter, *J. Org. Chem.*, **25**, 877 (1960); R. A. Smiley and C. Arnold, *J. Org. Chem.*, **25**, 257 (1960).
37. C. M. Starks, *J. Am. Chem. Soc.*, **93**, 195 (1971); C. M. Starks and R. M. Owens, *J. Am. Chem. Soc.*, **95**, 3613 (1973).
38. F. L. Cook, C. W. Bowers, and C. L. Liotta, *J. Org. Chem.*, **39**, 3416 (1974).




Ref. 39

Ether formation from alkoxides and alkylating reagents is a reaction of wide synthetic importance. The conversion of phenols to methoxyaromatics, for example, is a very common reaction. Methyl iodide, methyl tosylate, or dimethyl sulfate can be used as the alkylating agents. The reaction proceeds in the presence of a weak base, such as $Na_2CO_3$ or $K_2CO_3$, which deprotonates the phenol. The conjugate bases of alcohols are considerably more basic than phenoxides, so β-elimination can be a problem. Phase transfer conditions can be used in troublesome cases.[40] Fortunately, the most useful and commonly encountered ethers are methyl and benzyl ethers, where elimination is not a problem and the corresponding halides are especially reactive toward substitution.

Two methods for converting carboxylic acids to esters fall into the mechanistic group under discussion: the reaction of carboxylic acids with diazo compounds, especially diazomethane and alkylation of carboxylate anions by halides or sulfonates. The esterification of carboxylic acids with diazomethane is a very fast and clean reaction.[41] The alkylating agent is the extremely reactive methyldiazonium ion, which is generated by proton transfer from the carboxylic acid to diazomethane. The collapse of the resulting ion pair with loss of nitrogen is extremely rapid.

$$RCO_2H + CH_2N_2 \longrightarrow [RCO_2^- + CH_3\overset{+}{N}_2] \longrightarrow RCO_2CH_3 + N_2$$

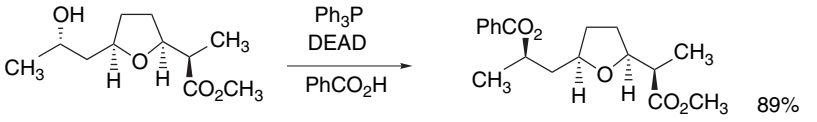
The main drawback to this reaction is the toxicity of diazomethane and some of its precursors. Diazomethane is also potentially explosive. Trimethylsilyldiazomethane is an alternative reagent,[42] which is safer and frequently used in preparation of methyl esters from carboxylic acids.[43] Trimethylsilyldiazomethane also O-methylates alcohols.[44] The latter reactions occur in the presence of fluoroboric acid in dichloromethane.

Especially for large-scale work, esters may be more safely and efficiently prepared by reaction of carboxylate salts with alkyl halides or tosylates. Carboxylate anions are not very reactive nucleophiles so the best results are obtained in polar aprotic solvents[45] or with crown ether catalysts.[46] The reactivity order for carboxylate salts is $Na^+ < K^+ < Rb^+ < Cs^+$. Cesium carboxylates are especially useful in polar aprotic solvents. The enhanced reactivity of the cesium salts is due to both high solubility and minimal ion pairing with the anion.[47] Acetone is a good solvent for reaction of carboxylate anions with alkyl iodides.[48] Cesium fluoride in DMF is another useful

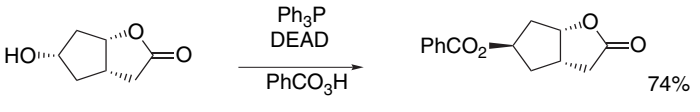
39. J. N. Ashley, H. J. Barber, A. J. Ewins, G. Newbery, and A. D. Self, *J. Chem. Soc.*, 103 (1942).
40. F. Lopez-Calahorra, B. Ballart, F. Hombrados, and J. Marti, *Synth. Commun.*, **28**, 795 (1998).
41. T. H. Black, *Aldrichimia Acta*, **16**, 3 (1983).
42. N. Hashimoto, T. Aoyama, and T. Shiori, *Chem. Pharm. Bull.*, **29**, 1475 (1981).
43. T. Shioiri and T. Aoyama, *Adv. Use Synthons Org. Chem.*, **1**, 51 (1993); A. Presser and A. Huefner, *Monatsh. Chem.*, **135**, 1015 (2004).
44. T. Aoyama and T. Shiori, *Tetrahedron Lett.*, **31**, 5507 (1990).
45. P. E. Pfeffer, T. A. Foglia, P. A. Barr, I. Schmeltz, and L. S. Silbert, *Tetrahedron Lett.*, 4063 (1972); J. E. Shaw, D. C. Kunerth, and J. J. Sherry, *Tetrahedron Lett.*, 689 (1973); J. Grundy, B. G. James, and G . Pattenden, *Tetrahedron Lett.*, 757 (1972).
46. C. L. Liotta, H. P. Harris, M. McDermott, T. Gonzalez, and K. Smith, *Tetrahedron Lett.*, 2417 (1974).
47. G. Dijkstra, W. H. Kruizinga, and R. M. Kellog, *J. Org. Chem.*, **52**, 4230 (1987).
48. G. G. Moore, T. A. Foglia, and T. J. McGahan, *J. Org. Chem.*, **44**, 2425 (1979).

combination.[49] Carboxylate alkylation procedures are particularly advantageous for preparation of hindered esters, which can be relatively difficult to prepare by the acid-catalyzed esterification method (Fisher esterification), which we discuss in Section 3.4.

During the course of synthesis, it is sometimes necessary to invert the configuration at an oxygen-substituted center. One of the best ways of doing this is to activate the hydroxy group to substitution by a carboxylate anion. The activation is frequently done using the Mitsunobu reaction.[50] Hydrolysis of the resulting ester give the alcohol of inverted configuration.



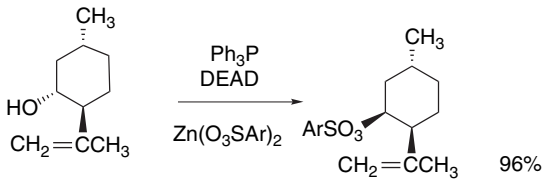

Ref. 51




Ref. 52

Carboxylate anions derived from somewhat stronger acids, such as *p*-nitrobenzoic acid and chloroacetic acid, seem to be particularly useful in this Mitsunobu inversion reaction.[53] Inversion can also be carried out on sulfonate esters using cesium carboxylates and DMAP as a catalyst in toluene.[54] The effect of the DMAP seems to involve complexation and solubilization of the cesium salts.

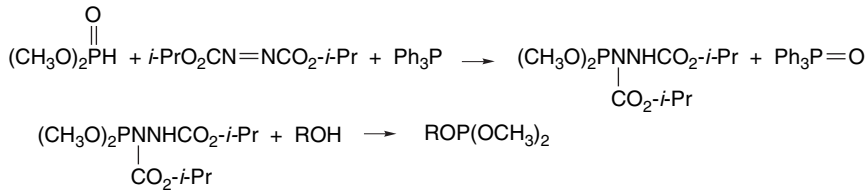
Sulfonate esters also can be prepared under Mitsunobu conditions. Use of zinc tosylate in place of the carboxylic acid gives a tosylate of inverted configuration.



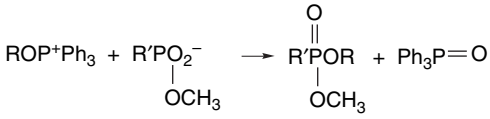

Ref. 55

The Mitsunobu conditions also can be used to effect a variety of other important and useful nucleophilic substitution reactions, such as conversion of alcohols to mixed phosphite esters.[56] The active phosphitylating agent is believed to be a mixed phosphoramidite.

49. T. Sato, J. Otera, and H. Nozaki, *J. Org. Chem.*, **57**, 2166 (1992).
50. D. L. Hughes, *Org. React.*, **42**, 335 (1992); D. L. Hughes, *Org. Prep. Proc. Intl.*, **28**, 127 (1996).
51. M. J. Arco, M. H. Trammel, and J. D. White, *J. Org. Chem.*, **41**, 2075 (1976).
52. C.-T. Hsu, N.-Y. Wang, L. H. Latimer, and C. J. Sih, *J. Am. Chem. Soc.*, **105,** 593 (1983).
53. J. A. Dodge, J. I. Tujillo, and M. Presnell, *J. Org. Chem.*, **59**, 234 (1994); M. Saiah, M.Bessodes, and K. Antonakis, *Tetrahedron Lett.*, **33**, 4317 (1992); S. F. Martin and J. A. Dodge, *Tetrahedron Lett.*, **32**, 3017 (1991); P. J. Harvey, M. von Itzstein, and I. D. Jenkins, *Tetrahedron*, **53**, 3933 (1997).
54. N. A. Hawryluk and B. B. Snider, *J. Org. Chem.*, **65**, 8379 (2000).
55. I. Galynker and W. C. Still, *Tetrahedron Lett.*, 4461 (1982).
56. I. D. Grice, P. J. Harvey, I. D. Jenkins, M. J. Gallagher, and M. G. Ranasinghe, *Tetrahedron Lett.*, **37**, 1087 (1996).

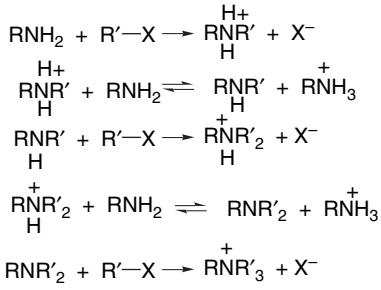


Mixed phosphonate acid esters can also be prepared from alkylphosphonate monoesters, although here the activation is believed occur at the alcohol.[57]



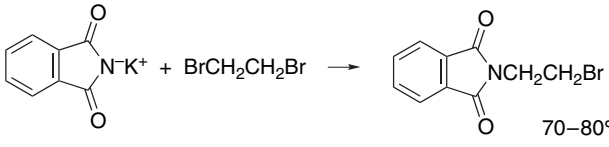
### 3.2.4. Nitrogen Nucleophiles

The alkylation of neutral amines by halides is complicated from a synthetic point of view by the possibility of multiple alkylation that can proceed to the quaternary ammonium salt in the presence of excess alkyl halide.



Even with a limited amount of the alkylating agent, the equilibria between protonated product and the neutral starting amine are sufficiently fast that a mixture of products may be obtained. For this reason, when monoalkylation of an amine is desired, the reaction is usually best carried out by *reductive amination*, a reaction that is discussed in Chapter 5. If complete alkylation to the quaternary salt is desired, use of excess alkylating agent and a base to neutralize the liberated acid normally results in complete reaction.

Amides are weakly nucleophilic and react only slowly with alkyl halides. The anions of amides are substantially more reactive. The classical Gabriel procedure for synthesis of amines from phthalimide is illustrative.[58]



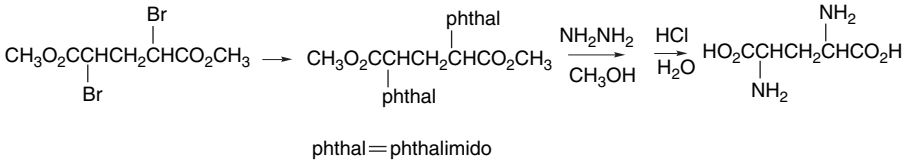
Ref. 59

[57] D. A. Campbell, *J. Org. Chem.*, **57**, 6331 (1992); D. A. Campbell and J. C. Bermak, *J. Org. Chem.*, **59**, 658 (1994).

[58] M. S. Gibson and R. N. Bradshaw, *Angew. Chem. Int. Ed. Engl.*, **7**, 919 (1968).

[59] P. L. Salzberg and J. V. Supniewski, *Org. Synth.*, **I**, 119 (1932).

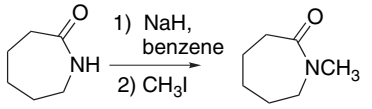
The enhanced acidity of the NH group in phthalimide permits formation of the anion, which is readily alkylated by alkyl halides or tosylates. The amine can then be liberated by reaction of the substituted phthalimide with hydrazine.



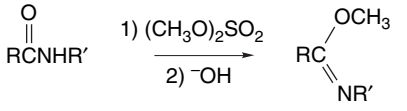

Ref. 60

It has been found that the deprotection phase of the Gabriel synthesis is accelerated by inclusion of NaOH.[61]

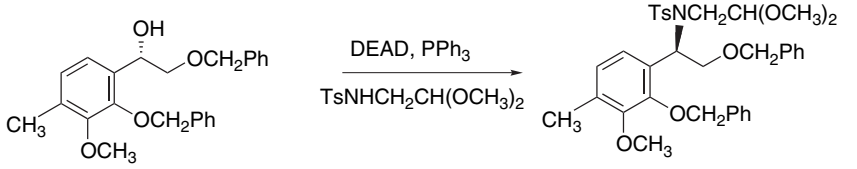
Secondary amides can be alkylated on nitrogen by using sodium hydride for deprotonation, followed by reaction with an alkyl halide.[62]




Neutral tertiary and secondary amides react with very reactive alkylating agents, such as triethyloxonium tetrafluoroborate, to give O-alkylation.[63] The same reaction occurs, but more slowly, with tosylates and dimethyl sulfate. Neutralization of the resulting salt provides iminoethers.

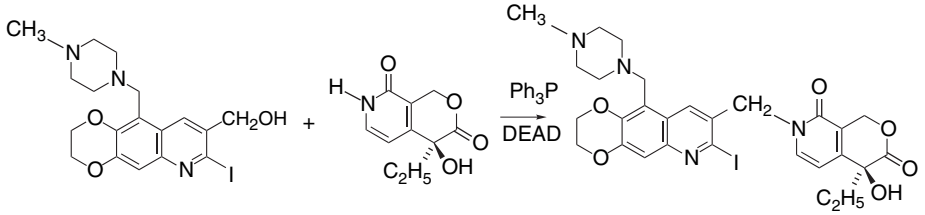



Sulfonamides are relatively acidic and their anions can serve as nitrogen nucleophiles.[64] Sulfonamido groups can be introduced at benzylic positions with a high level of inversion under Mitsunobu conditions.[65]



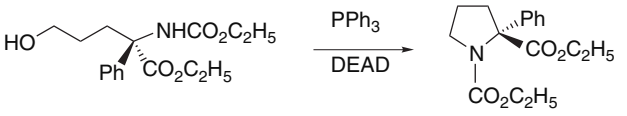

60. J. C. Sheehan and W. A. Bolhofer, *J. Am. Chem. Soc.*, **72**, 2786 (1950).
61. A. Ariffin, M. N. Khan, L. C. Lan, F. Y. May, and C. S. Yun, *Synth. Commun.*, **34**, 4439 (2004); M. N. Khan, *J. Org. Chem.*, **61**, 8063 (1996).
62. W. S. Fones, *J. Org. Chem.*, **14**, 1099 (1949); R. M. Moriarty, *J. Org. Chem.*, **29**, 2748 (1964).
63. L. Weintraub, S. R. Oles, and N. Kalish, *J. Org. Chem.*, **33**, 1679 (1968); H. Meerwein, E. Battenberg, H. Gold, E. Pfeil, and G. Willfang, *J. Prakt. Chem.*, **154**, 83 (1939).
64. D. Papaioannou, C. Athanassopoulos, V. Magafa, N. Karamanos, G. Stavropoulos, A Napoli, G. Sindona, D. W. Aksnes, and G. W. Francis, *Acta Chem. Scand.*, **48**, 324 (1994).
65. T. S. Kaufman, *Tetrahedron Lett.*, **37**, 5329 (1996).

The Mitsunobu conditions can be used for alkylation of 2-pyridones, as in the course of synthesis of analogs of the antitumor agent camptothecin.



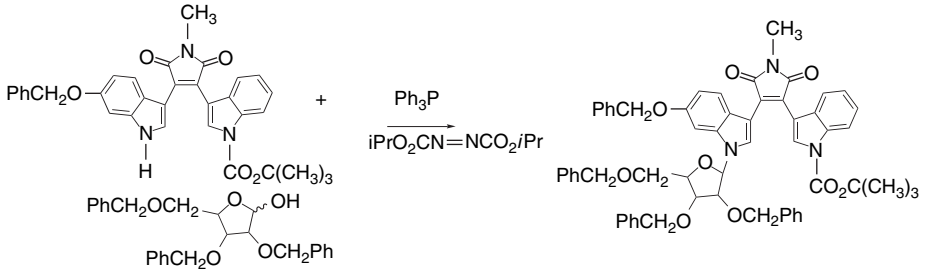
Ref. 66

Proline analogs can be obtained by cyclization of δ-hydroxyalkylamino acid carbamates.



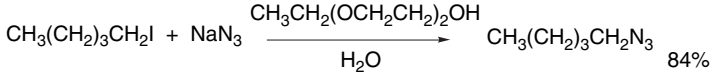
Ref. 67

Mitsunobu conditions are effective for glycosylation of weak nitrogen nucleophiles, such as indoles. This reaction has been used in the synthesis of antitumor compounds.



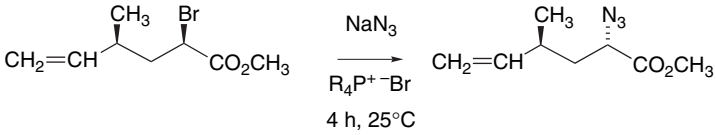
Ref. 68

Azides are useful intermediates for synthesis of various nitrogen-containing compounds. They can also be easily reduced to primary amines and undergo cycloaddition reactions, as is discussed in Section 6.2. Azido groups are usually introduced into aliphatic compounds by nucleophilic substitution.[69] The most reliable procedures involve heating an appropriate halide with sodium azide in DMSO[70] or DMF.[71] Alkyl azides can also be prepared by reaction in high-boiling alcohols.[72]



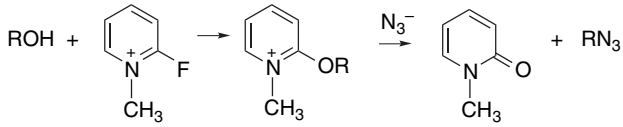
66. F. G. Fang, D. D. Bankston, E. M. Huie, M. R. Johnson, M.-C. Kang, C. S. LeHoullier, G. C. Lewis, T. C. Lovelace, M. W. Lowery, D. L. McDougald, C. A. Meerholz, J. J. Partridge, M. J. Sharp, and S. Xie, *Tetrahedron*, **53**, 10953 (1997).
67. J. van Betsbrugge, D. Tourwe, B. Kaptein, H. Kierkals, and R. Broxterman, *Tetrahedron*, **53**, 9233 (1997).
68. M. Ohkubo, T. Nishimura, H. Jona, T. Honma, S. Ito, and H. Morishima, *Tetrahedron*, **53**, 5937 (1997).
69. M. E. C. Biffin, J. Miller, and D. B. Paul, in *The Chemistry of the Azido Group*, S. Patai, ed., Interscience, New York, 1971, Chap. 2.
70. R. Goutarel, A. Cave, L. Tan, and M. Leboeuf, *Bull. Soc. Chim. France*, 646 (1962).
71. E. J. Reist, R. R. Spencer, B. R. Baker, and L. Goodman, *Chem. Ind. (London)*, 1794 (1962).
72. E. Lieber, T. S. Chao, and C. N. R. Rao, *J. Org. Chem.*, **22**, 238 (1957); H. Lehmkuhl, F. Rabet, and K. Hauschild, *Synthesis*, 184 (1977).

Phase transfer conditions are used as well for the preparation of azides.[73]

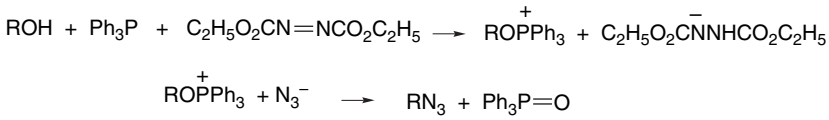



Tetramethylguanidinium azide, an azide salt that is readily soluble in halogenated solvents, is a useful source of azide ions in the preparation of azides from reactive halides such as α-haloketones, α-haloamides, and glycosyl halides.[74]

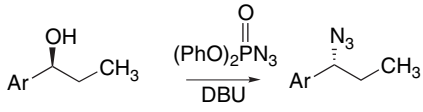
There are also useful procedures for preparation of azides directly from alcohols. Reaction of alcohols with 2-fluoro-1-methylpyridinium iodide followed by reaction with lithium azide gives good yields of alkyl azides.[75]




Diphenylphosphoryl azide reacts with alcohols in the presence of triphenylphosphine and DEAD.[76] Hydrazoic acid, $HN_3$, can also serve as the azide ion source under these conditions.[77] These reactions are examples of the Mitsunobu reaction.




Diphenylphosphoryl azide also gives good conversion of primary alkyl and secondary benzylic alcohols to azides in the presence of the strong organic base diazabicycloundecane (DBU). These reactions proceed by O-phosphorylation followed by $S_N2$ displacement.[78]

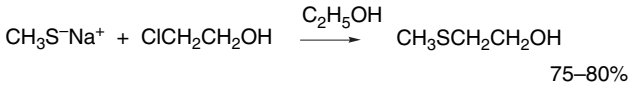



This reaction can be extended to secondary alcohols with the more reactive *bis*-(4-nitrophenyl)phosphorazidate.[79]

73. W. P. Reeves and M. L. Bahr, *Synthesis*, 823 (1976); B. B. Snider and J. V. Duncia, *J. Org. Chem.*, **46**, 3223 (1981).
74. Y. Pan, R. L. Merriman, L. R. Tanzer, and P. L. Fuchs, *Biomed. Chem. Lett.*, **2**, 967 (1992); C. Li, T.-L. Shih, J. U. Jeong, A. Arasappan, and P. L. Fuchs, *Tetrahedron Lett.*, **35**, 2645 (1994); C. Li, A. Arasappan, and P. L. Fuchs, *Tetrahedron Lett.*, **34**, 3535 (1993); D. A. Evans, T. C. Britton, J. A. Ellman, and R. L. Dorow, *J. Am. Chem. Soc.*, **112**, 4011 (1990).
75. K. Hojo, S. Kobayashi, K. Soai, S. Ikeda, and T. Mukaiyama, *Chem. Lett.*, 635 (1977).
76. B. Lal, B. N. Pramanik, M. S. Manhas, and A. K. Bose, *Tetrahedron Lett.*, 1977 (1977).
77. J. Schweng and E. Zbiral, *Justus Liebigs Ann. Chem.*, 1089 (1978); M. S. Hadley, F. D. King, B. McRitchie, D. H. Turner, and E. A. Watts, *J. Med. Chem.*, **28**, 1843 (1985).
78. A. S. Thompson, G. R. Humphrey, A. M. DeMarco, D. J. Mathre, and E. J. J. Grabowski, *J. Org. Chem.*, **58**, 5886 (1993).
79. M. Mizuno and T. Shioiri, *J. Chem. Soc., Chem. Commun.*, **22**, 2165 (1997).

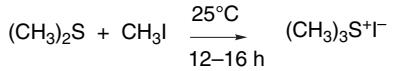
### 3.2.5. Sulfur Nucleophiles

Anions derived from thiols are strong nucleophiles and are easily alkylated by halides.

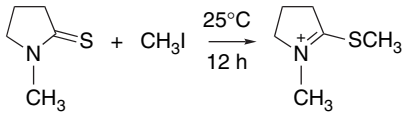



Ref. 80

Neutral sulfur compounds are also good nucleophiles, Sulfides and thioamides readily form salts with methyl iodide, for example.

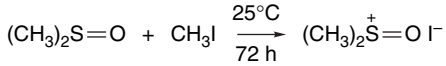



Ref. 81




Ref. 82

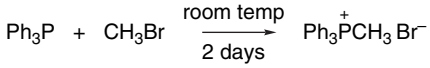
Even sulfoxides, in which nucleophilicity is decreased by the additional oxygen, can be alkylated by methyl iodide. These sulfoxonium salts have useful synthetic applications as discussed in Section 2.5.1.



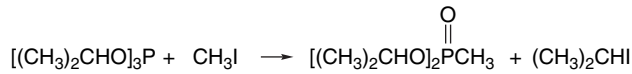

Ref. 83

### 3.2.6. Phosphorus Nucleophiles

Both neutral and anionic phosphorus compounds are good nucleophiles toward alkyl halides. We encountered examples of these reactions in Chapter 2 in connection with the preparation of the valuable phosphorane and phosphonate intermediates used for Wittig reactions.

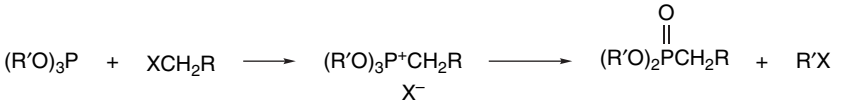



Ref. 84




Ref. 85

The reaction with phosphite esters is known as the *Michaelis-Arbuzov reaction* and proceeds through an unstable trialkoxyphopsphonium intermediate. The second stage is another example of the great tendency of alkoxyphosphonium ions to react with nucleophiles to break the O−C bond, resulting in formation of a phosphoryl P−O bond.



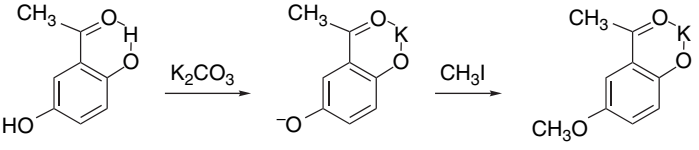

80. W. Windus and P. R. Shildneck, *Org. Synth.*, **II**, 345 (1943).
81. E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1353 (1965).
82. R. Gompper and W. Elser, *Org. Synth.*, **V**, 780 (1973).
83. R. Kuhn and H. Trischmann, *Justus Liebigs Ann. Chem.*, **611,** 117 (1958).
84. G. Wittig and U. Schoellkopf, *Org. Synth.*, **V**, 751 (1973).
85. A. H. Ford-Moore and B. J. Perry, *Org. Synth.*, **IV**, 325 (1963).

### 3.2.7. Summary of Nucleophilic Substitution at Saturated Carbon

Some of the nucleophilic substitution reactions at $sp^3$ carbon that are most valuable for synthesis were outlined in the preceding sections, and they all fit into the general mechanistic patterns that were discussed in Chapter 4 of Part A. The order of reactivity of alkylating groups is benzyl ~ allyl > methyl > primary > secondary. Tertiary halides and sulfonates are generally not satisfactory because of the preference for elimination over $S_N2$ substitution. Owing to their high reactivity toward nucleophilic substitution, α-haloesters, α-haloketones, and α-halonitriles are usually favorable reactants for substitution reactions. The reactivity of leaving groups is sulfonate ~ iodide > bromide > chloride. Steric hindrance decreases the rate of nucleophilic substitution. Thus projected synthetic steps involving nucleophilic substitution must be evaluated for potential steric problems.

Scheme 3.2 gives some representative examples of nucleophilic substitution processes drawn from *Organic Syntheses* and from other synthetic efforts. Entries 1 to 3 involve introduction of cyano groups via tosylates and were all conducted in polar aprotic solvents. Entries 4 to 8 are examples of introduction of the azido functional group by substitution. The reaction in Entry 4 was done under phase transfer conditions. A concentrated aqueous solution of $NaN_3$ was heated with the alkyl bromide and 5 mol % methyltrioctylammonium chloride. Entries 5 to 7 involve introduction of the azido group at secondary carbons with inversion of configuration in each case. The reactions in Entries 7 and 8 involve formation of phosphoryl esters as intermediates. These conditions were found preferable to the Mitsunobu conditions for the reaction in Entry 7. The electron-rich benzylic reactant gave both racemization and elimination via a carbocation intermediate under the Mitsunobu conditions. Entries 9 and 10 are cases of controlled alkylation of amines. In the reaction in Entry 9, the pyrrolidine was used in twofold excess. The ester EWGs have a rate-retarding effect that slows further alkylation to the quaternary salt. In the reaction in Entry 10, the monohydrochloride of piperazine is used as the reactant. The reaction was conducted in ethanol, and the dihydrochloride salt of the product precipitates as reaction proceeds, which helps minimize quaternization or *N*,*N*′-dialkylation. The yield of the dihydrochloride is 97–99%, and that of the amine is 65–75% after neutralization of the salt and distillation. The reaction in Entry 11 is the O-alkylation of an amide. The reaction was done in refluxing benzene, and the product was obtained by distillation after the neutralization.

Sections D through H of Scheme 3.2 involve oxygen nucleophiles. The hydrolysis reactions in Entries 12 and 13 both involve benzylic positions. The reaction site in Entry 13 is further activated by the ERG substituents on the ring. Entries 14 to 17 are examples of base-catalyzed ether formation. The selectivity of the reaction in Entry 17 for the *meta*-hydroxy group is an example of a fairly common observation in aromatic systems. The *ortho*-hydroxy group is more acidic and probably also stabilized by chelation, making it less reactive.

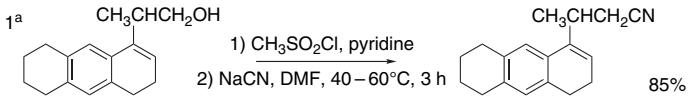



Dialkylation occurs if a stronger base (NaOH) and dimethyl sulfate is used. Entry 18 is a typical diazomethane methylation of a carboxylic acid. The toxicity of diazomethane

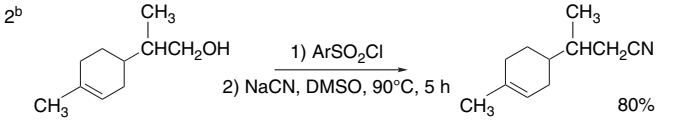
## Scheme 3.2. Transformations of Functional Groups by Nucleophilic Substitution

### A. Nitriles

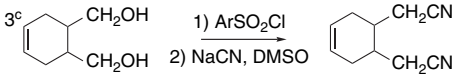
1[a]




2[b]

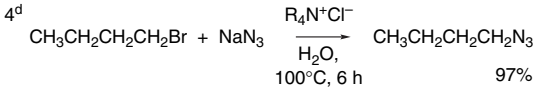



3[c]

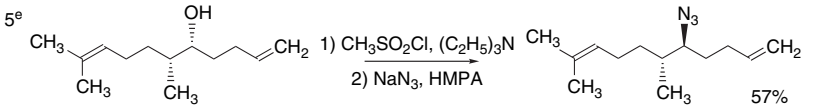



### B. Azides

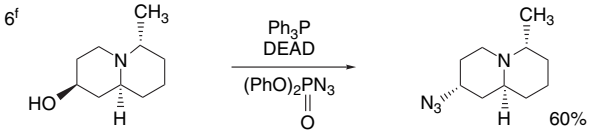
4[d]



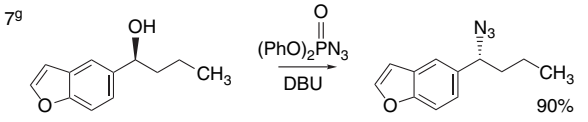

5[e]



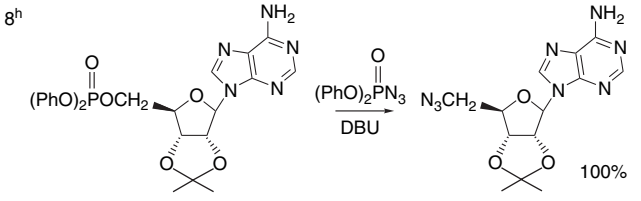

6[f]




7[g]

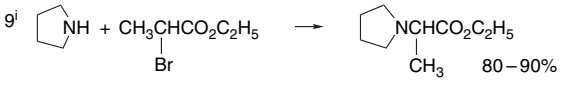



8[h]

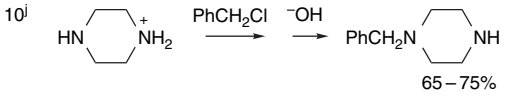



### C. Amines and amides

9[i]



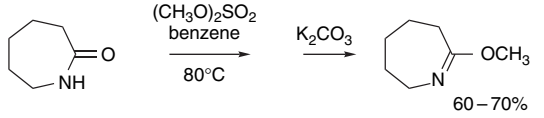

10[j]




(*Continued*)

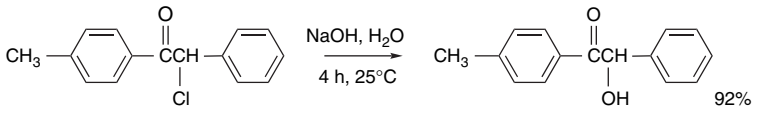
**Scheme 3.2. (*Continued*)**

11[k]

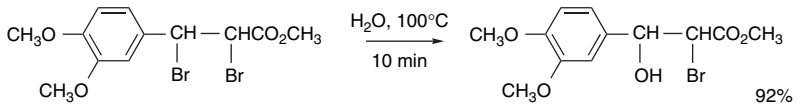



D. Hydrolysis by alkyl halides

12[l]

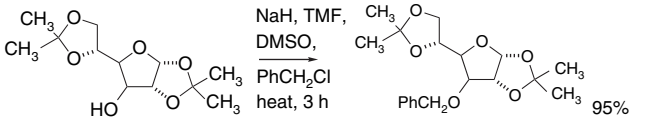



13[m]

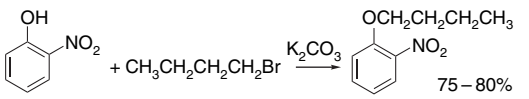



E. Ethers by base – catalyzed alkylation

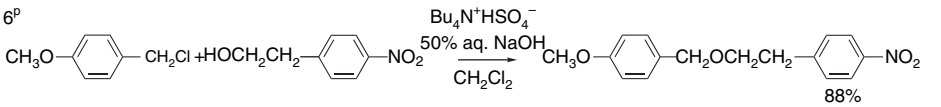
14[n]



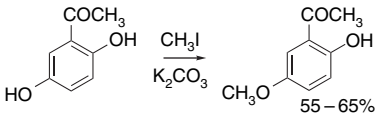

15[o]




16[p]

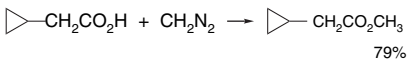



17[q]



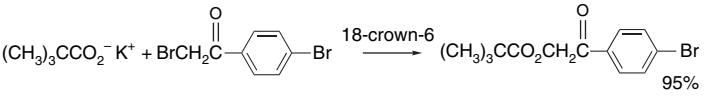

F. Esterification by diazoalkanes

18[r]

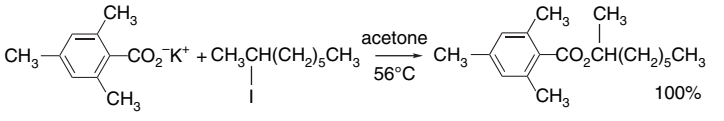



G. Esterification by nucleophilic substitution with carboxylate salts

19[s]



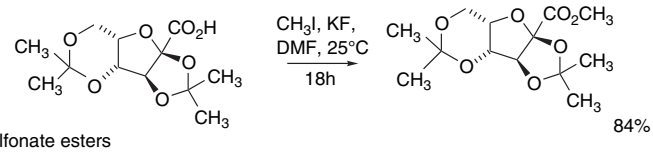

20[t]




(*Continued*)

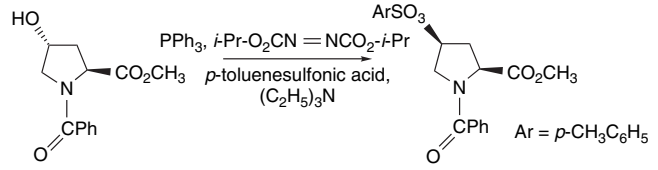
**Scheme 3.2. (*Continued*)**

21[u]




H. Sulfonate esters

22[v]




I. Phosphorus nucleophiles

23[w] $Ph_3P + BrCH_2CH_2OPh \longrightarrow Ph_3\overset{+}{P}CH_2CH_2OPh\ Br^-$

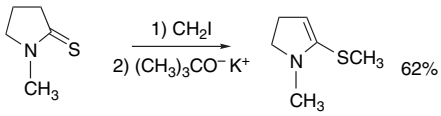
24[x] $[(CH_3)_2CHO]_3P + CH_3I \longrightarrow [(CH_3)_2CHO]_2\overset{O}{\overset{\|}{P}}CH_3 + (CH_3)_2CHI$ 85–90%

J. Sulfur nucleophiles

25[y] $CH_3(CH_2)_{10}CH_2Br + S{=}C(NH_2)_2 \xrightarrow[H_2O]{NaOH} CH_3(CH_2)_{10}CH_2SH$ 80%

26[z] $Na^+{}^-SCH_2CH_2S^-\,Na^+ + BrCH_2CH_2Br \longrightarrow$  55–60%

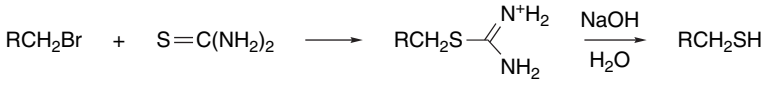
27[aa]




a. M. S. Newman and S. Otsuka, *J. Org. Chem.*, **23**, 797 (1958).
b. B. A. Pawson, H.-C. Cheung, S. Gurbaxani, and G. Saucy, *J. Am. Chem. Soc.*, **92**, 336 (1970).
c. J. J. Bloomfield and P. V. Fennessey, *Tetrahedron Lett.*, 2273 (1964).
d. W. P. Reeves and M. L. Bahr, *Synthesis*, 823 (1976).
e. D. F. Taber, M. Rahimizadeh, and K. K. You, *J. Org. Chem.*, **60**, 529 (1995).
f. M. S. Hadley, F. D. King, B. McRitchie, D. H. Turner, and E. A. Watts, *J. Med. Chem.*, **28**, 1843 (1985).
g. A. S. Thompson, G. G. Humphrey, A. M. De Marco, D. J. Mathre, and E. J. J. Grabowski, *J. Org. Chem.*, **58**, 5886 (1993).
h. P. Liu and D. J. Austin, *Tetrahedron Lett.*, **42**, 3153 (2001).
i. R. B. Moffett, *Org. Synth.*, **IV**, 466 (1963).
j. J. C. Craig and R. J. Young, *Org. Synth.*, **V**, 88 (1973).
k. R. E. Benson and T. L. Cairns, *Org. Synth.*, **IV**, 588 (1963).
l. R. N. McDonald and P. A. Schwab, *J. Am. Chem. Soc.*, **85**, 4004 (1963).
m. C. H. Heathcock, C. T. White, J. J. Morrison, and D. Van Derveer, *J. Org. Chem.*, **46**, 1296 (1981).
n. E. Adler and K. J. Bjorkquist, *Acta Chem. Scand.*, **5**, 241 (1951).
o. E. S. West and R. F. Holden, *Org. Synth.*, **III**, 800 (1955).
p. F. Lopez-Calahorra, B. Ballart, F. Hombrados, and J. Marti, *Synth. Commun.*, **28**, 795 (1998).
q. G. N. Vyas and M. N. Shah, *Org. Synth.*, **IV**, 836 (1963).
r. L. I. Smity and S. McKenzie, Jr., *J. Org. Chem.*, **15**, 74 (1950); A. I. Vogel, *Practical Organic Chemistry*, 3rd Edition, Wiley, 1956, p. 973.
s. H. D. Durst, *Tetrahedron Lett.*, 2421 (1974).
t. G. G. Moore, T. A. Foglia, and T. J. McGahan, *J. Org. Chem.*, **44**, 2425 (1979).
u. C. H. Heathcock, C.-T. White, J. Morrison, and D. VanDerveer, *J. Org. Chem.*, **46**, 1296 (1981).
v. N. G. Anderson, D. A. Lust, K. A. Colapret, J. H. Simpson, M. F. Malley, and J. Z. Gougoutas, *J. Org. Chem.*, **61**, 7955 (1996).
w. E. E. Schweizer and R. D. Bach, *Org. Synth.*, **V**, 1145 (1973).
x. A. H. Ford-Moore and B. J. Perry, *Org. Synth.*, **IV**, 325 (1963).
y. G. G. Urquhart, J. W. Gates, Jr., and P. Conor, *Org. Synth*, **III**, 363 (1965).
z. R. G. Gillis and A. B. Lacey, *Org. Synth.*, **IV**, 396 (1963).
aa. R. Gompper and W. Elser, *Org. Synth.*, **V**, 780 (1973).

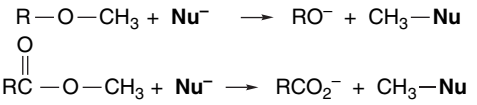
and its precursors, as well as the explosion hazard of diazomethane, requires that all recommended safety precautions be taken. Entries 19 to 21 involve formation of esters by alkylation of carboxylate salts. The reaction in Entry 19 was done in the presence of 5 mol % 18-crown-6. A number of carboxylic acids, including pivalic acid as shown in the example, were alkylated in high yield under these conditions. Entry 20 shows the alkylation of the rather hindered mesitoic acid by a secondary iodide. These conditions also gave high yields for unhindered acids and iodides. Entry 21 involves formation of a methyl ester using $CH_3I$ and KF as the base in DMF. Entry 22 involves formation of a sulfonate ester under Mitsunobu conditions with clean inversion of configuration. The conditions reported represent the optimization of the reaction as part of the synthesis of an antihypertensive drug, fosinopril.

Sections I and J of Scheme 3.2 show reactions with sulfur and phosphorus nucleophiles. The reaction in Entry 25 is a useful method for introducing thiol groups. The solid thiourea is a convenient source of sulfur. A thiouronium ion is formed and this avoids competition from formation of a dialkyl sulfide. The intermediate is readily hydrolyzed by base.




## 3.3. Cleavage of Carbon-Oxygen Bonds in Ethers and Esters

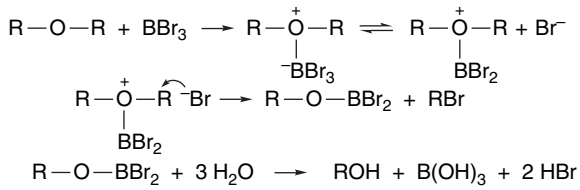
The cleavage of carbon-oxygen bonds in ethers or esters by nucleophilic substitution is frequently a useful synthetic transformation.




The alkoxide group is a poor leaving group and carboxy is only slightly better. As a result, these reactions usually require assistance from a protic or Lewis acid. The classical ether cleavage conditions involving concentrated hydrogen halides are much too strenuous for most polyfunctional molecules, so several milder reagents have been developed,[86] including boron tribromide,[87] dimethylboron bromide,[88] trimethylsilyl iodide,[89] and boron trifluoride in the presence of thiols.[90] The mechanism for ether cleavage with boron tribromide involves attack of bromide ion on an adduct formed

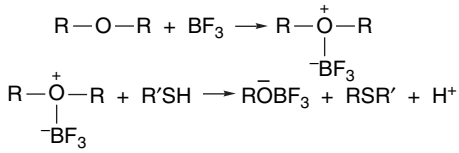
86. M. V. Bhatt and S. U. Kulkarni, *Synthesis*, 249 (1983).
87. J. F. W. McOmie, M. L. Watts, and D. E. West, *Tetrahedron*, **24**, 2289 (1968).
88. Y. Guindon, M. Therien, Y. Girard, and C. Yoakim, *J. Org. Chem.*, **52**, 1680 (1987).
89. M. E. Jung and M. A. Lyster, *J. Org. Chem.*, **42**, 3761 (1977).
90. (a) M. Node, H. Hori, and E. Fujita, *J. Chem. Soc., Perkin Trans. 1*, 2237 (1976); (b) K. Fuji, K. Ichikawa, M. Node, and E. Fujita, *J. Org. Chem.*, **44**, 1661 (1979).

from the ether and the electrophilic boron reagent. The cleavage step can occur by either an $S_N2$ or an $S_N1$ process, depending on the structure of the alkyl group.

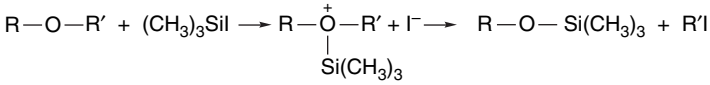


Good yields are generally observed, especially for methyl ethers. The combination of boron tribromide with dimethyl sulfide has been found to be particularly effective for cleaving aryl methyl ethers.[91]

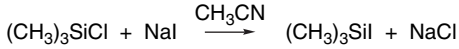
The boron trifluoride–alkyl thiol reagent combination also operates on the basis of nucleophilic attack on an oxonium ion generated by reaction of the ether with boron trifluoride.[90]



Trimethylsilyl iodide (TMSI) cleaves methyl ethers in a period of a few hours at room temperature.[89] Benzyl and *t*-butyl systems are cleaved very rapidly, whereas secondary systems require longer times. The reaction presumably proceeds via an initially formed silyl oxonium ion.



The direction of cleavage in unsymmetrical ethers is determined by the relative ease of O−R bond breaking by either $S_N2$ (methyl, benzyl) or $S_N1$ (*t*-butyl) processes. As trimethylsilyl iodide is rather expensive, alternative procedures that generate the reagent in situ have been devised.

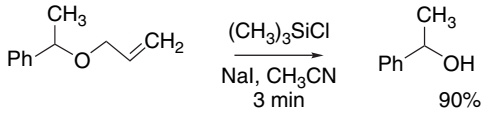


Ref. 92

Ref. 93

91. P. G. Williard and C. R. Fryhle, *Tetrahedron Lett.*, **21**, 3731 (1980).
92. T. Morita, Y. Okamoto, and H. Sakurai, *J. Chem. Soc., Chem. Commun.*, 874 (1978); G. A. Olah, S. C. Narang, B. G. B. Gupta, and R. Malhotra, *Synthesis*, 61 (1979).
93. T. L. Ho and G. A. Olah, *Synthesis*, 417 (1977); A. Benkeser, E. C. Mozdzen, and C. L. Muth, *J. Org. Chem.*, **44**, 2185 (1979).

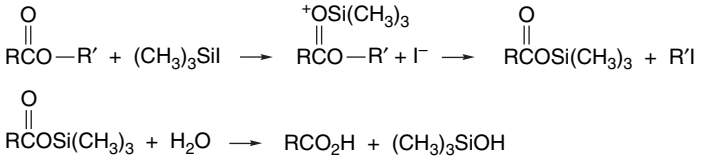
Allylic ethers are cleaved in a matter of a few minutes by TMSI under in situ conditions.




Ref. 94

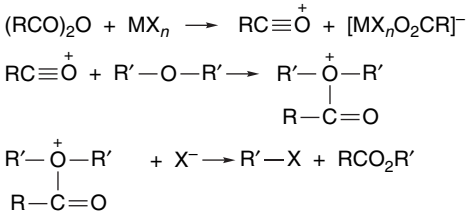
Diiodosilane, $SiH_2I_2$, is an especially effective reagent for cleaving secondary alkyl ethers.[95]

TMSI also effects rapid cleavage of esters. The cleavage step involves iodide attack on the O-silylated ester. The first products formed are trimethylsilyl esters, but these are hydrolyzed rapidly on exposure to water.[96]




Benzyl, methyl, and *t*-butyl esters are rapidly cleaved, but secondary esters react more slowly. In the case of *t*-butyl esters, the initial silylation is followed by a rapid ionization to the *t*-butyl cation.

Ether cleavage can also be effected by reaction with acetic anhydride and Lewis acids such as $BF_3$, $FeCl_3$, and $MgBr_2$.[97] Mechanistic investigations point to acylium ions generated from the anhydride and Lewis acid as the reactive electrophile.

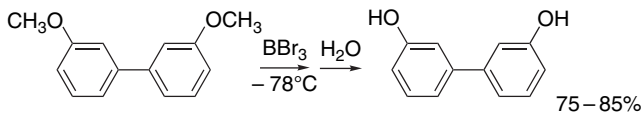



Scheme 3.3 gives some specific examples of ether and ester cleavage reactions. Entries 1 and 2 illustrate the use of boron tribromide for ether cleavage. The reactions are conducted at dry ice-acetone temperature and the exposure to water on workup hydrolyzes residual O−B bonds. In the case of Entry 2, the primary hydroxy group that is deprotected lactonizes spontaneously. The reaction in Entry 3 uses HBr in acetic acid to cleave a methyl aryl ether. This reaction was part of a scale-up of the synthesis of a drug candidate molecule. Entries 4 to 6 are examples of the cleavage of ethers and esters using TMSI. The selectivity exhibited in Entry 6 for

94. A. Kamal, E. Laxman, and N. V. Rao, *Tetrahedron Lett.*, **40**, 371 (1999).
95. E. Keinan and D. Perez, *J. Org. Chem.*, **52**, 4846 (1987).
96. T. L. Ho and G. A. Olah, *Angew. Chem. Int. Ed. Engl.*, **15**, 774 (1976); M. E. Jung and M. A. Lyster, *J. Am. Chem. Soc.*, **99**, 968 (1977).
97. C. R. Narayanan and K. N. Iyer, *J. Org. Chem.*, **30**, 1734 (1965); B. Ganem and V. R. Small, Jr., *J. Org. Chem.*, **39**, 3728 (1974); D. J. Goldsmith, E. Kennedy, and R. G. Campbell, *J. Org. Chem.*, **40**, 3571 (1975).

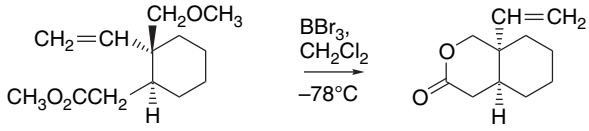
**Scheme 3.3. Cleavage of Ethers and Esters**

1[a]



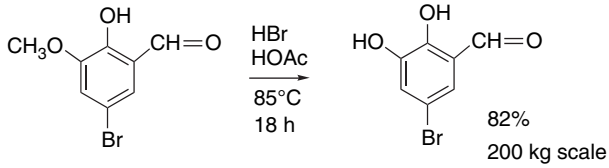

75 – 85%

2[b]



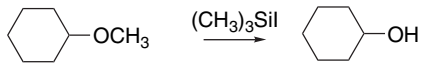

88%

3[c]



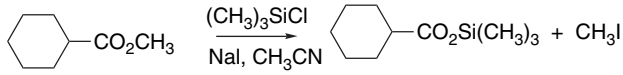

82%
200 kg scale

4[d]



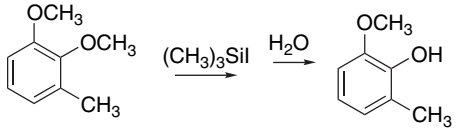

83–89%

5[e]

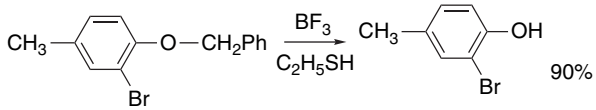



86%

6[f]

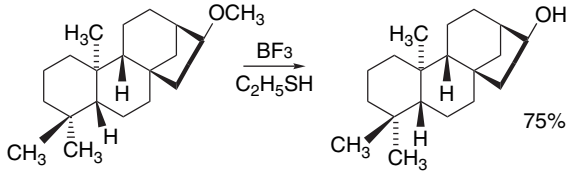



7[g]



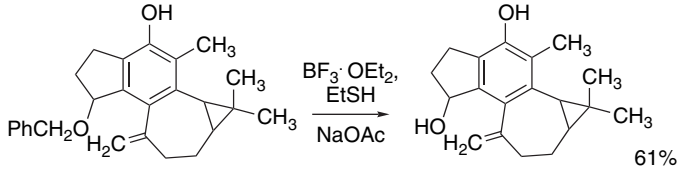

90%

8[h]



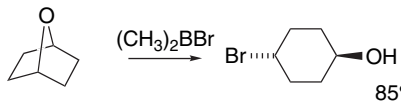

75%

9[i]



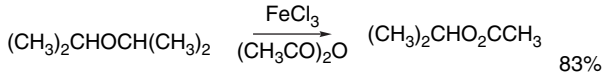

61%

10[j]




85%

11[k]



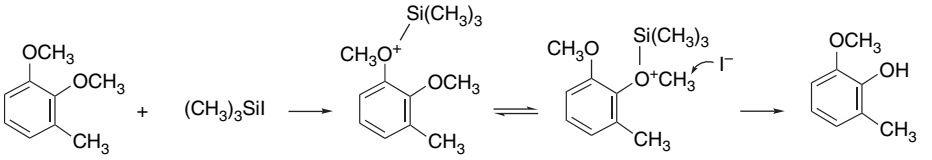

83%

(*Continued*)

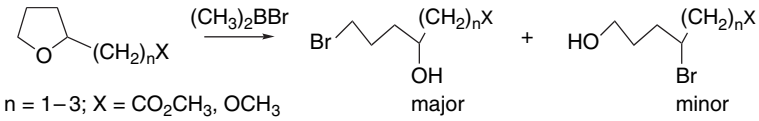
**Scheme 3.3. (*Continued*)**

a. J. F. W. McOmie and D. E. West, *Org. Synth.*, **V**, 412 (1973).
b. P. A. Grieco, K. Hiroi, J. J. Reap, and J. A. Noguez, *J. Org. Chem.*, **40**, 1450 (1975).
c. T. E. Jacks, D. T. Belmont, C. A. Briggs, N. M. Horne, G. D. Kanter, G. L. Karrick, J. J. Krikke, R. J. McCabe, J. G. Mustakis, T. N. Nanninga, G. S. Risendorph, R. E. Seamans, R. Skeean, D. D. Winkle, and T. M. Zennie, *Org. Proc. Res. Dev.*, **8**, 201 (2004).
d. M. E. Jung and M. A. Lyster, *Org. Synth.*, **59**, 35 (1980).
e. T. Morita, Y. Okamoto, and H. Sakurai, *J. Chem. Soc., Chem. Commun.*, 874 (1978).
f. E. H. Vickery, L. F. Pahler, and E. J. Eisenbraun, *J. Org. Chem.*, **44**, 4444 (1979).
g. K. Fuji, K. Ichikawa, M. Node, and E. Fujita, *J. Org. Chem.*, **44**, 1661 (1979).
h. M. Nobe, H. Hori, and E. Fujita, *J. Chem. Soc. Perkin Trans.*, **1**, 2237 (1976).
i. A. B. Smith, III, N. J. Liverton, N. J. Hrib, H. Sivaramakrishnan, and K. Winzenberg, *J. Am. Chem. Soc.*, **108**, 3040 (1986).
j. Y. Guidon, M. Therien, Y. Girard, and C. Yoakim, *J. Org. Chem.*, **52**, 1680 (1987).
k. B. Ganem and V. R. Small, Jr., *J. Org. Chem.*, **39**, 3728 (1974).

cleavage of the more hindered of the two ether groups may reflect a steric acceleration of the nucleophilic displacement step.




Entries 7 to 9 illustrate the use of the $BF_3$-EtSH reagent combination. The reaction in Entry 9 was described as "troublesome in the extreme." The problem is that the ether is both a primary benzylic ether and a secondary one, the latter associated with a ring having several ERG substituents. Electrophilic conditions lead to preferential cleavage of the secondary benzylic bond and formation of elimination products. The reaction was done successfully in the presence of excess NaOAc, which presumably allows the nucleophilic $S_N2$ cleavage of the primary benzyl bond to dominate by reducing the reactivity of the electrophilic species that are present. The cleavage of the cyclic ether shown in Entry 10 occurs with inversion of configuration at the reaction site, as demonstrated by the *trans* stereochemistry of the product. When applied to 2-substituted tetrahydrofurans, the reaction gives mainly cleavage of the C(5)−O bond, indicating that steric access of the nucleophilic component of the reaction is dominant in determining regioselectivity.

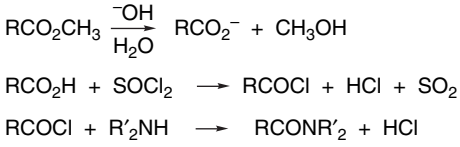



Entry 11 illustrates a cleavage reaction using an acylating agent in conjunction with a Lewis acid.

## 3.4. Interconversion of Carboxylic Acid Derivatives

The classes of compounds that are conveniently considered together as derivatives of carboxylic acids include the acyl chlorides, carboxylic acid anhydrides, esters, and amides. In the case of simple aliphatic and aromatic acids, synthetic transformations

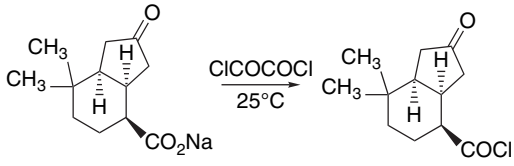
among these derivatives are usually straightforward, involving such fundamental reactions as ester saponification, formation of acyl chlorides, and the reactions of amines with acid anhydrides or acyl chlorides to form amides. The mechanisms of these reactions are discussed in Section 7.4 of Part A.



When a multistep synthesis is being undertaken with other sensitive functional groups present in the molecule, milder reagents and reaction conditions may be necessary. As a result, many alternative methods for effecting interconversion of the carboxylic acid derivatives have been developed and some of the most useful reactions are considered in the succeeding sections.

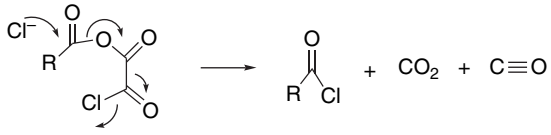
### 3.4.1. Acylation of Alcohols

The traditional method for transforming carboxylic acids into reactive acylating agents capable of converting alcohols to esters or amines to amides is by formation of the acyl chloride. Molecules devoid of acid-sensitive functional groups can be converted to acyl chlorides with thionyl chloride or phosphorus pentachloride. When milder conditions are necessary, the reaction of the acid or its sodium salt with oxalyl chloride provides the acyl chloride. When a salt is used, the reaction solution remains essentially neutral.

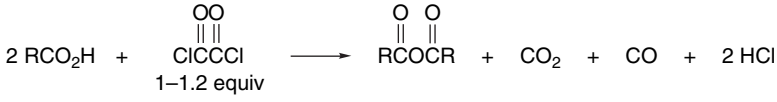


Ref. 98

This reaction involves formation of a mixed anhydride-chloride of oxalic acid, which then decomposes, generating both $CO_2$ and CO.

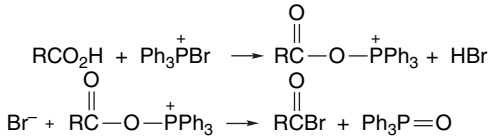


Treatment of carboxylic acids with half an equivalent of oxalyl chloride can generate anhydrides.[99]

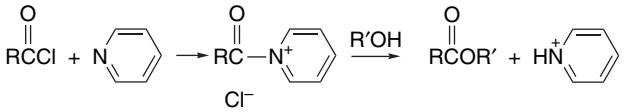


[98.] M. Miyano and C. R. Dorn, *J. Org. Chem.*, **37**, 268 (1972).
[99.] R. Adams and L. H. Urich, *J. Am. Chem. Soc.*, **42**, 599 (1920).

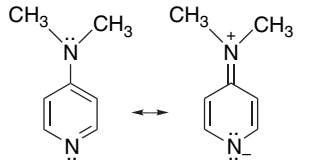
Carboxylic acids can be converted to acyl chlorides and bromides by a combination of triphenylphosphine and a halogen source. Triphenylphosphine and carbon tetrachloride convert acids to the corresponding acyl chloride.[100] Similarly, carboxylic acids react with the triphenyl phosphine-bromine adduct to give acyl bromides.[101] Triphenylphosphine–*N*-bromosuccinimide also generates acyl bromide in situ.[102] All these reactions involve acyloxyphosphonium ions and are mechanistically analogous to the alcohol-to-halide conversions that are discussed in Section 3.1.2.



Acyl chlorides are highly reactive acylating agents and react very rapidly with alcohols and other nucleophiles. Preparative procedures often call for use of pyridine as a catalyst. Pyridine catalysis involves initial formation of an acyl pyridinium ion, which then reacts with the alcohol. Pyridine is a better nucleophile than the neutral alcohol, but the acyl pyridinium ion reacts more rapidly with the alcohol than the acyl chloride.[103]



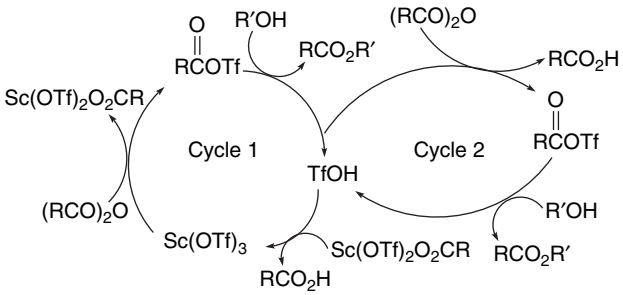
An even stronger catalytic effect is obtained when 4-dimethylaminopyridine (DMAP) is used.[104] The dimethylamino group acts as an electron donor, increasing both the nucleophilicity and basicity of the pyridine nitrogen.



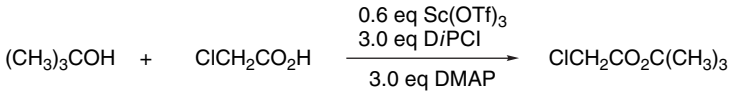
The inclusion of DMAP to the extent of 5–20 mol % in acylations by acid anhydrides and acyl chlorides increases acylation rates by up to four orders of magnitude and permits successful acylation of tertiary and other hindered alcohols. The reagent combination of an acid anhydride with $MgBr_2$ and a hindered tertiary amine, e.g., $(i\text{-Pr})_2NC_2H_5$ or 1,2,2,6,6,-pentamethylpiperidine, gives an even more reactive acylation system, which is useful for hindered and sensitive alcohols.[105]

100. J. B. Lee, *J. Am. Chem. Soc.*, **88**, 3440 (1966).
101. H. J. Bestmann and L. Mott, *Justus Liebigs Ann. Chem.*, **693**, 132 (1966).
102. K. Sucheta, G. S. R. Reddy, D. Ravi, and N. Rama Rao, *Tetrahedron Lett.*, **35**, 4415 (1994).
103. A. R. Fersht and W. P. Jencks, *J. Am. Chem. Soc.*, **92**, 5432, 5442 (1970).
104. G. Hoefle, W. Steglich, and H. Vorbruggen, *Angew. Chem. Int. Ed. Engl.*, **17**, 569 (1978); E. F. V. Scriven, *Chem. Soc. Rev.*, **12**, 129 (1983); R. Murugan and E. F. V. Scriven, *Aldrichimica Acta*, **36**, 21 (2003).
105. E. Vedejs and O. Daugulis, *J. Org. Chem.*, **61**, 5702 (1996).

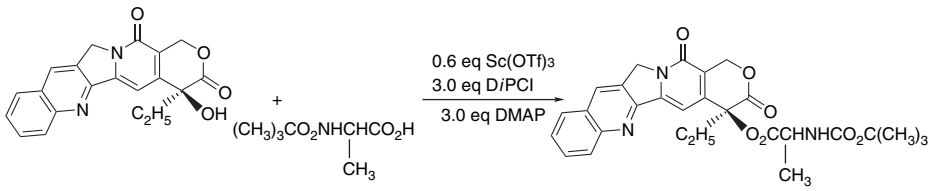
Another efficient catalyst for acylation is $Sc(O_3SCF_3)_3$, which can be used in combination with anhydrides[106] and other reactive acylating agents[107] and is a mild reagent for acylation of tertiary alcohols. Mechanistic investigation of $Sc(O_3SCF_3)_3$-catalyzed acylation indicates that triflic acid is involved. Acylation is stopped by the presence of a sterically hindered base such as 2,6-di-(*t*-butyl)-4-methylpyridine. The active acylating agent appears to be the acyl triflate. Two catalytic cycles operate. Cycle 2 requires only triflic acid, whereas Cycle 1 involves both the scandium salt and triflic acid.[108]




The acylation of tertiary alcohols can be effected by use of $Sc(O_3SCF_3)_3$ with diisopropylcarbodiimide (D-*i*-PCI) and DMAP.[109]



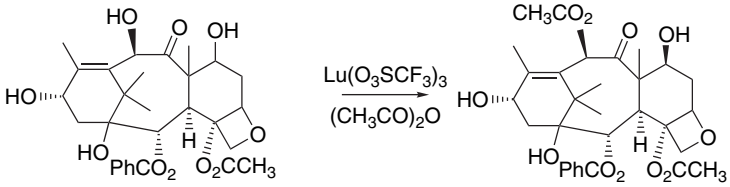

This method was effective for acylation of a hindered tertiary alcohol in the anticancer agent camptothecin by protected amino acids.



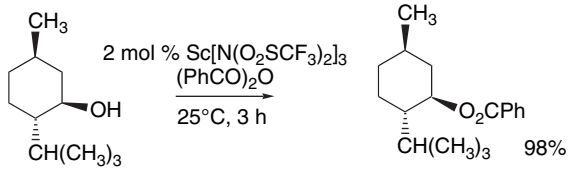

Ref. 110

Lanthanide triflates have similar catalytic effects. $Yb(O_3SCF_3)_3$ and $Lu(O_3SCF_3)_3$, for example, were used in selective acylation of 10-deacetylbaccatin III, an important intermediate for preparation of the antitumor agent paclitaxel.[111]

106. K. Ishihara, M. Kubota, H. Kurihara, and H. Yamamoto, *J. Org. Chem.*, **61**, 4560 (1996); A. G. M. Barrett and D. C. Braddock, *J. Chem. Soc., Chem. Commun.*, 351 (1997).
107. H. Zhao, A. Pendri, and R. B. Greenwald, *J. Org. Chem.*, **63**, 7559 (1998).
108. R. Dummeunier and I. E. Marko, *Tetrahedron Lett.*, **45**, 825 (2004).
109. H. Zhao, A. Pendri, and R. B. Greenwald, *J. Org. Chem.*, **63**, 7559 (1998).
110. R. R. Greenwald, A. Pendri, and H. Zhao, *Tetrahedron: Asymmetry*, **9**, 915 (1998).
111. E. W. P. Damen, L. Braamer, and H. W. Scheeren, *Tetrahedron Lett.*, **39**. 6081 (1998).

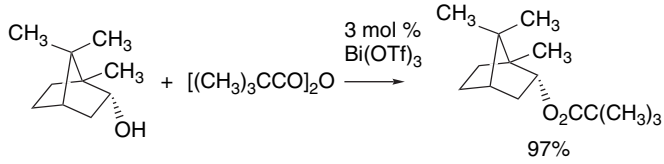



Scandium triflimidate, $Sc[N(SO_2CF_3)_2]_3$, is also a very active acylation catalyst.

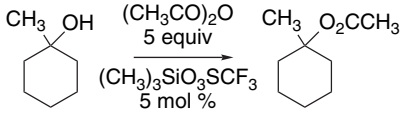



Ref. 112

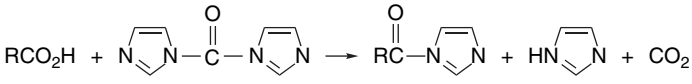
Bismuth(III) triflate is also a powerful acylation catalyst that catalyzes reactions with acetic anhydride and other less reactive anhydrides such as benzoic and pivalic anhydrides.[113] Good results are achieved with tertiary and hindered secondary alcohols, as well as with alcohols containing acid- and base-sensitive functional groups.




Trimethylsilyl triflate is also a powerful catalyst for acylation by anhydrides. Reactions of alcohols with a modest excess (1.5 equival) of anhydride proceed in inert solvents at 0° C. Even tertiary alcohols react rapidly.[114] The active acylation reagent is presumably generated by O-silylation of the anhydride.

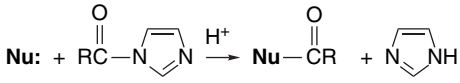



In addition to acyl halides and acid anhydrides, there are a number of milder and more selective acylating agents that can be readily prepared from carboxylic acids. Imidazolides, the *N*-acyl derivatives of imidazole, are examples.[115] Imidazolides are isolable substances and can be prepared directly from the carboxylic acid by reaction with carbonyldiimidazole.



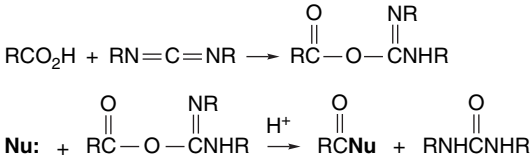

112. K. Ishihara, M. Kubota, and H. Yamamoto, *Synlett*, 265 (1996).
113. A. Orita, C. Tanahashi, A. Kakuda, and J. Otera, *J. Org. Chem.*, **66**, 8926 (2001).
114. P. A. Procopiou, S. P. D. Baugh, S. S. Flack, and G. G. A. Inglis, *J. Org. Chem.*, **63**, 2342 (1998).
115. H. A. Staab and W. Rohr, *Newer Methods Prep. Org. Chem.*, **5**, 61 (1968).

Two factors are responsible for the reactivity of the imidazolides as acylating reagents. One is the relative weakness of the "amide" bond. Owing to the aromatic character of imidazole nitrogens, there is little of the N → C=O delocalization that stabilizes normal amides. The reactivity of the imidazolides is also enhanced by protonation of the other imidazole nitrogen, which makes the imidazole ring a better leaving group.

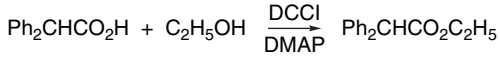


Imidazolides can also be activated by N-alkylation with methyl triflate.[116] Imidazolides react with alcohols on heating to give esters and react at room temperature with amines to give amides. Imidazolides are particularly appropriate for acylation of acid-sensitive materials.

Dicyclohexylcarbodiimide (DCCI) is an example of a reagent that converts carboxylic acids to reactive acylating agents. This compound has been widely applied in the acylation step in the synthesis of polypeptides from amino acids[117] (see also Section 13.3.1). The reactive species is an *O*-acyl isourea. The acyl group is highly reactive because the nitrogen is susceptible to protonation and the cleavage of the acyl-oxygen bond converts the carbon-nitrogen double bond of the isourea to a more stable carbonyl group.[118]



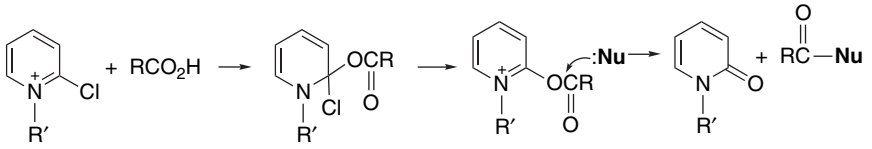
The combination of carboxyl activation by DCCI and catalysis by DMAP provides a useful method for in situ activation of carboxylic acids for reaction with alcohols. The reaction proceeds at room temperature.[119]



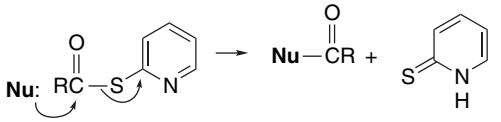
2-Chloropyridinium[120] and 3-chloroisoxazolium[121] cations also activate carboxy groups toward nucleophilic attack. In each instance the halide is displaced from the heterocycle by the carboxylate via an addition-elimination mechanism. Nucleophilic attack on the activated carbonyl group results in elimination of the heterocyclic ring, with the departing oxygen being converted to an amidelike structure. The positive

116. G. Ulibarri, N. Choret, and D. C. H. Bigg, *Synthesis*, 1286 (1996).
117. F. Kurzer and K. Douraghi-Zadeh, *Chem. Rev.*, **67**, 107 (1967).
118. D. F. DeTar and R. Silverstein, *J. Am. Chem. Soc.*, **88**, 1013, 1020 (1966); D. F. DeTar, R. Silverstein, and F. F. Rogers, Jr., *J. Am. Chem. Soc.*, **88**, 1024 (1966).
119. A. Hassner and V. Alexanian, *Tetrahedron Lett.*, 4475 (1978); B. Neises and W. Steglich, *Angew. Chem. Int. Ed. Engl.*, **17**, 522 (1978).
120. T. Mukaiyama, M. Usui, E. Shimada, and K. Saigo, *Chem. Lett.*, 1045 (1975).
121. K. Tomita, S. Sugai, T. Kobayashi, and T. Murakami, *Chem. Pharm. Bull.*, **27**, 2398 (1979).

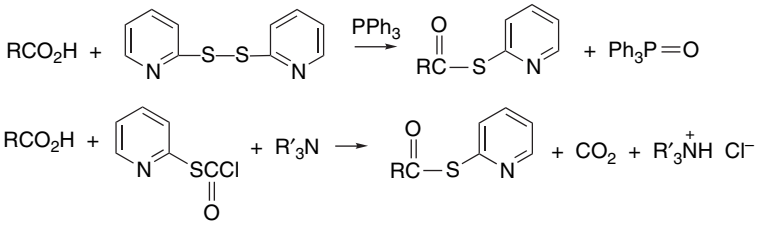
charge on the heterocyclic ring accelerates both the initial addition step and the subsequent elimination of the heterocycle.



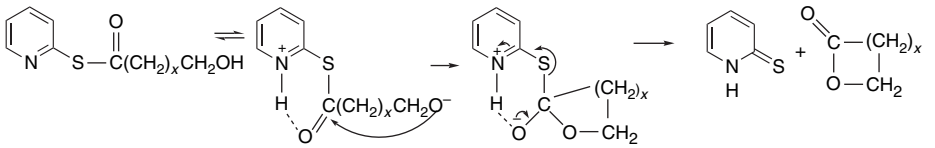
Carboxylic acid esters of thiols are considerably more reactive as acylating reagents than the esters of alcohols. Particularly reactive are esters of pyridine-2-thiol because there is an additional driving force in the formation of the more stable pyridine-2-thione tautomer.



Additional acceleration of acylation can be obtained by inclusion of cupric salts, which coordinate at the pyridine nitrogen. This modification is useful for the preparation of highly hindered esters.[122] Pyridine-2-thiol esters can be prepared by reaction of the carboxylic acid with 2,2′-dipyridyl disulfide and triphenylphosphine[123] or directly from the acid and 2-pyridyl thiochloroformate.[124]

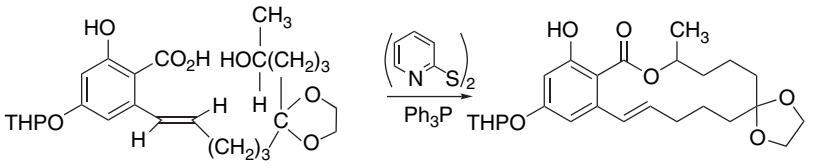


The 2-pyridyl and related 2-imidazolyl disulfides have found special use in the closure of large lactone rings.[125] Structures of this type are encountered in a number of antibiotics and other natural products and require mild conditions for cyclization because numerous other sensitive functional groups are present. It has been suggested that the pyridyl and imidazoyl thioesters function by a mechanism in which the heterocyclic nitrogen acts as a base, deprotonating the alcohol group. This proton transfer provides a cyclic TS in which hydrogen bonding can enhance the reactivity of the carbonyl group.[126]



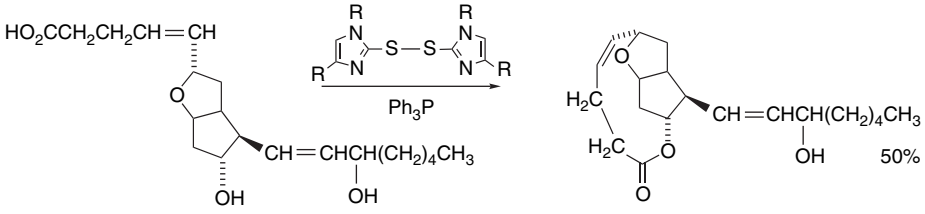
122. S. Kim and J. I. Lee, *J. Org. Chem.*, **49**, 1712 (1984).
123. T. Mukaiyama, R. Matsueda, and M. Suzuki, *Tetrahedron Lett.*, 1901 (1970).
124. E. J. Corey and D. A. Clark, *Tetrahedron Lett.*, 2875 (1979).
125. E. J. Corey and K. C. Nicolaou, *J. Am. Chem. Soc.*, **96**, 5614 (1974); K. C. Nicolaou, *Tetrahedron*, **33**, 683 (1977).
126. E. J. Corey, K. C. Nicolaou, and L. S. Melvin, Jr., *J. Am. Chem. Soc.*, **97**, 654 (1975); E. J. Corey, D. J. Brunelle, and P. J. Stork, *Tetrahedron Lett.*, 3405 (1976).

Good yields of large ring lactones are achieved by this method.



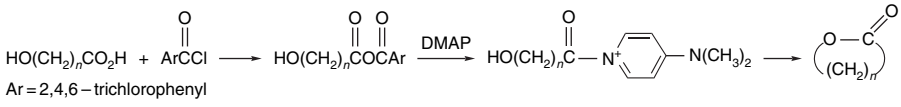

75%

Ref. 96

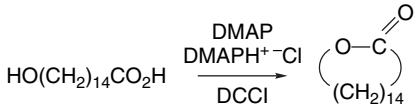



Ref. 127

Use of 2,4,6-trichlorobenzoyl chloride, $Et_3N$, and DMAP, known as the *Yamaguchi method*,[128] is frequently used to effect macrolactonization. The reaction is believed to involve formation of the mixed anhydride with the aroyl chloride, which then forms an acyl pyridinium ion on reaction with DMAP.[129]




Intramolecular lactonization can also be carried out with DCCI and DMAP. As with most other macrolactonizations, the reactions must be carried out in rather dilute solution to promote the intramolecular cyclization in competition with intermolecular reaction, which leads to dimers or higher oligomers. A study with 15-hydroxypentadecanoic acid demonstrated that a proton source is beneficial under these conditions and found the hydrochloride of DMAP to be convenient.[130]



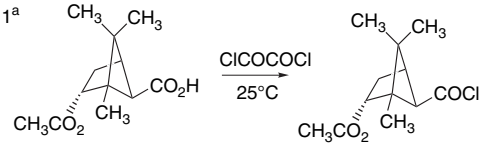

Scheme 3.4 gives some typical examples of the preparation and use of active acylating agents from carboxylic acids. Entries 1 and 2 show generation of acyl chlorides by reaction of carboxylic acids or salts with oxalyl chloride. Entry 3 shows a convenient preparation of 2-pyridylthio esters, which are themselves potential acylating agents (see p. 248). Entries 4 to 6 employ various coupling agents to form esters. Entries 7 and 8 illustrate acylations catalyzed by DMAP. Entries 9 to 13 are

127. E. J. Corey, H. L. Pearce, I. Szekely, and M. Ishiguro, *Tetrahedron Lett.*, 1023 (1978).
128. H. Saiki, T. Katsuki, and M. Yamaguchi, *Bull. Chem. Soc. Jpn.*, **52**, 1989 (1979).
129. M. Hikota, H. Tone, K. Horita, and O. Yonemitsu, *J. Org. Chem.*, **55**, 7 (1990).
130. E. P. Boden and G. E. Keck, *J. Org. Chem.*, **50**, 2394 (1985).

## Scheme 3.4. Preparation and Reactions of Active Acylating Agents

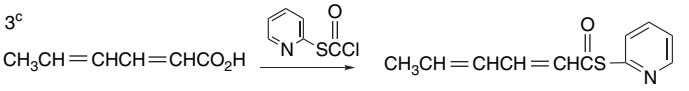
A. Generation of acylation reagents

1[a]



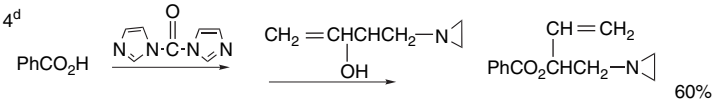

2[b]


3[c]

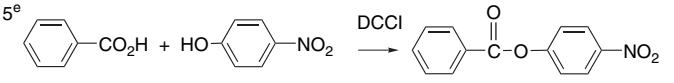



B. Esterification.

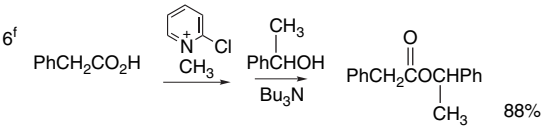
4[d]



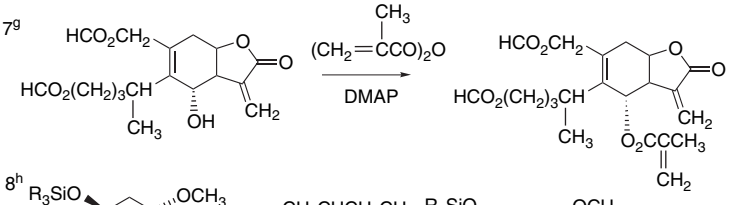

5[e]



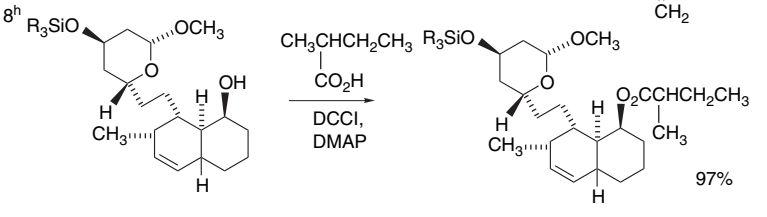

6[f]




7[g]

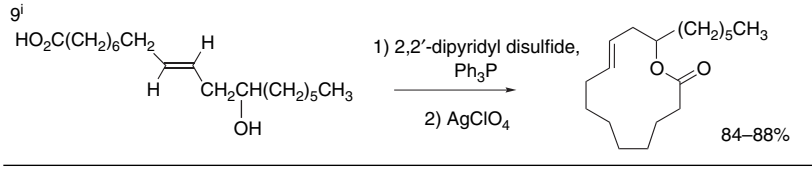



8[h]

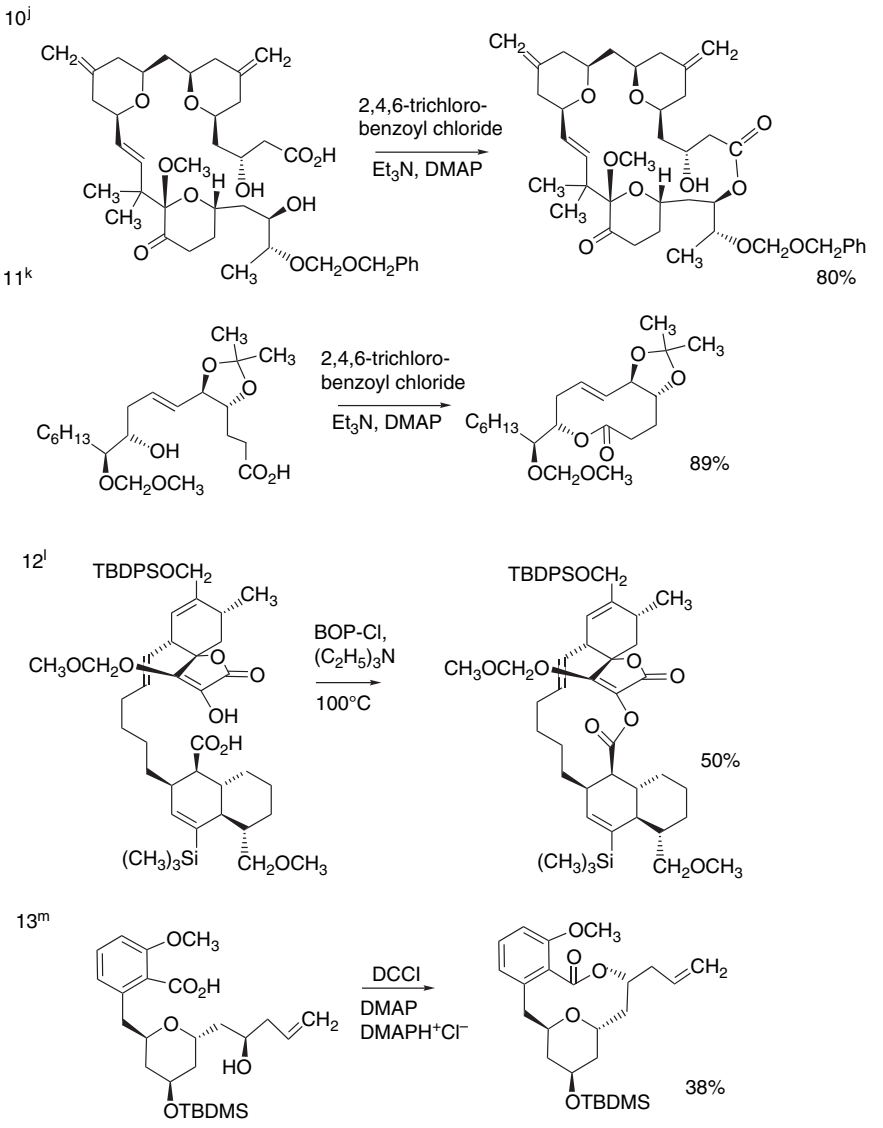



C. Macrolactonization

9[i]




(*Continued*)




a. J. Meinwald, J. C. Shelton, G. L. Buchanan, and A. Courtain, *J. Org. Chem.*, **33**, 99 (1968).
b. U. T. Bhalerao, J. J. Plattner, and H. Rapoport, *J. Am. Chem. Soc.*, **92**, 3429 (1970).
c. E. J. Corey and D. A. Clark, *Tetrahedron Lett.*, 2875 (1979).
d. H. A. Staab and Rohr, *Chem. Ber.*, **95**, 1298 (1962).
e. S. Neeklakantan, R. Padmasani, and T. R. Seshadri, *Tetrahedron*, **21**, 3531 (1965).
f. T. Mukaiyama, M. Usui, E. Shimada, and K. Saigo, *Chem. Lett.*, 1045 (1970).
g. P. A. Grieco, T. Oguri, S. Gilman, and G. DeTitta, *J. Am. Chem. Soc.*, **100**, 1616 (1978).
h. Y.-L. Yang, S. Manna, and J. R. Falck, *J. Am. Chem. Soc.*, **106**, 3811 (1984).
i. A. Thalman, K. Oertle, and H. Gerlach, *Org. Synth.*, **63**, 192 (1984).
j. G. E. Keck and A. P. Troung, *Org. Lett.*, **7**, 2153 (2005).
k. P. Kumar and S. V. Naidu, *J. Org. Chem.*, **70**, 4207 (2005).
l. W. R. Roush and and R. J. Sciotti, *J. Am. Chem. Soc.*, **120**, 7411 (1998).
m. A. Lewis, I. Stefanuti, S. A. Swain, S. A. Smith, and R. J. K. Taylor, *Org. Biomol. Chem.*, **1**, 81 (2003)

examples of macrocyclizations. Entry 9 uses the di-2-pyridyl disulfide-$Ph_3P$ method. The cyclization was done in approximately 0.02 *M* acetonitrile by dropwise addition of the disulfide. Entries 10 and 11 are examples of application of the Yamaguchi macrolactonization procedure via the mixed anhydride with 2,4,6-trichlorobenzoyl chloride. The reaction in Entry 12 uses BOP-Cl as the coupling reagent. This particular reagent gave the best results among the several alternatives that were explored. Further discussion of this reagent can be found in Section 13.3.1. Entry 13 is an example of the use of the DCCI-DMAP reagent combination.

### 3.4.2. Fischer Esterification

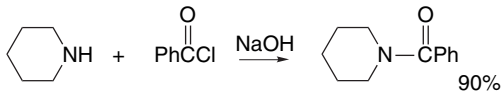
As noted in the preceding section, one of the most general methods of synthesis of esters is by reaction of alcohols with an acyl chloride or other activated carboxylic acid derivative. Section 3.2.5 dealt with two other important methods, namely, reactions with diazoalkanes and reactions of carboxylate salts with alkyl halides or sulfonate esters. There is also the acid-catalyzed reaction of carboxylic acids with alcohols, which is called the *Fischer esterification*.

$$RCO_2H + R'OH \xrightarrow{H^+} RCO_2R' + H_2O$$

This is an equilibrium process and two techniques are used to drive the reaction to completion. One is to use a large excess of the alcohol, which is feasible for simple and inexpensive alcohols. The second method is to drive the reaction forward by irreversible removal of water, and azeotropic distillation is one way to accomplish this. Entries 1 to 4 in Scheme 3.5 are examples of acid-catalyzed esterifications. Entry 5 is the preparation of a diester starting with an anhydride. The initial opening of the anhydride ring is followed by an acid-catalyzed esterification.

### 3.4.3. Preparation of Amides

The most common method for preparation of amides is the reaction of ammonia or a primary or secondary amine with one of the reactive acylating reagents described in Section 3.4.1. Acid anhydrides give rapid acylation of most amines and are convenient if available. However, only one of the two acyl groups is converted to an amide. When acyl halides are used, some provision for neutralizing the hydrogen halide that is formed is necessary because it will react with the amine to form the corresponding salt. The *Schotten-Baumann conditions*, which involve shaking an amine with excess anhydride or acyl chloride and an alkaline aqueous solution, provide a very satisfactory method for preparation of simple amides.




Ref. 131

A great deal of work has been done on the in situ activation of carboxylic acids toward nucleophilic substitution by amines. This type of reaction is fundamental for synthesis of polypeptides (see also Section 13.3.1). Dicyclohexylcarbodiimide

[131.] C. S. Marvel and W. A. Lazier, *Org. Synth.*, **I**, 99 (1941).

**Scheme 3.5. Acid-Catalyzed Esterification**

1[a]

$$CH_3CO_2H + HOCH_2CH_2CH_2Cl \xrightarrow[\text{benzene, removal of water}]{ArSO_3H} CH_3CO_2CH_2CH_2CH_2Cl \quad 93–95\%$$

2[b]

$$HO_2CC{\equiv}CCO_2H + CH_3OH \text{ (20 equiv)} \xrightarrow[25°C,\ 4\ days]{H_2SO_4} CH_3O_2CC{\equiv}CCO_2CH_3 \quad 72–88\%$$

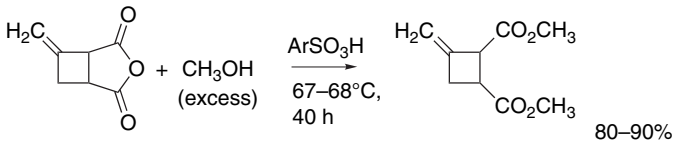
3[c]

$$CH_3CH{=}CHCO_2H + CH_3CH(OH)CH_2CH_3 \xrightarrow[\text{benzene, removal of water}]{H_2SO_4} CH_3CH{=}CHCO_2CH(CH_3)CH_2CH_3 \quad 85–90\%$$

4[d]

$$PhCH(OH)CO_2H + C_2H_5OH \text{ (excess)} \xrightarrow[78°C,\ 5\ h]{HCl} PhCH(OH)CO_2C_2H_5 \quad 82–86\%$$

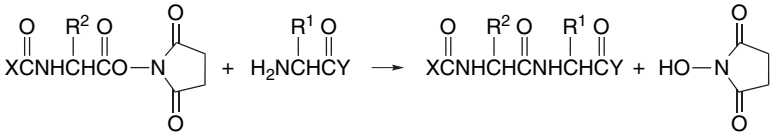
5[e]




80–90%

a. C. F. H. Allen and F. W. Spangler, *Org. Synth.*, **III**, 203 (1955).
b. E. H. Huntress, T. E. Lesslie, and J. Bornstein, *Org. Synth.*, **IV**, 329 (1963).
c. J. Munch-Petersen, *Org. Synth.*, **V**, 762 (1973).
d. E. L. Eliel, M. T. Fisk, and T. Prosser, *Org. Synth.*, **IV**, 169 (1963).
e. H. B. Stevenson, H. N. Cripps, and J. K. Williams, *Org. Synth.*, **V**, 459 (1973).

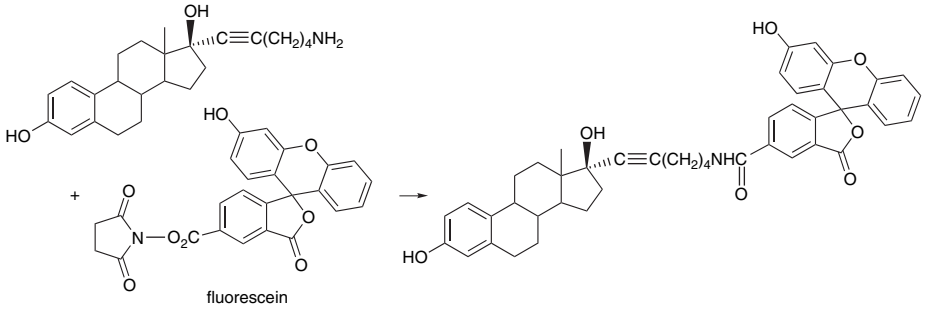
(DCCI) is often used for coupling carboxylic acids and amines to give amides. Since amines are better nucleophiles than alcohols, the leaving group in the acylation reagent need not be as reactive as is necessary for alcohols. The *p*-nitrophenyl[132] and 2,4,5-trichlorophenyl[133] esters of amino acids are sufficiently reactive toward amines to be useful in amide synthesis. Acyl derivatives of *N*-hydroxysuccinimide are also useful for synthesis of peptides and other types of amides.[134,135] Like the *p*-nitrophenyl esters, the acylated *N*-hydroxysuccinimides can be isolated and purified, but react rapidly with free amino groups.




The *N*-hydroxysuccinimide that is liberated is easily removed because of its solubility in dilute base. The relative stability of the anion of *N*-hydroxysuccinimide is also responsible for the acyl derivative being reactive toward nucleophilic attack by an

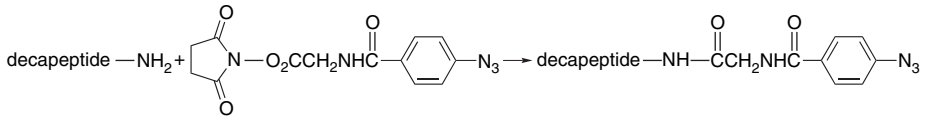
132. M. Bodanszky and V. DuVigneaud, *J. Am. Chem. Soc.*, **81**, 5688 (1959).
133. J. Pless and R. A. Boissonnas, *Helv. Chim. Acta*, **46**, 1609 (1963).
134. G. W. Anderson, J. E. Zimmerman, and F. M. Callahan, *J. Am. Chem. Soc.*, **86**, 1839 (1964).
135. E. Wunsch and F. Drees, *Chem. Ber.*, **99**, 110 (1966); E. Wunsch, A. Zwick, and G. Wendlberger, *Chem. Ber.*, **100**, 173 (1967).

amino group. Esters of *N*-hydroxysuccinimide are also used to carry out chemical modification of peptides, proteins, and other biological molecules by acylation of nucleophilic groups in these molecules. For example, detection of estradiol antibodies can be accomplished using an estradiol analog to which a fluorescent label has been attached.

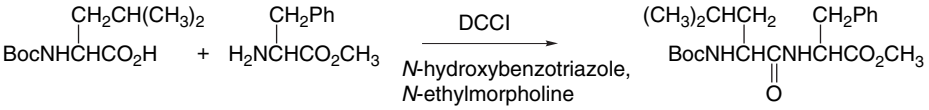



Ref. 136

Similarly, photolabels, such as 4-azidobenzoylglycine can be attached to peptides and used to detect binding sites in proteins.[137]



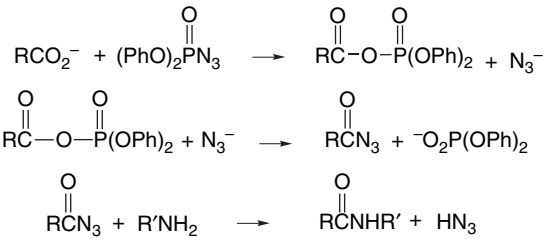

1-Hydroxybenzotriazole is also useful in conjunction with DCCI.[138] For example, Boc-protected leucine and the methyl ester of phenylalanine can be coupled in 88% yield with these reagents.



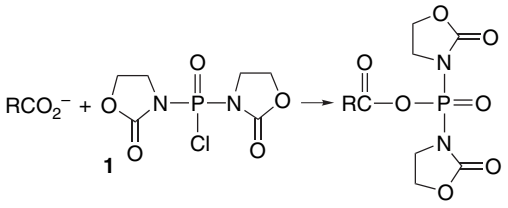

Ref. 139

Carboxylic acids can also be activated by the formation of mixed anhydrides with various phosphoric acid derivatives. Diphenyl phosphoryl azide, for example, is an effective reagent for conversion of amines to amides.[140] The proposed mechanism involves formation of the acyl azide as a reactive intermediate.

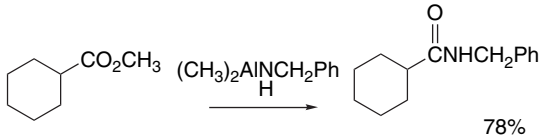
136. M. Adamczyk, Y.-Y. Chen, J. A. Moore, and P. G. Mattingly, *Biorg. Med. Chem. Lett.*, **8**, 1281 (1998); M. Adamczyk, J. R. Fishpaugh, and K. J. Heuser, *Bioconjugate Chem.*, **8**, 253 (1997).
137. G. C. Kundu, I. Ji, D. J. McCormick, and T. H. Ji, *J. Biol. Chem.*, **271**, 11063 (1996).
138. W. Konig and R. Geiger, *Chem. Ber.*, **103**, 788 (1970).
139. M. Bodanszky and A. Bodanszky, *The Practice of Peptide Synthesis*, 2nd Edition, Springer-Verlag, Berlin, 1994, pp. 119–120.
140. T. Shioiri and S. Yamada, *Chem. Pharm. Bull.*, **22**, 849 (1974); T. Shioiri and S. Yamada, *Chem. Pharm. Bull.*, **22**, 855 (1974); T. Shioiri and S. Yamada, *Chem. Pharm. Bull.*, **22**, 859 (1974).



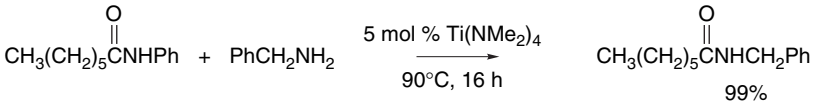
Another useful reagent for amide formation is compound **1**, known as BOP-Cl,[141] which also proceeds by formation of a mixed carboxylic phosphoric anhydride.



Another method for converting esters to amides involves aluminum amides, which can be prepared from trimethylaluminum and the amine. These reagents convert esters directly to amides at room temperature.[142]



The driving force for this reaction is the strength of the aluminum-oxygen bond relative to the aluminum-nitrogen bond. This reaction provides a good way of making synthetically useful amides of *N*-methoxy-*N*-methylamine.[143] Trialkylaminotin and *bis*-(hexamethyldisilylamido)tin amides, as well as *tetrakis*-(dimethylamino)titanium, show similar reactivity.[144] These reagents can also catalyze exchange reactions between amines and amides under moderate conditions.[145] For example, whereas exchange of benzylamine into *N*-phenylheptanamide occurs very slowly at 90° C in the absence of catalyst (> months), the conversion is effected in 16 h by $Ti[N(CH_3)_2]_4$.



[141] J. Diago-Mesequer, A. L. Palomo-Coll, J. R. Fernandez-Lizarbe, and A. Zugaza-Bilbao, *Synthesis*, 547 (1980); R. D. Tung, M. K. Dhaon, and D. H. Rich, *J. Org. Chem.*, **51**, 3350 (1986); W. J. Collucci, R. D. Tung, J. A. Petri, and D. H. Rich, *J. Org. Chem.*, **55**, 2895 (1990); J. Jiang, W. R. Li, R. M. Przeslawski, and M. M. Joullie, *Tetrahedron Lett.*, **34**, 6705 (1993).

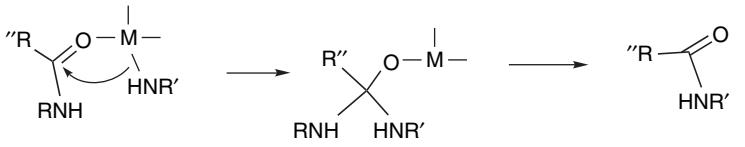
[142] A. Basha, M. Lipton, and S. M. Weinreb, *Tetrahedron Lett.*, 4171 (1977); A. Solladie-Cavallo and M. Bencheqroun, *J. Org. Chem.*, **57**, 5831 (1992).

[143] J. I. Levin, E. Turos, and S. M. Weinreb, *Synth. Commun.*, **12**, 989 (1982); T. Shimizu, K. Osako, and T. Nakata, *Tetrahedron Lett.*, **38**, 2685 (1997).

[144] G. Chandra, T. A. George, and M. F. Lappert, *J. Chem. Soc. C*, 2565 (1969); W.-B. Wang and E. J. Roskamp, *J. Org. Chem.*, **57**, 6101 (1992); W.-B. Wang, J. A. Restituyo, and E. J. Roskamp, *Tetrahedron Lett.*, **34**, 7217 (1993).

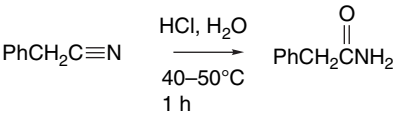
[145] S. E. Eldred, D. A. Stone, S. M. Gellman, and S. S. Stahl, *J. Am. Chem. Soc.*, **125**, 3423 (2003).

*Tris*-(dimethylamino)aluminum also promotes similar exchange reactions. The catalysis by titanium and aluminum amides may involve bifunctional catalysis in which the metal center acts as a Lewis acid while also delivering the nucleophilic amide.

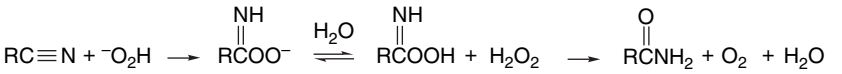



Interestingly, $Sc(O_3SCF_3)_3$ is also an active catalyst for these exchange reactions.

The cyano group is at the carboxylic acid oxidation level, so nitriles are potential precursors of primary amides. Partial hydrolysis is sometimes possible.[146]




A milder procedure involves the reaction of a nitrile with an alkaline solution of hydrogen peroxide.[147] The strongly nucleophilic hydrogen peroxide adds to the nitrile and the resulting adduct gives the amide. There are several possible mechanisms for the subsequent decomposition of the peroxycarboximidic adduct.[148]




In all the mechanisms, the hydrogen peroxide is converted to oxygen and water, leaving the organic substrate hydrolyzed, but at the same oxidation level.

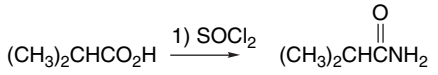
Scheme 3.6 illustrates some of the means of preparation of amides. Entries 1 and 2 are cases of preparation of simple amides by conversion of the carboxylic acid to an acyl chloride using $SOCl_2$. Entry 3 is the acetylation of glycine by acetic anhydride. The reaction is done in concentrated aqueous solution ($\sim 3\,M$) using a twofold excess of the anhydride. The reaction is exothermic and the product crystallizes from the reaction mixture when it is cooled. Entries 4 and 5 are ester aminolysis reactions. The cyano group is an activating group for the ester in Entry 4, and this reaction occurs at room temperature in concentrated ammonia solution. The reaction in Entry 5 involves a less nucleophilic and more hindered amine, but involves a relatively reactive aryl ester. A much higher temperature is required for this reaction. Entries 6 to 8 illustrate the use of several of the coupling reagents for preparation of amides. Entries 9 and 10 show preparation of primary amides by hydrolysis of nitriles. The first reaction involves partial hydrolysis, whereas the second is an example of peroxide-accelerated hydrolysis.

146. W. Wenner, *Org. Synth.*, **IV**, 760 (1963).
147. C. R. Noller, *Org. Synth.*, **II**, 586 (1943); J. S. Buck and W. S. Ide, *Org. Synth.*, **II**, 44 (1943).
148. K. B. Wiberg, *J. Am. Chem. Soc.*, **75**, 3961 (1953); *J. Am. Chem. Soc.*, **77**, 2519 (1955); J. E. McIsaac, Jr., R. E. Ball, and E. J. Behrman, *J. Org. Chem.*, **36**, 3048 (1971).

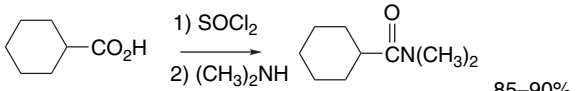
## Scheme 3.6. Synthesis of Amides

A. From acyl chlorides and anhydrides

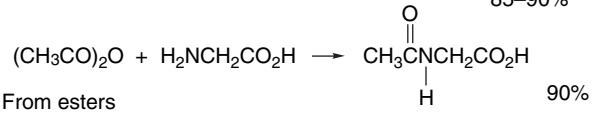
1[a]




2[b]

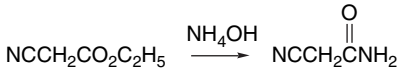



3[c]

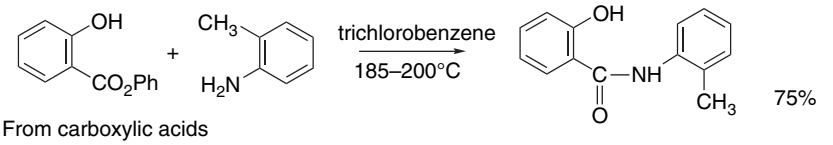



B. From esters

4[d]



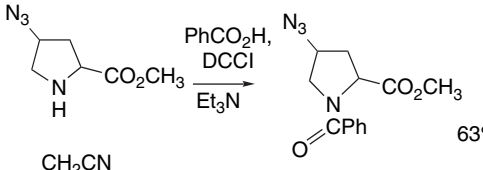

5[e]



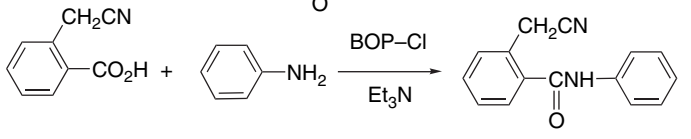

C. From carboxylic acids

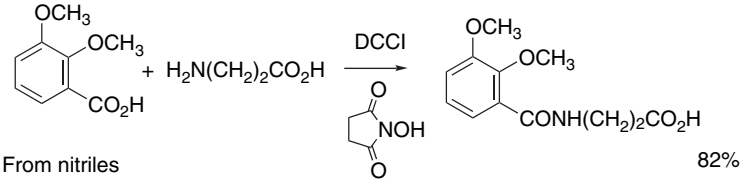
6[f]

7[g]



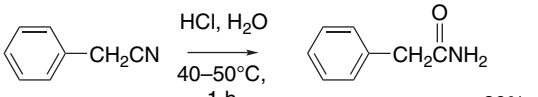

8[h]



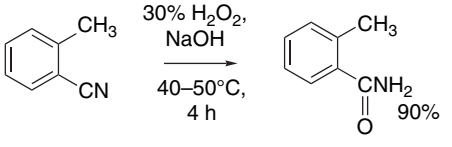




D. From nitriles

9[i]




10[j]




(*Continued*)

**Scheme 3.6. (*Continued*)**

a. R. E. Kent and S. M. McElvain, *Org. Synth.*, **III**, 490 (1955).
b. A. C. Cope and E. Ciganek, *Org. Synth.*, **IV**, 339 (1963).
c. R. M. Herbst and D. Shemin, *Org. Synth.*, **II**, 11 (1943).
d. B. B. Corson, R. W. Scott, and C. E. Vose, *Org. Synth.*, **I**, 179 (1941).
e. C. F. H. Allen and J. Van Allen, *Org. Synth.*, **III**, 765 (1955).
f. D. J. Abraham, M. Mokotoff, L. Sheh, and J. E. Simmons, *J. Med. Chem.*, **26**, 549 (1983).
g. J. Diago-Mesenguer, A. L. Palamo-Coll, J. R. Fernandez-Lizarbe, and A. Zugaza-Bilbao, *Synthesis*, 547 (1980).
h. R. J. Bergeron, S. J. Kline, N. J. Stolowich, K. A. McGovern, and P. S. Burton, *J. Org. Chem.*, **46**, 4524 (1981).
i. W. Wenner, *Org. Synth.*, **IV**, 760 (1963).
j. C. R. Noller, *Org. Synth.*, **II**, 586 (1943).

## 3.5. Installation and Removal of Protective Groups

*Protective groups* play a key role in multistep synthesis. When the synthetic target is a relatively complex molecule, a sequence of reactions that would be expected to lead to the desired product must be devised. At the present time, syntheses requiring 15–20 steps are common and many that are even longer have been completed. In the planning and execution of such multistep syntheses, an important consideration is the compatibility of the functional groups that are already present with the reaction conditions required for subsequent steps. It is frequently necessary to modify a functional group in order to prevent interference with some reaction in the synthetic sequence. A protective group can be put in place and then subsequently removed in order to prevent an undesired reaction or other adverse influence. For example, alcohols are often protected as trisubstituted silyl ethers and carbonyl groups as acetals. The silyl group masks both the acidity and nucleophilicity of the hydroxy group. An acetal group can prevent both unwanted nucleophilic additions or enolate formation at a carbonyl group.

$$R{-}OH + R'_3SiX \longrightarrow R{-}O{-}SiR'_3$$

$$R_2C{=}O + R'OH \longrightarrow R_2C(OR')_2$$

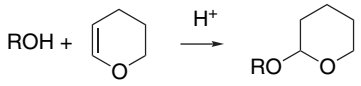
Three considerations are important in choosing an appropriate protective group: (1) the nature of the group requiring protection; (2) the reaction conditions under which the protective group must be stable; and (3) the conditions that can be tolerated for removal of the protecting group. No universal protective groups exist. The state of the art has been developed to a high level, however, and the many mutually complementary protective groups provide a great degree of flexibility in the design of syntheses of complex molecules.[149] Protective groups play a passive role in synthesis, but each operation of introduction and removal of a protective group adds steps to the synthetic sequence. It is thus desirable to minimize the number of such operations. Fortunately, the methods for protective group installation and removal have been highly developed and the yields are usually excellent.

### 3.5.1. Hydroxy-Protecting Groups

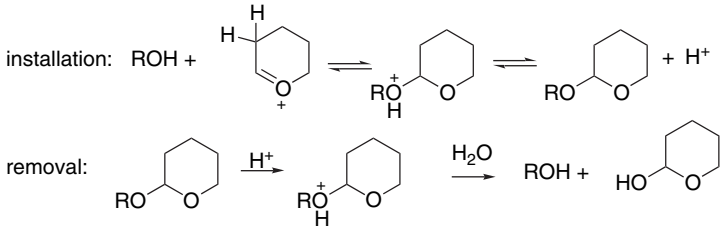
*3.5.1.1. Acetals as Protective Groups.* A common requirement in synthesis is that a hydroxy group be masked as a derivative lacking the proton. Examples of this requirement are reactions involving Grignard or other strongly basic organometallic

149. T. W. Green and P. G. Wuts, *Protective Groups in Organic Synthesis*, 3rd Edition, Wiley, New York, 1999; P. J. Kocienski, *Protective Groups*, Thieme, New York, 2000.

reagents. The acidic proton of a hydroxy group will destroy one equivalent of a strongly basic organometallic reagent and possibly adversely affect the reaction in other ways. In some cases, protection of the hydroxy group also improves the solubility of alcohols in nonpolar solvents. The choice of the most appropriate group is largely dictated by the conditions that can be tolerated in subsequent removal of the protecting group. The tetrahydropyranyl ether (THP) is applicable when mildly acidic hydrolysis is an appropriate method for deprotection.[150] The THP group, like other acetals and ketals, is inert to basic and nucleophilic reagents and is unchanged under such conditions as hydride reduction, organometallic reactions, or base-catalyzed reactions in aqueous solution. It also protects the hydroxy group against oxidation. The THP group is introduced by an acid-catalyzed addition of the alcohol to the vinyl ether moiety in dihydropyran. *p*-Toluenesulfonic acid or its pyridinium salt are frequently used as the catalyst,[151] although other catalysts are advantageous in special cases.




The THP group can be removed by dilute aqueous acid. The chemistry involved in both the introduction and deprotection stages is the reversible acid-catalyzed formation and hydrolysis of an acetal (see Part A, Section 7.1).

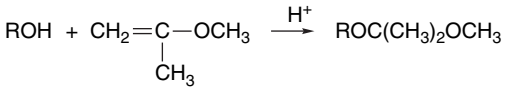



Various Lewis acids also promote hydrolysis of THP groups. Treatment with five equivalents of LiCl and ten equivalents of $H_2O$ in DMSO removes THP groups in high yield.[152] $PdCl_2(CH_3CN)_2$ smoothly removes THP groups from primary alcohols.[153] $CuCl_2$ is also reported to catalyze hydrolysis of the THP group.[154] These procedures may involve generation of protons by interaction of water with the metal cations.

A disadvantage of the THP group is the fact that a new stereogenic center is produced at C(2) of the tetrahydropyran ring. This presents no difficulties if the alcohol is achiral, since a racemic mixture results. However, if the alcohol is chiral, the reaction gives a mixture of diastereomers, which may complicate purification and/or characterization. One way of avoiding this problem is to use methyl 2-propenyl ether in place of dihydropyran (abbreviated MOP, for methoxypropyl). No new chiral center

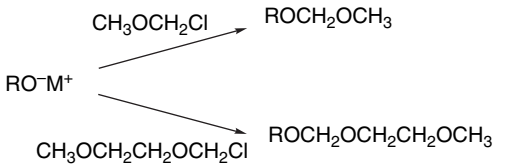
150. W. E. Parham and E. L. Anderson, *J. Am. Chem. Soc.*, **70**, 4187 (1948).
151. J. H. van Boom, J. D. M. Herscheid, and C. B. Reese, *Synthesis*, 169 (1973); M. Miyashita, A. Yoshikoshi, and P. A. Grieco, *J. Org. Chem.*, **42**, 3772 (1977).
152. G. Maiti and S. C. Roy, *J. Org. Chem.*, **61**, 6038 (1996).
153. Y.-G. Wang, X.-X. Wu, and S.-Y. Jiang, *Tetrahedron Lett.*, **45**, 2973 (2004).
154. J. K. Davis, U. T. Bhalerao, and B. V. Rao, *Ind. J. Chem. B*, **39B**, 860 (2000); J. Wang, C. Zhang, Z. Qu, Y. Hou, B. Chen, and P. Wu, *J. Chem. Res. Syn.*, 294 (1999).

is introduced, and this acetal offers the further advantage of being hydrolyzed under somewhat milder conditions than those required for THP ethers.[155]

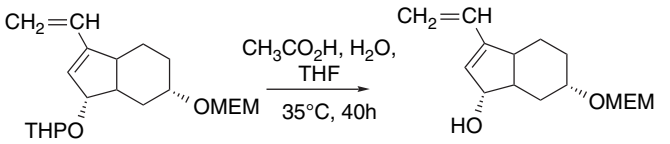



Ethyl vinyl ether is also useful for hydroxy group protection. The resulting derivative (1-ethoxyethyl ether) is abbreviated as the EE group.[156] As with the THP group, the EE group introduces an additional stereogenic center.

The methoxymethyl (MOM) and β-methoxyethoxymethyl (MEM) groups are used to protect alcohols and phenols as formaldehyde acetals. These groups are normally introduced by reaction of an alkali metal salt of the alcohol with methoxymethyl chloride or β-methoxyethoxymethyl chloride.[157]




The MOM and MEM groups can be cleaved by pyridinium tosylate in moist organic solvents.[158] An attractive feature of the MEM group is the ease with which it can be removed under nonaqueous conditions. Reagents such as zinc bromide, magnesium bromide, titanium tetrachloride, dimethylboron bromide, or trimethylsilyl iodide permit its removal.[159] The MEM group is cleaved in preference to the MOM or THP groups under these conditions. Conversely, the MEM group is more stable to acidic aqueous hydrolysis than the THP group. These relative reactivity relationships allow the THP and MEM groups to be used in a complementary fashion when two hydroxy groups must be deprotected at different points in a synthetic sequence.




Ref. 160

The methylthiomethyl (MTM) group is a related alcohol-protecting group. There are several methods for introducing the MTM group. Alkylation of an alcoholate by

155. A. F. Kluge, K. G. Untch, and J. H. Fried, *J. Am. Chem. Soc.*, **94**, 7827 (1972).
156. H. J. Sims, H. B. Parseghian, and P. L. DeBenneville, *J. Org. Chem.*, **23**, 724 (1958).
157. G. Stork and T. Takahashi, *J. Am. Chem. Soc.*, **99**, 1275 (1977); R. J. Linderman, M. Jaber, and B. D. Griedel, *J. Org. Chem.*, **59**, 6499 (1994); P. Kumar, S. V. N. Raju, R. S. Reddy, and B. Pandey, *Tetrahedron Lett.*, **35**, 1289 (1994).
158. H. Monti, G. Leandri, M. Klos-Ringuet, and C. Corriol, *Synth. Commun.*, **13**, 1021 (1983); M. A. Tius and A. M. Fauq, *J. Am. Chem. Soc.*, **108**, 1035 (1986).
159. E. J. Corey, J.-L. Gras, and P. Ulrich, *Tetrahedron Lett.*, 809 (1976); Y. Quindon, H. E. Morton, and C. Yoakim, *Tetrahedron Lett.*, **24**, 3969 (1983); J. H. Rigby and J. Z. Wilson, *Tetrahedron Lett.*, **25**, 1429 (1984); S. Kim, Y. H. Park, and I. S. Kee, *Tetrahedron Lett.*, **32**, 3099 (1991).
160. E. J. Corey, R. L. Danheiser, S. Chandrasekaran, P. Siret, G. E. Keck, and J.-L. Gras, *J. Am. Chem. Soc.*, **100**, 8031 (1978).

methylthiomethyl chloride is efficient if catalyzed by iodide ion.[161] Alcohols are also converted to MTM ethers by reaction with dimethyl sulfoxide in the presence of acetic acid and acetic anhydride,[162] or with benzoyl peroxide and dimethyl sulfide.[163] The latter two methods involve the generation of the methylthiomethylium ion by ionization of an acyloxysulfonium ion (Pummerer reaction).

$$RO^-M^+ + CH_3SCH_2Cl \xrightarrow{I^-} ROCH_2SCH_3$$

$$ROH + CH_3SOCH_3 \xrightarrow[(CH_3CO)_2O]{CH_3CO_2H} ROCH_2SCH_3$$

$$ROH + (CH_3)_2S + (PhCO_2)_2 \longrightarrow ROCH_2SCH_3$$

The MTM group is selectively removed under nonacidic conditions in aqueous solutions containing $Ag^+$ or $Hg^{2+}$ salts. The THP and MOM groups are stable under these conditions.[161] The MTM group can also be removed by reaction with methyl iodide, followed by hydrolysis of the resulting sulfonium salt in moist acetone.[162]

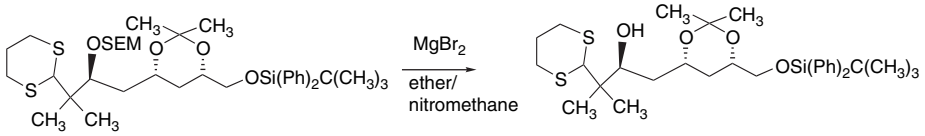
Two substituted alkoxymethoxy groups are designed for cleavage involving β-elimination. The 2,2,2-trichloroethoxymethyl groups can be cleaved by reducing agents, including zinc, samarium diiodide, and sodium amalgam.[164] The β-elimination results in the formation of a formaldehyde hemiacetal, which decomposes easily.

$$Cl_3CCH_2OCH_2OR \xrightarrow{2e^-} Cl^- + Cl_2C{=}CH_2 + CH_2{=}O + {}^-OR$$

The 2-(trimethylsilyl)ethoxymethyl group (SEM) can be removed by various fluoride sources, including TBAF, pyridinium fluoride, and HF.[165] This deprotection involves nucleophilic attack at silicon, which triggers β-elimination.

$$F^- + (CH_3)_3SiCH_2{-}CH_2OCH_2OR \longrightarrow (CH_3)_3SiF + CH_2{=}CH_2 + CH_2{=}O + {}^-OR$$

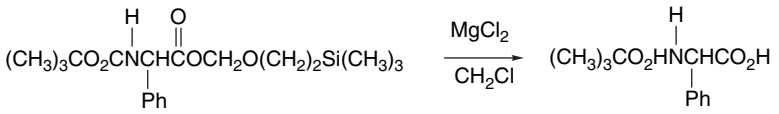
The SEM group can also be cleaved by $MgBr_2$. A noteworthy aspect of this method is that trisubstituted silyl ethers (see below) can survive.




Ref. 166

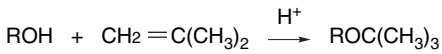
161. E. J. Corey and M. G. Bock, *Tetrahedron Lett.*, 3269 (1975).
162. P. M. Pojer and S. J. Angyal, *Tetrahedron Lett.*, 3067 (1976).
163. J. C. Modina, M. Salomon, and K. S. Kyler, *Tetrahedron Lett.*, **29**, 3773 (1988).
164. R. M. Jacobson and J. W. Clader, *Synth. Commun.*, **9**, 57 (1979); D. A. Evans, S. W. Kaldor, T. K. Jones, J. Clardy, and T. J. Stout, *J. Am. Chem. Soc.*, **112**, 7001 (1990).
165. B. H. Lipshutz and J. J. Pegram, *Tetrahedron Lett.*, **21**, 3343 (1980); B. H. Lipshutz and T. A. Miller, *Tetrahedron Lett.*, **30**, 7149 (1989); T. Kan, M. Hashimoto, M. Yanagiya, and H. Shirahama, *Tetrahedron Lett.*, **29**, 5417 (1988); J. D. White and M. Kawasaki, *J. Am. Chem. Soc.*, **112**, 4991 (1990); K. Sugita, K. Shigeno, C. F. Neville, H. Sasai, and M. Shibasaki, *Synlett*, 325 (1994).
166. A. Vakalopoulos and H. M. R. Hoffmann, *Org. Lett.*, **2**, 1447 (2000).

$MgBr_2$ removal of SEM groups is also useful for deprotection of carboxy groups in N-protected amino acids.



Ref. 167

*3.5.1.2. Ethers as Protective Groups.* The simple alkyl groups are generally not very useful for protection of alcohols as ethers. Although they can be introduced readily by alkylation, subsequent cleavage requires strongly electrophilic reagents such as boron tribromide (see Section 3.3). The *t*-butyl group is an exception and has found some use as a hydroxy-protecting group. Owing to the stability of the *t*-butyl cation, *t*-butyl ethers can be cleaved under moderately acidic conditions. Trifluoroacetic acid in an inert solvent is frequently used.[168] *t*-Butyl ethers can also be cleaved by acetic anhydride–$FeCl_3$ in ether.[169] The *t*-butyl group is normally introduced by reaction of the alcohol with isobutylene in the presence of an acid catalyst.[170] Acidic ion exchange resins are effective catalysts.[171]

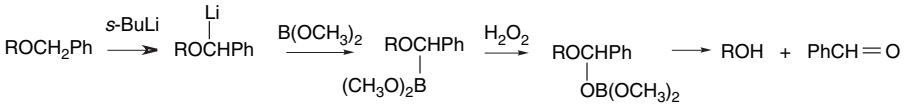


The triphenylmethyl (trityl, abbreviated Tr) group is removed under even milder conditions than the *t*-butyl group and is an important hydroxy-protecting group, especially in carbohydrate chemistry.[172] This group is introduced by reaction of the alcohol with triphenylmethyl chloride via an $S_N1$ substitution. Owing to their steric bulk, triarylmethyl groups are usually introduced only at primary hydroxy groups. Reactions at secondary hydroxy groups can be achieved using stronger organic bases such as DBU.[173] Hot aqueous acetic acid suffices to remove the trityl group. The ease of removal can be increased by addition of ERG substituents. The *p*-methoxy (PMTr) and *p*,*p*′-dimethoxy (DMTr) derivatives are used in this way.[174] Trityl groups can also be removed oxidatively using $Ce(NH_3)_6(NO_3)_3$ (CAN) on silica.[175] This method involves a single-electron oxidation and, as expected, the rate of reaction is DMTr > PMTr > Tr. The DMTr group is especially important in the protection of primary hydroxy groups in nucleotide synthesis (see Section 13.3.2).

The benzyl group can serve as a hydroxy-protecting group if acidic conditions for ether cleavage cannot be tolerated. The benzyl C−O bond is cleaved by catalytic hydrogenolysis,[176] or by electron-transfer reduction using sodium in liquid ammonia or

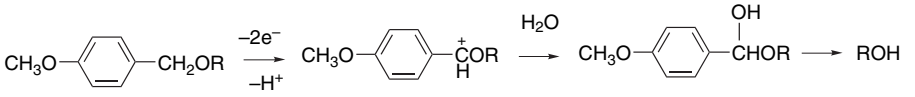
167. W.-C. Chen, M. D. Vera, and M. M. Joullie, *Tetrahedron Lett.*, **38**, 4025 (1997).
168. H. C. Beyerman and G. J. Heiszwolf, *J. Chem. Soc.*, 755 (1963).
169. B. Ganem and V. R. Small, Jr., *J. Org. Chem.*, **39**, 3728 (1974).
170. J. L. Holcombe and T. Livinghouse, *J. Org. Chem.*, **51**, 111 (1986).
171. A. Alexakis, M. Gardette, and S. Colin, *Tetrahedron Lett.*, **29**, 2951 (1988).
172. O. Hernandez, S. K. Chaudhary, R. H. Cox, and J. Porter, *Tetrahedron Lett.*, **22**, 1491 (1981); S. K. Chaudhary and O. Hernandez, *Tetrahedron Lett.*, **20**, 95 (1979).
173. S. Colin-Messager, J.-P. Girard, and J.-C. Rossi, *Tetrahedron Lett.*, **33**, 2689 (1992).
174. M. Smith, D. H. Rammler, I. H. Goldberg, and H. G. Khorana, *J. Am. Chem. Soc.*, **84**, 430 (1962).
175. J. R. Hwu, M. L. Jain, F.-Y. Tsai, S.-C. Tsay, A. Balakumar, and G. H. Hakimelahi, *J. Org. Chem.*, **65**, 5077 (2000).
176. W. H. Hartung and R. Simonoff, *Org. React.*, **7**, 263 (1953).

aromatic radical anions.[177] Benzyl ethers can also be cleaved using formic acid, cyclohexene, or cyclohexadiene as hydrogen sources in transfer hydrogenolysis catalyzed by platinum or palladium.[178] Several nonreductive methods for cleavage of benzyl ether groups have also been developed. Treatment with *s*-butyllithium, followed by reaction with trimethyl borate and then hydrogen peroxide liberates the alcohol.[179] The lithiated ether forms an alkyl boronate, which is oxidized as discussed in Section 4.5.2.



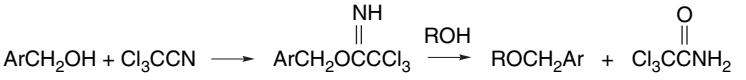
Lewis acids such as $FeCl_3$ and $SnCl_4$ also cleave benzyl ethers.[180]

Benzyl groups having 4-methoxy (PMB) or 3,5-dimethoxy (DMB) substituents can be removed oxidatively by dichlorodicyanoquinone (DDQ).[181] These reactions presumably proceed through a benzylic cation and the methoxy substituent is necessary to facilitate the oxidation.



These reaction conditions do not affect most of the other common hydroxy-protecting groups and the methoxybenzyl group is therefore useful in synthetic sequences that require selective deprotection of different hydroxy groups. 4-Methoxybenzyl ethers can also be selectively cleaved by dimethylboron bromide.[182]

Benzyl groups are usually introduced by the Williamson reaction (Section 3.2.3). They can also be prepared under nonbasic conditions if necessary. Benzyl alcohols are converted to trichloroacetimidates by reaction with trichloroacetonitrile. These then react with an alcohol to transfer the benzyl group.[183]



Phenyldiazomethane can also be used to introduce benzyl groups.[184]

177. E. J. Reist, V. J. Bartuska, and L. Goodman, *J. Org. Chem.*, **29**, 3725 (1964); R. E. Ireland, D. W. Norbeck, G. S. Mandel, and N. S. Mandel, *J. Am. Chem. Soc.*, **107**, 3285 (1985); R. E. Ireland and M. G. Smith, *J. Am. Chem. Soc.*, **110**, 854 (1988); H.-J. Liu, J. Yip, and K.-S. Shia, *Tetrahedron Lett.*, **38**, 2253 (1997).

178. B. El Amin, G. M. Anatharamaiah, G. P. Royer, and G. E. Means, *J. Org. Chem.*, **44**, 3442 (1979); A. M. Felix, E. P. Heimer, T. J. Lambros, C. Tzougraki, and J. Meienhofer, *J. Org. Chem.*, **43**, 4194 (1978); A. E. Jackson and R. A. W. Johnstone, *Synthesis*, 685 (1976); G. M. Anatharamaiah and K. M. Sivandaiah, *J. Chem. Soc., Perkin Trans.*, **I**, 490 (1977).

179. D. A. Evans, C. E. Sacks, W. A. Kleschick, and T. R. Taber, *J. Am. Chem. Soc.*, **101**, 6789 (1979).

180. M. H. Park, R. Takeda, and K. Nakanishi, *Tetrahedron Lett.*, **28**, 3823 (1987).

181. Y. Oikawa, T. Yoshioka, and O. Yonemitsu, *Tetrahedron Lett.*, **23**, 885 (1982); Y. Oikawa, T. Tanaka, K. Horita, T. Yoshioka, and O. Yonemitsu, *Tetrahedron Lett.*, **25**, 5393 (1984); N. Nakajima, T. Hamada, T. Tanaka, Y. Oikawa, and O. Yonemitsu, *J. Am. Chem. Soc.*, **108**, 4645 (1986).

182. N. Hebert, A. Beck, R. B. Lennox, and G. Just, *J. Org. Chem.*, **57**, 1777 (1992).

183. H.-P. Wessel, T. Iverson, and D. R. Bundle, *J. Chem. Soc., Perkin Trans.*, **I**, 2247 (1985); N. Nakajima, K. Horita, R. Abe, and O. Yonemitsu, *Tetrahedron Lett.*, **29**, 4139 (1988); S. J. Danishefsky, S. DeNinno, and P. Lartey, *J. Am. Chem. Soc.*, **109**, 2082 (1987).

184. L. J. Liotta and B. Ganem, *Tetrahedron Lett.*, **30**, 4759 (1989).

4-Methoxyphenyl (PMP) ethers find occasional use as hydroxy protecting groups. Unlike benzylic groups, they cannot be made directly from the alcohol. Instead, the phenoxy group must be introduced by a nucleophilic substitution.[185] Mitsunobu conditions are frequently used.[186] The PMP group can be cleaved by oxidation with CAN.

Allyl ethers can be removed by conversion to propenyl ethers, followed by acidic hydrolysis of the resulting enol ether.

$$ROCH_2CH{=}CH_2 \longrightarrow ROCH{=}CHCH_3 \xrightarrow{H_3O^+} ROH + CH_3CH_2CH{=}O$$

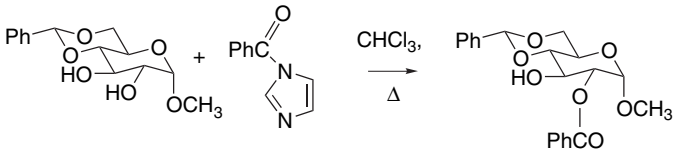
The isomerization of an allyl ether to a propenyl ether can be achieved either by treatment with potassium *t*-butoxide in dimethyl sulfoxide[187] or by catalysts such as $Rh(PPh_3)_3Cl$[188] or $RhH(PPh_3)_4$.[189] Heating allyl ethers with Pd-C in acidic methanol can also effect cleavage of allyl ethers.[190] This reaction, too, is believed to involve isomerization to the 1-propenyl ether. Other very mild conditions for allyl group cleavage include Wacker oxidation conditions[191] (see Section 8.2.1) and DiBAlH with catalytic $NiCl_2$(dppp).[192]

*3.5.1.3. Silyl Ethers as Protective Groups.* Silyl ethers play a very important role as hydroxy-protecting groups.[193] Alcohols can be easily converted to trimethylsilyl (TMS) ethers by reaction with trimethylsilyl chloride in the presence of an amine or by heating with hexamethyldisilazane. Trimethylsilyl groups are easily removed by hydrolysis or by exposure to fluoride ions. *t*-Butyldimethylsilyl (TBDMS) ethers are also very useful. The increased steric bulk of the TBDMS group improves the stability of the group toward such reactions as hydride reduction and Cr(VI) oxidation. The TBDMS group is normally introduced using a tertiary amine as a catalyst in the reaction of the alcohol with *t*-butyldimethylsilyl chloride or triflate. Cleavage of the TBDMS group is slow under hydrolytic conditions, but anhydrous tetra-*n*-butylammonium fluoride (TBAF),[194] methanolic $NH_4F$,[195] aqueous HF,[196] $BF_3$,[197] or $SiF_4$[198] can be used for its removal. Other highly substituted silyl groups, such as dimethyl(1,2,2-trimethylpropyl)silyl[199] and *tris*-isopropylsilyl,[200] (TIPS) are even more

185. Y. Masaki, K. Yoshizawa, and A. Itoh, *Tetrahedron Lett.*, **37**, 9321 (1996); S. Takano, M. Moriya, M. Suzuki, Y. Iwabuchi, T. Sugihara, and K. Ogaswawara, *Heterocycles*, **31**,1555 (1990).
186. T. Fukuyama, A. A. Laird, and L. M. Hotchkiss, *Tetrahedron Lett.*, **26**, 6291 (1985); M. Petitou, P. Duchaussoy, and J. Choay, *Tetrahedron Lett.*, **29**, 1389 (1988).
187. R. Griggs and C. D. Warren, *J. Chem. Soc. C*, 1903 (1968).
188. E. J. Corey and J. W. Suggs, *J. Org. Chem.*, **38**, 3224 (1973).
189. F. E. Ziegler, E. G. Brown, and S. B. Sobolov, *J. Org. Chem.*, **55**, 3691 (1990).
190. R. Boss and R Scheffold, *Angew. Chem. Int. Ed. Engl.*, **15**, 558 (1976).
191. H. B. Mereyala and S. Guntha, *Tetrahedron Lett.*, **34**, 6929 (1993).
192. T. Taniguchi and K. Ogasawara, *Angew. Chem. Int. Ed. Engl.*, **37**, 1136 (1998).
193. J. F. Klebe, in *Advances in Organic Chemistry: Methods and Results*, Vol. 8, E. C. Taylor, ed., Wiley-Interscience, New York, 1972, pp. 97–178; A. E. Pierce, *Silylation of Organic Compounds*, Pierce Chemical Company, Rockford, IL, 1968.
194. E. J. Corey and A. Venkataswarlu, *J. Am. Chem. Soc.*, **94**, 6190 (1972).
195. W. Zhang and M. J. Robins, *Tetrahedron Lett.*, **33**, 1177 (1992).
196. R. F. Newton, D. P. Reynolds, M. A. W. Finch, D. R. Kelly, and S. M. Roberts, *Tetrahedron Lett.*, 3981 (1979).
197. D. R. Kelly, S. M. Roberts, and R. F. Newton, *Synth. Commun.*, **9**, 295 (1979).
198. E. J. Corey and K. Y. Yi, *Tetrahedron Lett.*, **32,** 2289 (1992).
199. H. Wetter and K. Oertle, *Tetrahedron Lett.*, **26**, 5515 (1985).
200. R. F. Cunico and L. Bedell, *J. Org. Chem.*, **45**, 4797 (1980).

sterically hindered than the TBDMS group and can be used when added stability is required. The triphenylsilyl (TPS) and *t*-butyldiphenylsilyl (TBDPS) groups are also used.[201] The hydrolytic stability of the various silyl protecting groups is in the order TMS < TBDMS < TIPS < TBDPS.[202] All the groups are also susceptible to TBAF cleavage, but the TPS and TBDPS groups are cleaved more slowly than the trialkylsilyl groups.[203] Bromine in methanol readily cleaves TBDMS and TBDPS groups.[204]

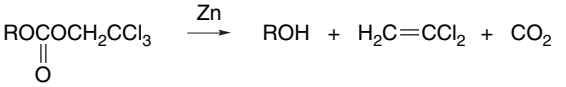
*3.5.1.4. Esters as Protective Groups.* Protection of an alcohol function by esterification sometimes offers advantages over use of acetal or ether groups. Generally, esters are stable under acidic conditions, and they are especially useful in protection during oxidations. Acetates, benzoates, and pivalates, which are the most commonly used derivatives, can be conveniently prepared by reaction of unhindered alcohols with acetic anhydride, benzoyl chloride, or pivaloyl chloride, respectively, in the presence of pyridine or other tertiary amines. 4-Dimethylaminopyridine (DMAP) is often used as a catalyst. The use of *N*-acylimidazolides (see Section 3.4.1) allows the acylation reaction to be carried out in the absence of added base.[205] Imidazolides are less reactive than the corresponding acyl chloride and can exhibit a higher degree of selectivity in reactions with a molecule possessing several hydroxy groups.




78% Ref. 206

Hindered hydroxy groups may require special acylation procedures. One approach is to increase the reactivity of the hydroxy group by converting it to an alkoxide ion with strong base (e.g., *n*-BuLi or KH). When this conversion is not feasible, a more reactive acylating reagent is used. Highly reactive acylating agents are generated in situ when carboxylic acids are mixed with trifluoroacetic anhydride. The mixed anhydride exhibits increased reactivity because of the high reactivity of the trifluoroacetate ion as a leaving group.[207] Dicyclohexylcarbodiimide is another reagent that serves to activate carboxy groups.

Ester groups can be removed readily by base-catalyzed hydrolysis. When basic hydrolysis is inappropriate, special acyl groups are required. Trichloroethyl carbonate esters, for example, can be reductively removed with zinc.[208]




201. S. Hanessian and P. Lavallee, *Can. J. Chem.*, **53**, 2975 (1975); S. A. Hardinger and N. Wijaya, *Tetrahedron Lett.*, **34**, 3821 (1993).
202. J. S. Davies, C. L. Higginbotham, E. J. Tremeer, C. Brown, and R. S. Treadgold, *J. Chem. Soc., Perkin Trans.*, **1**, 3043 (1992).
203. J. W. Gillard, R. Fortin, H. E. Morton, C. Yoakim, C. A. Quesnelle, S. Daignault, and Y. Guindon, *J. Org. Chem.*, **53**, 2602 (1988).
204. M. T. Barros, C. D. Maycock, and C. Thomassigny, *Synlett*, 1146 (2001).
205. H. A. Staab, *Angew. Chem.*, **74**, 407 (1962).
206. F. A. Carey and K. O. Hodgson, *Carbohydr. Res.*, **12**, 463 (1970).
207. R. C. Parish and L. M. Stock, *J. Org. Chem.*, **30**, 927 (1965); J. M. Tedder, *Chem. Rev.*, **55**, 787 (1955).
208. T. B. Windholz and D. B. R. Johnston, *Tetrahedron Lett.*, 2555 (1967).

Allyl carbonate esters are also useful hydroxy-protecting groups and are introduced using allyl chloroformate. A number of Pd-based catalysts for allylic deprotection have been developed.[209] They are based on a catalytic cycle in which $Pd^0$ reacts by oxidative addition and activates the allylic bond to nucleophilic substitution. Various nucleophiles are effective, including dimedone,[210] pentane-2,4-dione,[211] and amines.[212]

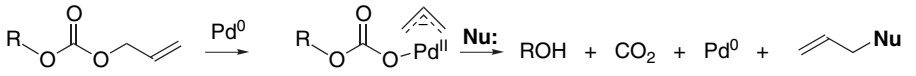
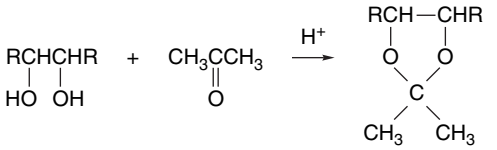
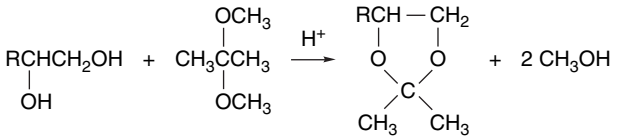



Table 3.1 gives the structure and common abbreviation of some of the most frequently used hydroxy-protecting groups.

*3.5.1.5. Protective Groups for Diols.* Diols represent a special case in terms of applicable protecting groups. 1,2- and 1,3-diols easily form cyclic acetals with aldehydes and ketones, unless cyclization is precluded by molecular geometry. The isopropylidene derivatives (also called acetonides) formed by reaction with acetone are a common example.



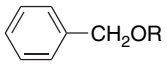
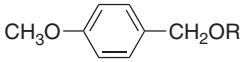
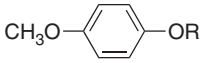
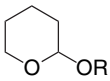

The isopropylidene group can also be introduced by acid-catalyzed exchange with 2,2-dimethoxypropane.[213]




This acetal protective group is resistant to basic and nucleophilic reagents, but is readily removed by aqueous acid. Formaldehyde, acetaldehyde, and benzaldehyde are also used as the carbonyl component in the formation of cyclic acetals, and they function in the same manner as acetone. A disadvantage in the case of acetaldehyde and benzaldehyde is the possibility of forming a mixture of diastereomers, because of the new stereogenic center at the acetal carbon. Owing to the multiple hydroxy groups present in carbohydrates, the use of cyclic acetal protecting groups is common.

209. F. Guibe, *Tetrahedron*, **53**, 13509 (1997).
210. H. Kunz and H. Waldmann, *Angew. Chem. Int. Ed. Engl.*, **23**, 71 (1984).
211. A. De Mesmaeker, P. Hoffmann, and B. Ernst, *Tetrahedron Lett.*, **30**, 3773 (1989).
212. H. Kunz, H. Waldmann, and H. Klinkhammer, *Helv. Chim. Acta*, **71**, 1868 (1988); S. Friedrich-Bochnitschek, H. Waldman, and H. Kunz, *J. Org. Chem.*, **54**, 751 (1989); J. P. Genet, E. Blart, M. Savignac, S. Lemeune, and J.-M. Paris, *Tetrahedron Lett.*, **34**, 4189 (1993).
213. M. Tanabe and B. Bigley, *J. Am. Chem. Soc.*, **83**, 756 (1961).

**Table 3.1. Common Hydroxy-Protecting Groups**

| Structure | Name | Abbreviation |
|---|---|---|
| A. Ethers | | |
|  | Benzyl | Bn |
|  | *p*-Methoxybenzyl | PMB |
| $CH_2{=}CHCH_2OR$ | Allyl | |
| $Ph_3COR$ | Triphenylmethyl (trityl) | Tr |
|  | *p*-Methoxyphenyl | PMP |
| B. Acetals | | |
|  | Tetrahydropyranyl | THP |
| $CH_3OCH_2OR$ | Methoxymethyl | MOM |
| $CH_3CH_2OCHOR$ (CH$_3$ below CHOR) | 1-Ethoxyethyl | EE |
| $(CH_3)_2COR$ (OCH$_3$ below COR) | 2-Methoxy-2-propyl | MOP |
| $Cl_3CCH_2OCH_2OR$ | 2,2,2-Trichloroethoxymethyl | |
| $CH_3OCH_2CH_2OCH_2OR$ | 2-Methoxyethoxymethyl | MEM |
| $(CH_3)_3SiCH_2CH_2OCH_2OR$ | 2-Trimethylsilylethoxymethyl | SEM |
| $CH_3SCH_2OR$ | Methylthiomethyl | MTM |
| C. Silyl ethers | | |
| $(CH_3)_3SiOR$ | Trimethylsilyl | TMS |
| $(C_2H_5)_3SiOR$ | Triethylsilyl | TES |
| $[(CH_3)_2CH]_3OR$ | Tri-*i*-propylsilyl | TIPS |
| $Ph_3SiOR$ | Triphenylsilyl | TPS |
| $(CH_3)_3CSi(CH_3)_2SiOR$ | *t*-Butyldimethylsilyl | TBDMS |
| $(CH_3)_3CSi(Ph)_2SiOR$ | *t*-Butyldiphenylsilyl | TBDPS |
| D. Esters | | |
| $CH_3CO_2R$ | Acetate | Ac |
| $PhCO_2R$ | Benzoate | Bz |
| $(CH_3)_3CO_2R$ | Pivalate | Piv |
| $CH_2{=}CHCH_2O_2COR$ | Allyl carbonate | |
| $Cl_3CCH_2O_2COR$ | 2,2,2-Trichloroethyl carbonate | Troc |
| $(CH_3)_3SiCH_2CH_2O_2COR$ | 2-Trimethylsilylethyl carbonate | |

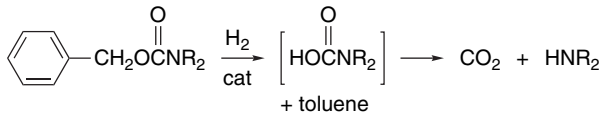
Cyclic carbonate esters are easily prepared from 1,2- and 1,3-diols. These are commonly prepared by reaction with *N*,*N*′-carbonyldiimidazole[214] or by transesterification with diethyl carbonate.

### 3.5.2. Amino-Protecting Groups

Amines are nucleophilic and easily oxidized. Primary and secondary amino groups are also sufficiently acidic that they are deprotonated by many organometallic reagents. If these types of reactivity are problematic, the amino group must be protected. The

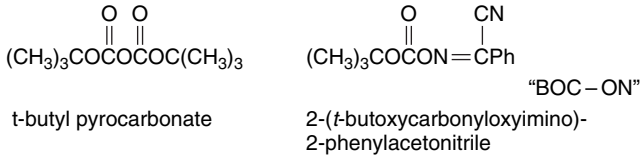
[214] J. P. Kutney and A. H. Ratcliffe, *Synth. Commun.*, 547 (1975).

most general way of masking nucleophilicity is by acylations, and carbamates are particularly useful. A most effective group for this purpose is the carbobenzyloxy (Cbz) group,[215] which is introduced by acylation of the amino group using benzyl chloroformate. The amine can be regenerated from a Cbz derivative by hydrogenolysis of the benzyl C–O bond, which is accompanied by spontaneous decarboxylation of the resulting carbamic acid.




In addition to standard catalytic hydrogenolysis, methods for transfer hydrogenolysis using hydrogen donors such as ammonium formate or formic acid with Pd-C catalyst are available.[216] The Cbz group also can be removed by a combination of a Lewis acid and a nucleophile: for example, boron trifluoride in conjunction with dimethyl sulfide or ethyl sulfide.[217]

The *t*-butoxycarbonyl (*t*Boc) group is another valuable amino-protecting group. The removal in this case is done with an acid such as trifluoroacetic acid or *p*-toluenesulfonic acid.[218] *t*-Butoxycarbonyl groups are introduced by reaction of amines with *t*-butylpyrocarbonate or a mixed carbonate-imidate ester known as "BOC-ON."[219]

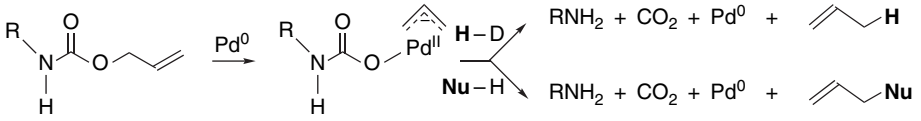



Another carbamate protecting group is 2,2,2-trichloroethyloxycarbonyl, known as Troc. 2,2,2-Trichloroethylcarbamates can be reductively cleaved by zinc.[220]

Allyl carbamates also can serve as amino-protecting groups. The allyloxy group is removed by Pd-catalyzed reduction or nucleophilic substitution. These reactions involve formation of the carbamic acid by oxidative addition to the palladium. The allyl-palladium species is reductively cleaved by stannanes,[221] phenylsilane,[222] formic acid,[223] and $NaBH_4$,[224] which convert the allyl group to propene. Reagents

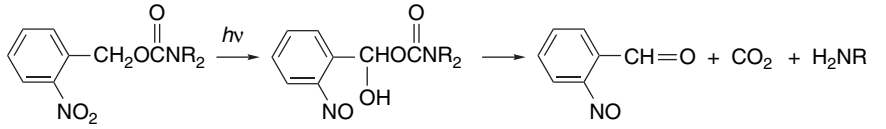
215. W. H. Hartung and R. Simonoff, *Org. React.*, **7**, 263 (1953).
216. S. Ram and L. D. Spicer, *Tetrahedron Lett.*, **28**, 515 (1987); B. El Amin, G. Anantharamaiah, G. Royer, and G. Means, *J. Org. Chem.*, **44**, 3442 (1979).
217. I. M. Sanchez, F. J. Lopez, J. J. Soria, M. I. Larraza, and H. J. Flores, *J. Am. Chem. Soc.*, **105**, 7640 (1983); D. S. Bose and D. E. Thurston, *Tetrahedron Lett.*, **31**, 6903 (1990).
218. E. Wunsch, *Methoden der Organischen Chemie*, Vol. 15, 4th Edition, Thieme, Stuttgart, 1975.
219. O. Keller, W. Keller, G. van Look, and G. Wersin, *Org. Synth.*, **63**, 160 (1984); W. J. Paleveda, F. W. Holly, and D. F. Weber, *Org. Synth.*, **63**, 171 (1984).
220. G. Just and K. Grozinger, *Synthesis*, 457 (1976).
221. O. Dangles, F. Guibe, G. Balavoine, S. Lavielle, and A. Marquet, *J. Org. Chem.*, **52**, 4984 (1987).
222. M. Dessolin, M.-G. Guillerez, N. T. Thieriet, F. Guibe, and A. Loffet, *Tetrahedron Lett.*, **36**, 5741 (1995).
223. I. Minami, Y. Ohashi, I. Shimizu, and J. Tsuji, *Tetrahedron Lett.*, **26**, 2449 (1985); Y. Hayakawa, S. Wakabashi, H. Kato, and R. Noyori, *J. Am. Chem. Soc.*, **112**, 1691 (1990).
224. R. Beugelmans, L. Neville, M. Bois-Choussy, J. Chastanet, and J. Zhu, *Tetrahedron Lett.*, **36**, 3129 (1995).

used for nucleophilic cleavage include *N*,*N*′-dimethylbarbituric acid,[225] and silylating agents, including TMS-$N_3$/$NH_4F$,[226] $TMSN(Me)_2$,[227] and $TMSN(CH_3)COCF_3$.[219] The silylated nucleophiles trap the deallylated product prior to hydrolytic workup.

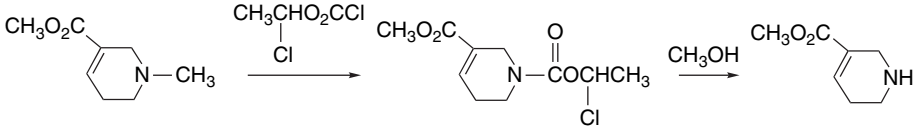



Allyl groups attached directly to amine or amide nitrogen can be removed by isomerization and hydrolysis. [228] These reactions are analogous to those used to cleave allylic ethers (see p. 266). Catalysts that have been found to be effective include Wilkinson's catalyst,[229] other rhodium catalysts,[230] and iron pentacarbonyl.[45] Treatment of *N*-allyl amines with $Pd(PPh_3)_4$ and *N*,*N*′-dimethylbarbituric acid also cleaves the allyl group.[231]

Sometimes it is useful to be able to remove a protecting group by photolysis. 2-Nitrobenzyl carbamates meet this requirement. The photoexcited nitro group abstracts a hydrogen from the benzylic position, which is then converted to a α-hydroxybenzyl carbamate that readily hydrolyzes.[232]



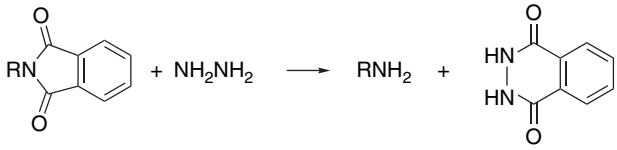

*N*-Benzyl groups can be removed from tertiary amines by reaction with chloroformates. This can be a useful method for protective group manipulation if the resulting carbamate is also easily cleaved. A particularly effective reagent is α-chloroethyl chloroformate, which can be removed by subsequent solvolysis,[233] and it has been used to remove methyl and ethyl groups. These reactions are related to ether cleavage by acylation reagents (see Section 3.3).



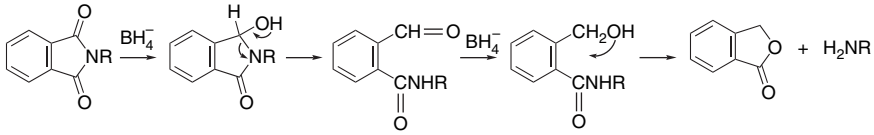

Simple amides are satisfactory protecting groups only if the rest of the molecule can resist the vigorous acidic or alkaline hydrolysis necessary for removal. For this

225. P. Braun, H. Waldmann, W. Vogt, and H. Kunz, *Synlett*, 105 (1990).
226. G. Shapiro and D. Buechler, *Tetrahedron Lett.*, **35**, 5421 (1994).
227. A. Merzouk, F. Guibe, and A. Loffet, *Tetrahedron Lett.*, **33**, 477 (1992).
228. I. Minami, M. Yuhara, and J. Tsuji, *Tetrahedron Lett.*, **28**, 2737 (1987); M. Sakaitani, N. Kurokawa, and Y. Ohfune, *Tetrahedron Lett.*, **27**, 3753 (1986).
229. B. C. Laguzza and B. Ganem, *Tetrahedron Lett.*, **22**, 1483 (1981).
230. J. K. Stille and Y. Becker, *J. Org. Chem.*, **45**, 2139 (1980); R. J. Sundberg, G. S. Hamilton, and J. P. Laurino, *J. Org. Chem.*, **53**, 976 (1988).
231. F. Garro-Helion, A. Merzouk, and F. Guibe, *J. Org. Chem.*, **52**, 6109 (1993).
232. J. F. Cameron and J. M. J. Frechet, *J. Am. Chem. Soc.*, **113**, 4303 (1991).
233. R. A. Olofson, J. T. Martz, J.-P. Senet, M. Piteau, and T. Malfroot, *J. Org. Chem.*, **49**, 2081 (1984).

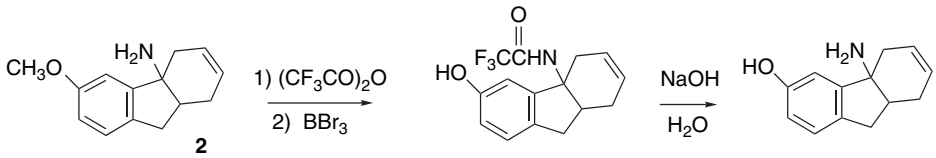
reason, only amides that can be removed under mild conditions are useful as amino-protecting groups. Phthalimides, which are used to protect primary amino groups, can be cleaved by treatment with hydrazine, as in the Gabriel synthesis of amines (see Section 3.2.4). This reaction proceeds by initial nucleophilic addition at an imide carbonyl, followed by an intramolecular acyl transfer.



A similar sequence that takes place under milder conditions uses 4-nitrophthalimides as the protecting group and *N*-methylhydrazine for deprotection.[234] Reduction by $NaBH_4$ in aqueous ethanol is an alternative method for deprotection of phthalimides. This reaction involves formation of an *o*-(hydroxymethyl)benzamide in the reduction step. Intramolecular displacement of the amino group follows.[235]

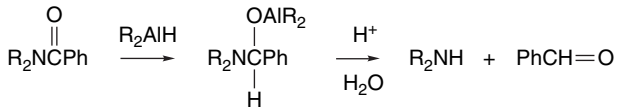


Owing to the strong EWG effect of the trifluoromethyl group, trifluoroacetamides are subject to hydrolysis under mild conditions. This has permitted trifluoroacetyl groups to be used as amino-protecting groups in some situations. For example, the amino group was protected by trifluoroacetylation during $BBr_3$ demethylation of **2**.



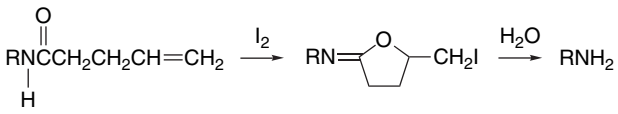
Ref. 236

Amides can also be deacylated by partial reduction. If the reduction proceeds only to the carbinolamine stage, hydrolysis can liberate the deprotected amine. Trichloroacetamides are readily cleaved by sodium borohydride in alcohols by this mechanism.[237] Benzamides, and probably other simple amides, can be removed by careful partial reduction with diisobutylaluminum hydride (see Section 5.3.1.1).[238]



[234] H. Tsubouchi, K. Tsuji, and H. Ishikawa, *Synlett*, 63 (1994).
[235] J. O. Osborn, M. G. Martin, and B. Ganem, *Tetrahedron Lett.*, **25**, 2093 (1984).
[236] Y.-P. Pang and A. P. Kozikowski, *J. Org. Chem.*, *56*, 4499 (1991).
[237] F. Weygand and E. Frauendorfer, *Chem. Ber.*, **103**, 2437 (1970).
[238] J. Gutzwiller and M. Uskokovic, *J. Am. Chem. Soc.*, **92**, 204 (1970); K. Psotta and A. Wiechers, *Tetrahedron*, **35**, 255 (1979).

The 4-pentenoyl group is easily removed from amides by $I_2$ and can be used as a protecting group. The mechanism of cleavage involves iodocyclization and hydrolysis of the resulting iminolactone (see Section 4.2.1).[239]



Sulfonamides are very difficult to hydrolyze. However, a photoactivated reductive method for desulfonylation has been developed.[240] Sodium borohydride is used in conjunction with 1,2- or 1,4-dimethoxybenzene or 1,5-dimethoxynaphthalene. The photoexcited aromatic serves as an electron donor toward the sulfonyl group, which then fragments to give the deprotected amine. The $NaBH_4$ reduces the radical cation and the sulfonyl radical.

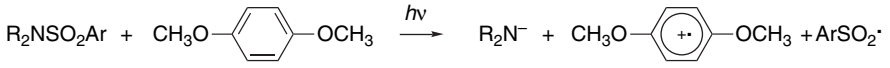
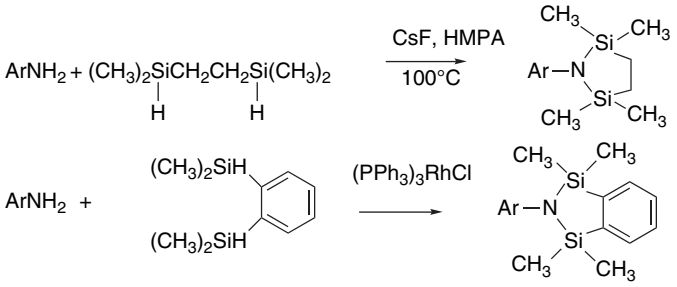


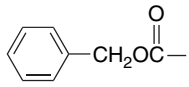
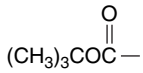
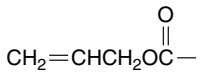
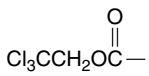
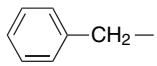
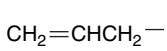
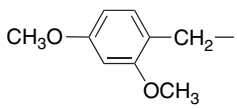
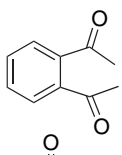
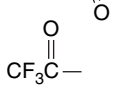
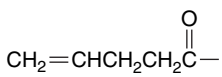
Table 3.2 summarizes the common amine-protecting groups. Reagents that permit protection of primary amino groups as cyclic *bis*-silyl derivatives have been developed. Anilines, for example, can be converted to disilazolidines.[241] These groups are stable to a number of reaction conditions, including generation and reaction of organometallic reagents.[242] They are readily removed by hydrolysis.



Amide nitrogens can be protected by 4-methoxy or 2,4-dimethoxyphenyl groups. The protecting group can be removed by oxidation with ceric ammonium nitrate.[243] 2,4-Dimethoxybenzyl groups can be removed using anhydrous trifluoroacetic acid.[244]

239. R. Madsen, C. Roberts, and B. Fraser-Reid, *J. Org. Chem.*, **60**, 7920 (1995).
240. T. Hamada, A. Nishida, and O. Yonemitsu, *Heterocycles*, **12**, 647 (1979); T. Hamada, A. Nishida, Y. Matsumoto, and O. Yonemitsu, *J. Am. Chem. Soc.*, **102**, 3978 (1980).
241. R. P. Bonar-Law, A. P. Davis, and B. J. Dorgan, *Tetrahedron Lett.*, **31**, 6721 (1990); R. P. Bonar-Law, A. P. Davis, B. J. Dorgan, M. T. Reetz, and A. Wehrsig, *Tetrahedron Lett.*, **31**, 6725 (1990); S. Djuric, J. Venit, and P. Magnus, *Tetrahedron Lett.*, **22**, 1787 (1981); T. L. Guggenheim, *Tetrahedron Lett.*, **25**, 1253 (1984); A. P. Davis and P. J. Gallagher, *Tetrahedron Lett.*, **36**, 3269 (1995).
242. R. P. Bonar-Law, A. P. Davis, and J. P. Dorgan, *Tetrahedron*, **49**, 9855 (1993); K. C. Grega, M. R. Barbachyn, S. J. Brickner, and S. A. Mizsak, *J. Org. Chem.*, **60**, 5255 (1995).
243. M. Yamaura, T. Suzuki, H. Hashimoto, J. Yoshimura, T. Okamoto, and C. Shin, *Bull. Chem. Soc. Jpn.*, **58**, 1413 (1985); R. M. Williams, R. W. Armstrong, and J.-S. Dung, *J. Med. Chem.*, **28**, 733 (1985).
244. R. H. Schlessinger, G. R. Bebernitz, P. Lin, and A. J. Pos, *J. Am. Chem. Soc.*, **107**, 1777 (1985); P. DeShong, S. Ramesh, V. Elango, and J. J. Perez, *J. Am. Chem. Soc.*, **107**, 5219 (1985).

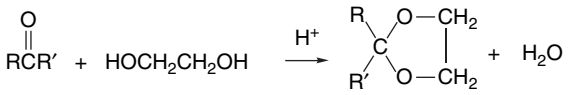
**Table 3.2. Common Amine-Protecting Groups**

| Structure | Name | Abbreviation |
|---|---|---|
| A. Carbamates | | |
|  | Carbobenzyloxy (Benzyloxycarbonyl) | Cbz |
|  | *t*-Butoxycarbonyl | *t*-Boc |
|  | Allyloxycarbonyl | |
|  | Trichloroethoxycarbonyl | Troc |
| B. *N*-Substituents | | |
|  | Benzyl | Bn |
|  | Allyl | |
|  | 2,4-Dimethoxybenzyl | DMB |
| C. Amides and Imides | | |
|  | Phthaloyl | Phthal |
|  | Trifluoroacetyl | |
|  | 4-Pentenoyl | |

### 3.5.3. Carbonyl-Protecting Groups

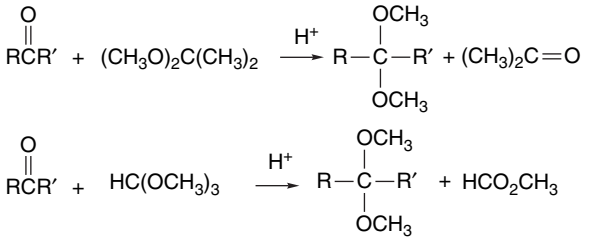
Conversion to acetals is a very general method for protecting aldehydes and ketones against nucleophilic addition or reduction.[245] Ethylene glycol, which gives a cyclic dioxolane derivative, is frequently employed for this purpose. The dioxolanes are usually prepared by heating a carbonyl compound with ethylene glycol in the presence of an acid catalyst, with provision for azeotropic removal of water.

[245] A. R. Hajipour, S. Khoee, and A. E. Ruoho, *Org. Prep. Proced. Int.*, **35**, 527 (2003).

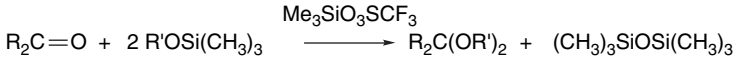


Scandium triflate is also an effective catalyst for dioxolane formation.[246]

Dimethyl or diethyl acetals can be prepared by acid-catalyzed exchange with an acetal such as 2,2-dimethoxypropane or an orthoester.[247]

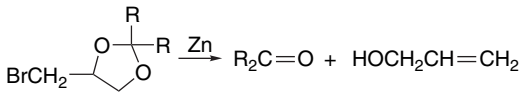


Acetals can be prepared under very mild conditions by reaction of the carbonyl compound with a trimethylsilyl ether, using trimethylsilyl trifluoromethylsulfonate as the catalyst.[248]



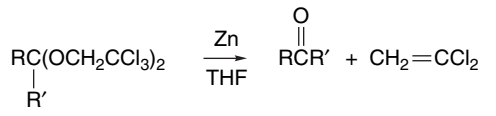
The carbonyl group can be deprotected by acid-catalyzed hydrolysis by the general mechanism for acetal hydrolysis (see Part A, Section 7.1). A number of Lewis acids have also been used to remove acetal protective groups. Hydrolysis is promoted by $LiBF_4$ in acetonitrile.[249] Bismuth triflate promotes hydrolysis of dimethoxy, diethoxy, and dioxolane acetals.[250] The dimethyl and diethyl acetals are cleaved by 0.1–1.0 mol % of catalyst in aqueous THF at room temperature, whereas dioxolanes require reflux. Bismuth nitrate also catalyzes acetal hydrolysis.[251]

If the carbonyl group must be regenerated under nonhydrolytic conditions, β-halo alcohols such as 3-bromopropane-1,2-diol or 2,2,2-trichloroethanol can be used for acetal formation. These groups can be removed by reduction with zinc, which leads to β-elimination.



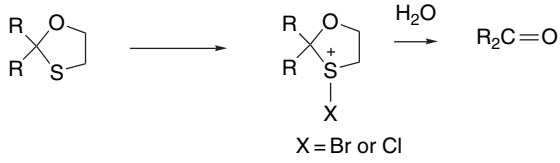
Ref. 252

246. K. Ishihara, Y. Karumi, M. Kubota, and H. Yamamoto, *Synlett*, 839 (1996).
247. C. A. MacKenzie and J. H. Stocker, *J. Org. Chem.*, **20**, 1695 (1955); E. C. Taylor and C. S. Chiang, *Synthesis*, 467 (1977).
248. T. Tsunoda, M. Suzuki, and R. Noyori, *Tetrahedron Lett.*, **21**, 1357 (1980).
249. B. H. Lipshutz and D. F. Harvey, *Synth. Commun.*, **12**, 267 (1982).
250. M. D. Carrigan, D. Sarapa, R. C. Smith, L. C. Wieland, and R. S. Mohan, *J. Org. Chem.*, **67**, 1027 (2002).
251. N. Srivasta, S. K. Dasgupta, and B. K. Banik, *Tetrahedron Lett.*, **44**, 1191 (2003).
252. E. J. Corey and R. A. Ruden, *J. Org. Chem.*, **38**, 834 (1973).

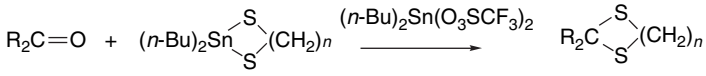


Ref. 253

Another carbonyl-protecting group is the 1,3-oxathiolane derivative, which can be prepared by reaction with mercaptoethanol in the presence of a number of Lewis acids including $BF_3$[254] and $In(OTf)_3$[255] or by heating with an acid catalyst with azeotropic removal of water.[256] The 1,3-oxathiolanes are particularly useful when nonacidic conditions are required for deprotection. The 1,3-oxathiolane group can be removed by treatment with Raney nickel in alcohol, even under slightly alkaline conditions.[257] Deprotection can also be accomplished by treating with a mild halogenating agent, such as NBS,[258] tetrabutylammonium tribromide,[259] or chloramine-T.[260] These reagents oxidize the sulfur to a halosulfonium salt and activate the ring to hydrolytic cleavage.



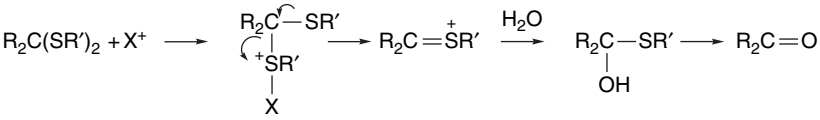
Dithioketals, especially the cyclic dithiolanes and dithianes, are also useful carbonyl-protecting groups.[261] These can be formed from the corresponding dithiols by Lewis acid–catalyzed reactions. The catalysts that are used include $BF_3$, $Mg(O_3SCF_3)_2$, $Zn(O_3SCF_3)_2$, and $LaCl_3$.[262] *S*-Trimethylsilyl ethers of thiols and dithiols also react with ketones to form dithioketals.[263] *Bis*-trimethylsilyl sulfate in the presence of silica also promotes formation of dithiolanes.[264] Di-*n*-butylstannyldithiolates also serve as sources of dithiolanes and dithianes. These reactions are catalyzed by di-*n*-butylstannyl ditriflate.[265]



The regeneration of carbonyl compounds from dithioacetals and dithiolanes is often done with reagents that oxidize or otherwise activate the sulfur as a leaving

253. J. L. Isidor and R. M. Carlson, *J. Org. Chem.*, **38**, 544 (1973).
254. G. E. Wilson, Jr., M. G. Huang, and W. W. Scholman, Jr., *J. Org. Chem.*, **33**, 2133 (1968).
255. K. Kazahaya, N. Hamada, S. Ito, and T. Sato, *Synlett*, 1535 (2002).
256. C. Djerassi and M. Gorman, *J. Am. Chem. Soc.*, **75**, 3704 (1953).
257. C. Djerassi, E. Batres, J. Romo, and G. Rosenkranz, *J. Am. Chem. Soc.*, **74**, 3634 (1952).
258. B. Karimi, H. Seradj, and M. H. Tabaei, *Synlett*, 1798 (2000).
259. E. Mondal, P. R. Sahu, G. Bose, and A. T. Khan, *Tetrahedron Lett.*, **43**, 2843 (2002).
260. D. W. Emerson and H. Wynberg, *Tetrahedron Lett.*, 3445 (1971).
261. A. K. Banerjee and M. S. Laya, *Russ. Chem. Rev.*, **69**, 947 (2000).
262. L. F. Fieser, *J. Am. Chem. Soc.*, **76**, 1945 (1954); E. J. Corey and K. Shimoji, *Tetrahedron Lett.*, **24**, 169 (1983); L. Garlaschelli and G. Vidari, *Tetrahedron Lett.*, **31**, 5815 (1990); A. T. Khan, E. Mondal, P. R. Satu, and S. Islam, *Tetrahedron Lett.*, **44**, 919 (2003).
263. D. A. Evans, L. K. Truesdale, K. G. Grimm, and S. L. Nesbitt, *J. Am. Chem. Soc.*, **99**, 5009 (1977).
264. H. K. Patney, *Tetrahedron Lett.*, **34**, 7127 (1993).
265. T. Sato, J. Otero, and H. Nozaki, *J. Org. Chem.*, **58**, 4971 (1993).

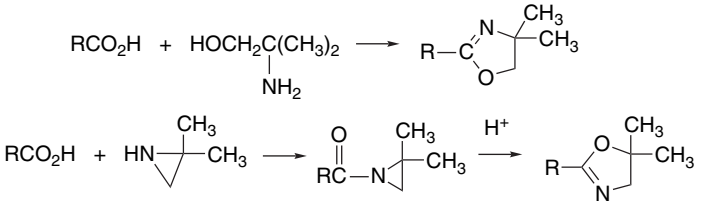
group and facilitate hydrolysis. Among the reagents that have been found effective are nitrous acid, *t*-butyl hypochlorite, $NaClO_2$, $PhI(O_2CCF_3)_2$, DDQ, $SbCl_5$, and cupric salts.[266]



### 3.5.4. Carboxylic Acid–Protecting Groups

If only the O–H, as opposed to the carbonyl, of a carboxyl group has to be masked, it can be readily accomplished by esterification. Alkaline hydrolysis is the usual way for regenerating the acid. *t*-Butyl esters, which are readily cleaved by acid, can be used if alkaline conditions must be avoided. 2,2,2-Trichloroethyl esters, which can be reductively cleaved with zinc, are another possibility.[267] Some esters can be cleaved by treatment with anhydrous TBAF. These reactions proceed best for esters of relatively acidic alcohols, such as 4-nitrobenzyl, 2,2,2-trichloroethyl, and cyanoethyl.[268]

The more difficult problem of protecting the carbonyl group can be accomplished by conversion to a oxazoline derivative. One example is the 4,4-dimethyl derivative, which can be prepared from the acid by reaction with 2-amino-2-methylpropanol or with 2,2-dimethylaziridine.[269]



The heterocyclic derivative successfully protects the acid from attack by Grignard or hydride-transfer reagents. The carboxylic acid group can be regenerated by acidic hydrolysis or converted to an ester by acid-catalyzed reaction with the appropriate alcohol.

Carboxylic acids can also be protected as orthoesters. Orthoesters derived from simple alcohols are very easily hydrolyzed, and the 4-methyl-2,6,7-trioxabicyclo[2.2.2]octane structure is a more useful orthoester protecting group. These

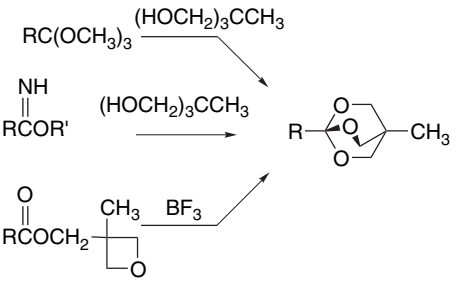
266. M. T. M. El-Wassimy, K. A. Jorgensen, and S. O. Lawesson, *J. Chem. Soc., Perkin Trans. 1*, 2201 (1983); J. Lucchetti and A. Krief, *Synth. Commun.*, **13**, 1153 (1983); G. Stork and K. Zhao, *Tetrahedron Lett.*, **30**, 287 (1989); L. Mathew and S. Sankararaman, *J. Org. Chem.*, **58**, 7576 (1993); J. M. G. Fernandez, C. O. Mellet, A. M. Marin, and J. Fuentes, *Carbohydrate Res.*, **274**, 263 (1995); K. Tanemura, H. Dohya, M. Imamura, T. Suzuki, and T. Horaguchi, *J. Chem. Soc., Perkin Trans. 1*, 453 (1996); M. Kamata, H. Otogawa, and E. Hasegawa, *Tetrahedron Lett.*, **32**, 7421 (1991); T. Ichige, A. Miyake, N. Kanoh, and M. Nakata, *Synlett*, 1686 (2004).

267. R. B. Woodward, K. Heusler, J. Gostelli, P. Naegeli, W. Oppolzer, R. Ramage, S. Ranganathan, and H. Vorbruggen, *J. Am. Chem. Soc.*, **88**, 852 (1966).

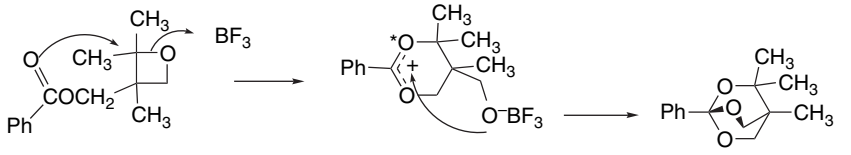
268. M. Namikoshi, B. Kundu, and K. L. Rinehart, *J. Org. Chem.*, **56**, 5464 (1991); Y. Kita, H. Maeda, F. Takahashi, S. Fukui, and T. Ogawa, *Chem. Pharm. Bull.*, **42**, 147 (1994).

269. A. I. Meyers, D. L. Temple, D. Haidukewych, and E. Mihelich, *J. Org. Chem.*, **39**, 2787 (1974).

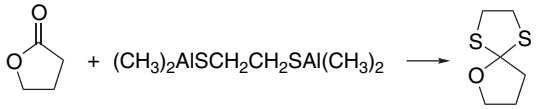
derivatives can be prepared by exchange with other orthoesters,[270] by reaction with iminoethers,[271] or by rearrangement of the ester derived from 3-hydroxymethyl-3-methyloxetane.[272]




The latter method is improved by use of the 2,2-dimethyl derivative.[273] The rearrangement is faster and the stability of the orthoester to hydrolysis is better. Isotopic labeling showed that the rearrangement occurs by ionization at the tertiary position.

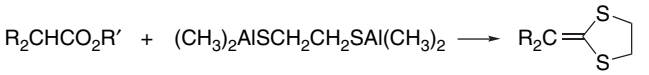



Lactones can be protected as dithiolane derivatives using a method that is analogous to ketone protection. The required reagent is readily prepared from trimethylaluminum and ethanedithiol.




Ref. 274

Acyclic esters react with this reagent to give ketene dithio acetals.



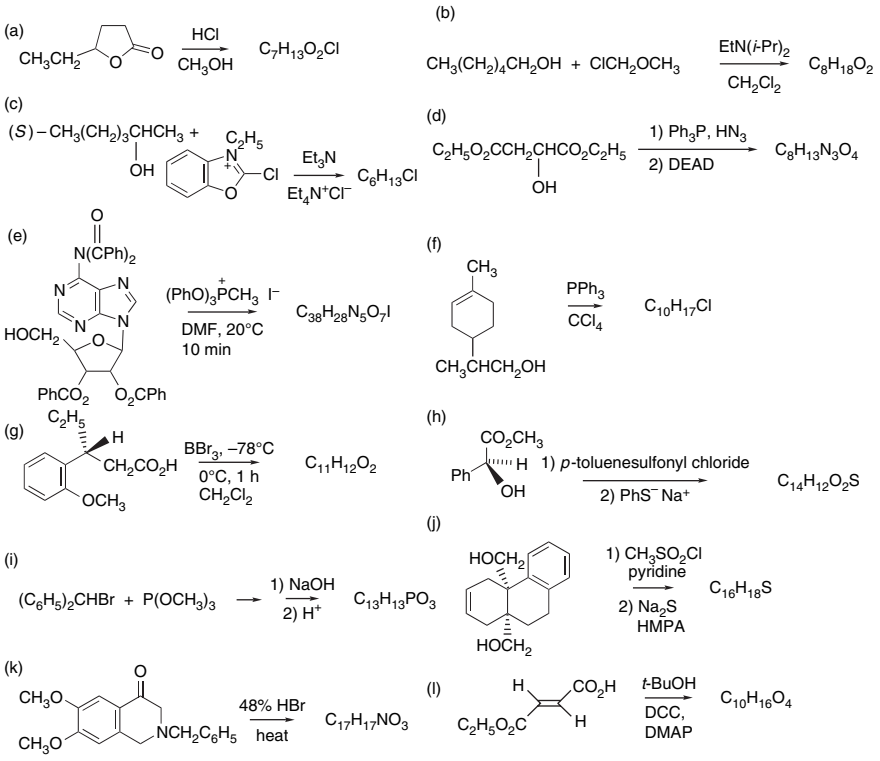

In general, the methods for protection and deprotection of carboxylic acids and esters are not as convenient as for alcohols, aldehydes, and ketones. It is therefore common to carry potential carboxylic acids through synthetic schemes in the form of protected primary alcohols or aldehydes. The carboxylic acid can then be formed at a late stage in the synthesis by an appropriate oxidation. This strategy allows one to utilize the wider variety of alcohol and aldehyde protective groups indirectly for carboxylic acid protection.

270. M. P. Atkins, B. T. Golding, D. A. Howe, and P. J. Sellers, *J. Chem. Soc., Chem. Commun.*, 207 (1980).
271. E. J. Corey and K. Shimoji, *J. Am. Chem. Soc.*, **105**, 1662 (1983).
272. E. J. Corey and N. Raju, *Tetrahedron Lett.*, **24**, 5571 (1983).
273. J.-L. Griner, *Org. Lett.*, **7**, 499 (2005).
274. E. J. Corey and D. J. Beames, *J. Am. Chem. Soc.*, **95**, 5829 (1973).

## Problems

(*References for these problems will be found on page 1275.*)

3.1. Give the products that would be expected to be formed under the specified reaction conditions. Be sure to specify all aspects of the stereochemistry.




3.2. When (*R*)-(−)-5-hexen-2-ol was treated with $Ph_3P$ in refluxing, $CCl_4$, (+)-5-chloro-1-hexene was obtained. Conversion of (*R*)-(−)-5-hexen-2-ol to its 4-bromobenzenesulfonate ester and subsequent reaction with LiCl gave (+)-5-chloro-1-hexene. Reaction of (*S*)-(+)-5-hexen-2-ol with $PCl_5$ in ether gave (−)-5-chloro-1-hexene.

a. Write chemical equations for each of these reactions and specify whether each occurs with net retention or inversion of configuration.
b. What is the sign of rotation of (*R*)-5-chloro-1-hexene?

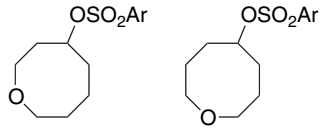
3.3. A careful investigation of the extent of isomeric products formed by reaction of several alcohols with thionyl chloride has been reported. The product compositions for several of the alcohols are given below. Identify the structural features that promote isomerization and show how each of the rearranged products is formed.

$$ROH \xrightarrow[100°C]{SOCl_2} RCl$$

| R | Percent unrearranged RCl | Structure and amount of rearranged RCl |
|---|---|---|
| $CH_3CH_2CH_2CH_2-$ | 100 | |
| $(CH_3)_2CHCH_2-$ | 99.7 | |
| $(CH_3)_2CHCH_2CH_2-$ | 100 | $(CH_3)_2CHCH_3$ (Cl) 0.3% |
| $CH_3CH_2CHCH_2-$ ($CH_3$) | 78 | $CH_3CHCH_2CH_2CH_3$ (Cl) 1%; $CH_3CH_2CHCH_2CH_3$ (Cl) 11%; $CH_3CH_2C(CH_3)_2$ (Cl) 10% |
| $(CH_3)_3CCH_2-$ | 2 | $CH_3CH_2C(CH_3)_2$ (Cl) 98% |
| $CH_3CH_2CH_2CHCH_3$ | 98 | $CH_3CH_2CHCH_2CH_3$ (Cl) 2% |
| $CH_3CH_2CHCH_2CH_3$ | 90 | $CH_3CH_2CH_2CHCH_3$ (Cl) 10% |
| $(CH_3)_2CHCHCH_3$ | 5 | $CH_3CH_2C(CH_3)_2$ (Cl) 95% |

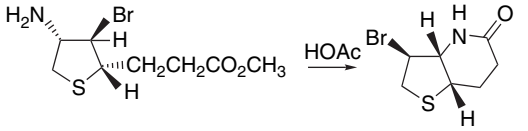
3.4. Give a reaction mechanism that would explain the following observations and reactions.

a. Kinetic measurements reveal that solvolytic displacement of sulfonate is about $5 \times 10^5$ faster for **4B** than for **4A**.

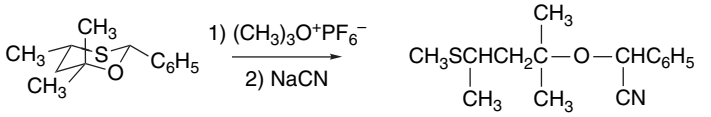



**4A** **4B**

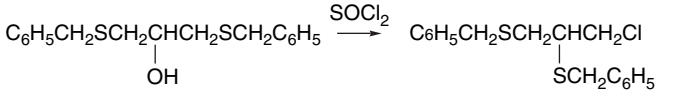
b.



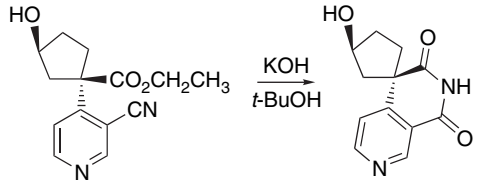

c.



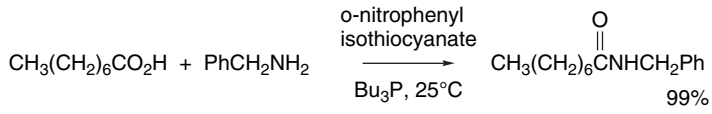

d.



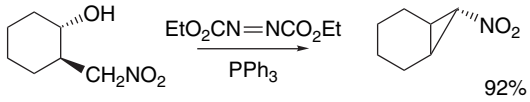
e.



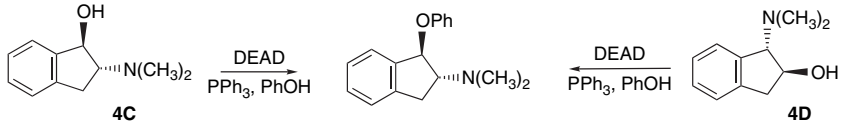

f.




g.

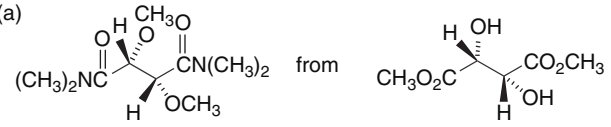



h. Both **4C** and **4D** gave the same product when subjected to Mitsunobu conditions with phenol as the nucleophile.

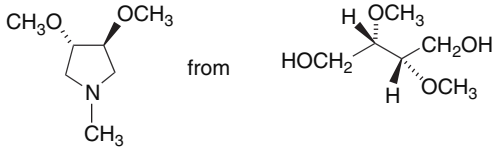



3.5. Substances such as carbohydrates and amino acids as well as other small molecules available from natural sources are valuable starting materials in enantiospecific syntheses. Suggest reagents that could effect the following transformations, taking particular care to ensure that the product will be enantiomerically pure.

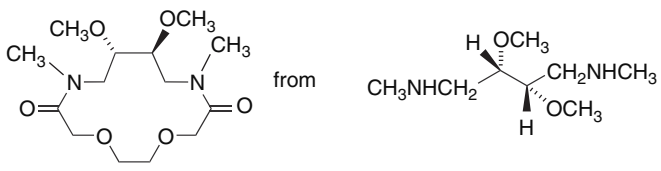
(a)

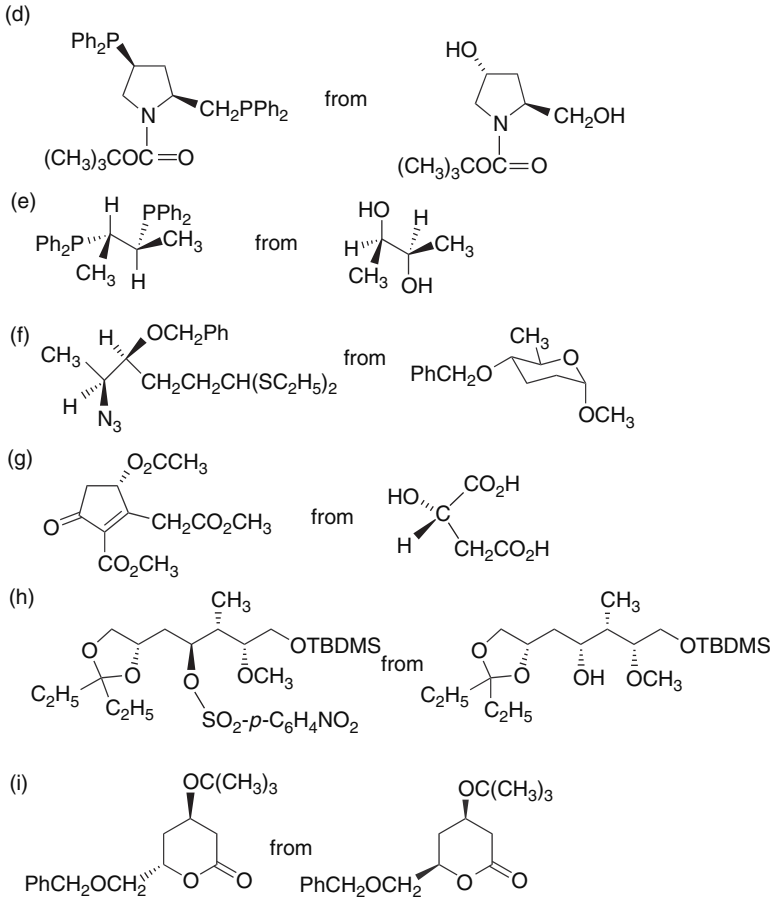



(b)

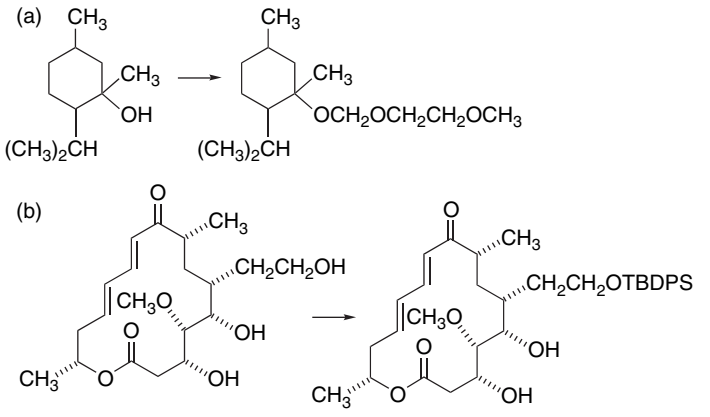



(c)

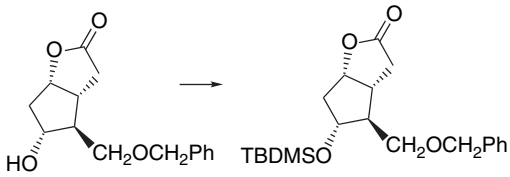




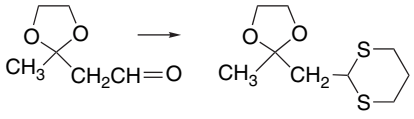

3.6. Indicate conditions that would be appropriate for the following transformations involving introduction or removal of protective groups:



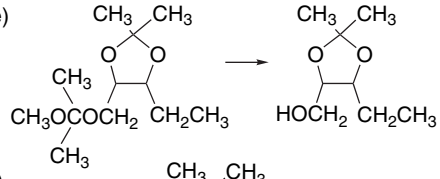
(c)



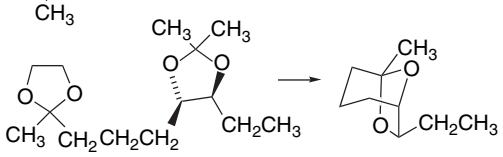

(d)




(e)

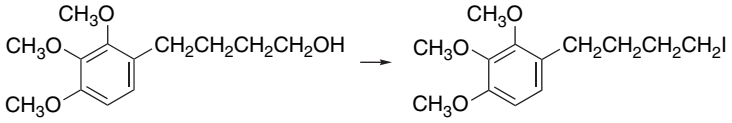



(f)

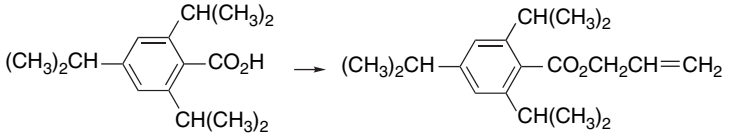



3.7. Suggest reagents and approximate reaction conditions that would effect the following conversions. Note any special features of the reactant that should be taken into account in choosing a reagent system.

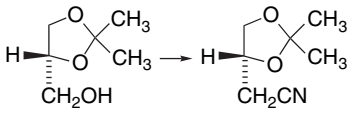
(a)



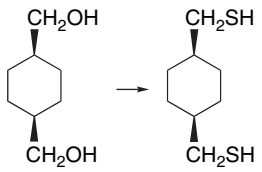

(b)



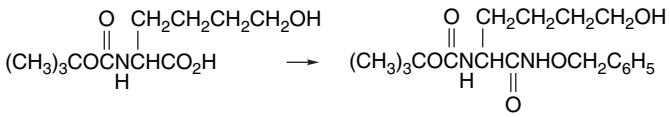

(c)

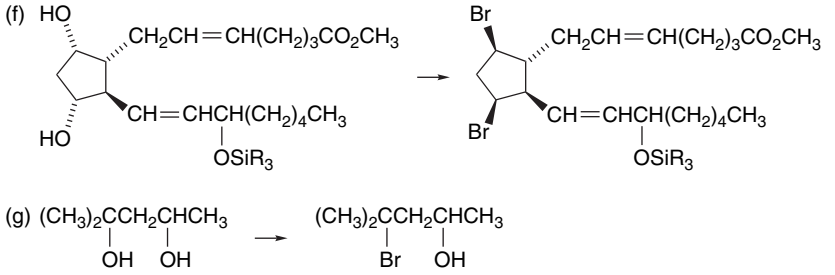



(d)



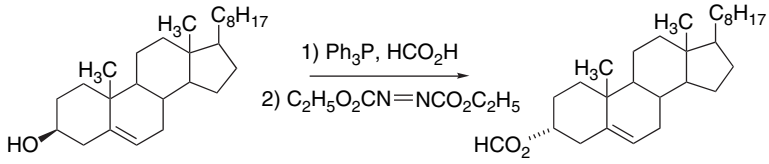

(e)





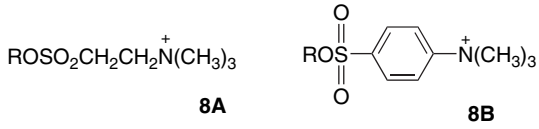

3.8. Provide a mechanistic interpretation of the following reactions and observations.

a. Show the mechanism for inversion of a hydroxyl site under the Mitsunobu conditions, as illustrated by the reaction of cholesterol.



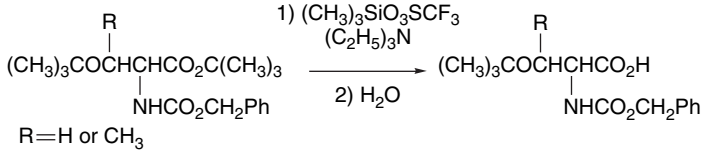

b. Triphenylphosphine oxide reacts with trifluoromethylsulfonic anhydride to give an ionic substance having the composition of a 1:1 adduct. When this substance is added to a solution containing a carboxylic acid, followed by addition of an amine, amides are formed in good yield. Similarly, esters are formed on reaction with alcohols. What is the structure of the adduct and how does it activate the carboxylic acids to nucleophilic substitution?

c. Sulfonate esters having quaternary nitrogen substituents, such as **8A** and **8B**, show high reactivity toward nucleophilic substitution. Sulfonates **8A** are comparable in reactivity to 2,2,2-trifluoroethylsulfonate in homogeneous solution and are even more reactive in two-phase solvent mixtures.

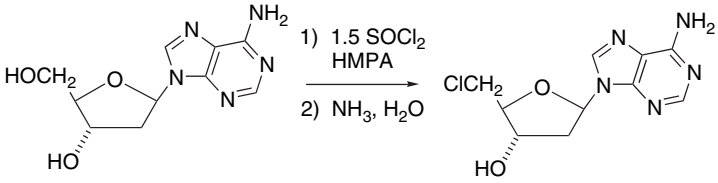



d. Alcohols react with hexachloroacetone in the presence of DMF to give alkyl trichloroacetates in good yield. Primary alcohols react faster than secondary alcohols, but tertiary alcohols are unreactive under these conditions.

e. The β-hydroxy-α-amino acids serine and threonine can be converted to their respective *bis*-*O*-*t*-butyl derivatives on reaction with isobutene and $H_2SO_4$. Subsequent treatment with one equivalent of trimethylsilyl triflate and then water cleaves the ester group, but not the ether group. What is the basis for this selectivity?

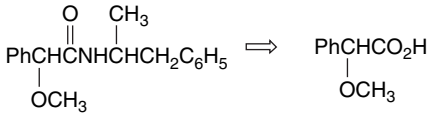


f. 2′-Deoxyadenosine can be cleanly converted to its 5′-chloro analog by reaction with 1.5 equivalent of $SOCl_2$ in HMPA. The reaction proceeds through an intermediate of composition $C_{20}H_{22}N_{10}Cl_2O_5S$, which is converted to the product on exposure to aqueous ammonia. With larger amounts of $SOCl_2$, the 3′5′-dichloro derivative is formed.

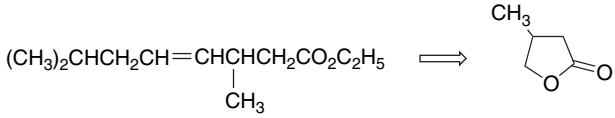



3.9. Short synthetic sequences have been used to obtain the material on the left from the starting material on the right. Suggest an appropriate method. No more than three steps should be required.

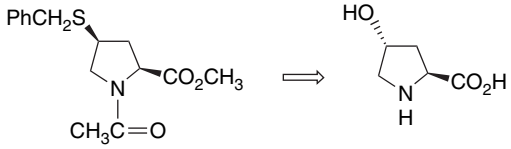
(a)



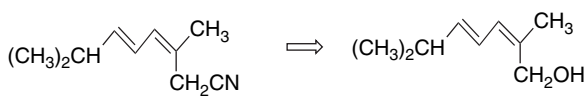

(b)



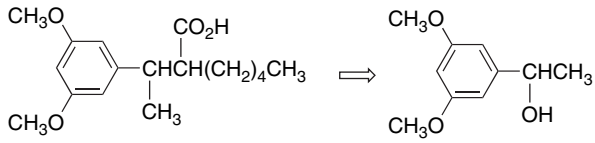

(c)



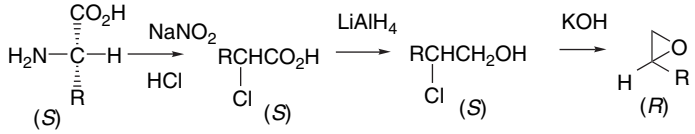

(d)




(e)

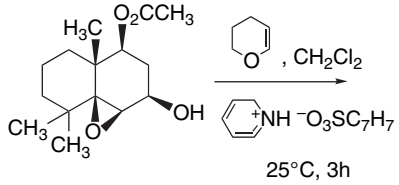



3.10. Amino acids can be converted to epoxides of high enantiomeric purity by the reaction sequence below. Analyze the stereochemistry of each step of the reaction sequence.

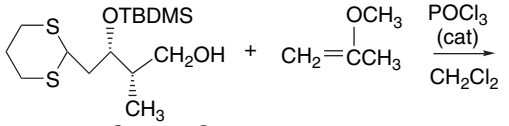


3.11. Indicate the product to be expected under the following reaction conditions:

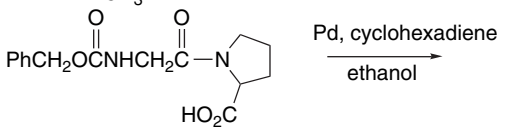
(a)



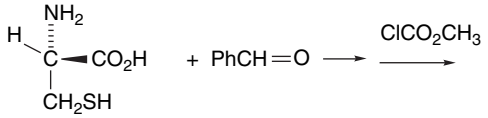

(b)



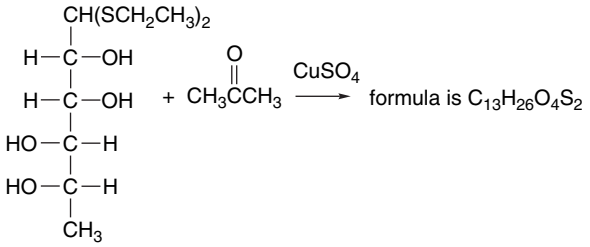

(c)




(d)

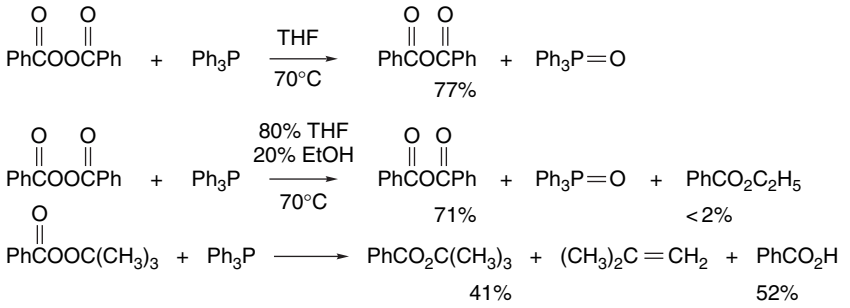



(e)




3.12. A reagent that can introduce benzyloxycarbonyl protecting groups on amino groups in nucleosides is prepared by allowing benzyl chloroformate to react first with imidazole and then with trimethyloxonium tetrafluoroborate. What is the structure of the resulting reagent (a salt) and why is it an especially reactive acylating agent?

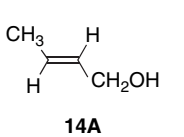
3.13. Triphenylphosphine reacts with peroxides to give intermediates that are related to those formed in the Mitsunobu reaction. The following reactions are examples:

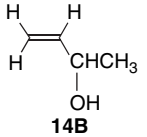


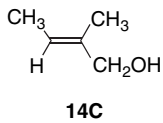

What properties of the intermediates in the Mitsunobu reaction are suggested by these reactions?

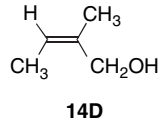
3.14. The scope of the reaction of $Ph_3P$-$Cl_3CCOCCl_3$ with allylic alcohols has been studied. Primary and some secondary alcohols, such as **14A** and **14B**, give good

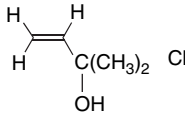
yields of unrearranged allylic chlorides. The reaction also exhibits retention of *E*,*Z*-configuration at the allylic double bonds (**14C** and 1**4D**). Certain other alcohols, such as **14E** and **14F**, give more complex mixtures. What structural features determine how cleanly the alcohol is converted to chloride? How are these structural features related to the mechanism of the reaction?

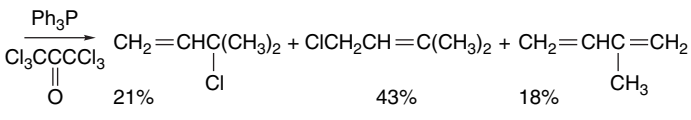

**14A**

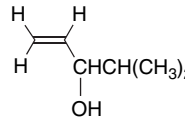

**14B**

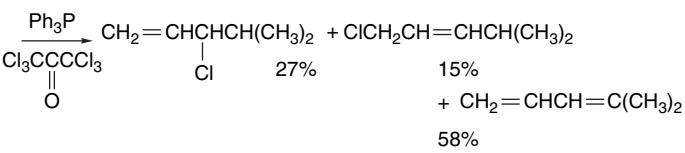

**14C**


**14D**


**14E**

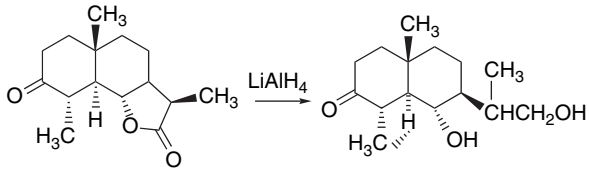




**14F**

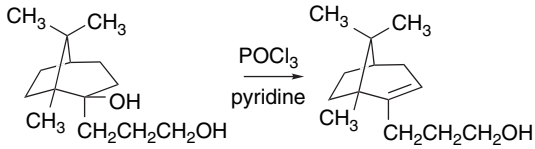



3.15. In each of the synthetic transformations shown, the reagents are appropriate for the desired transformation but the reaction would not succeed as written. Suggest a protective group strategy that would permit each transformation to be carried out to give the desired product.

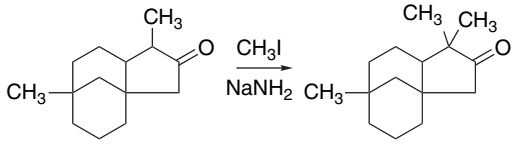
(a)



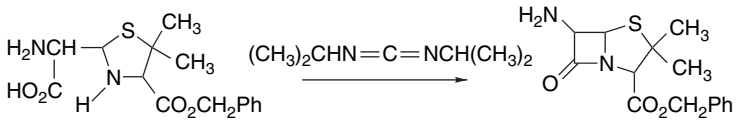

(b)



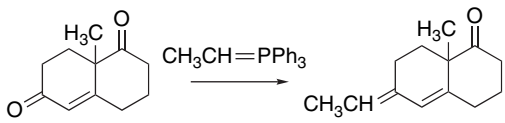

(c)



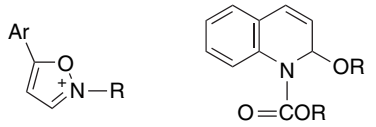

(d)




(e)

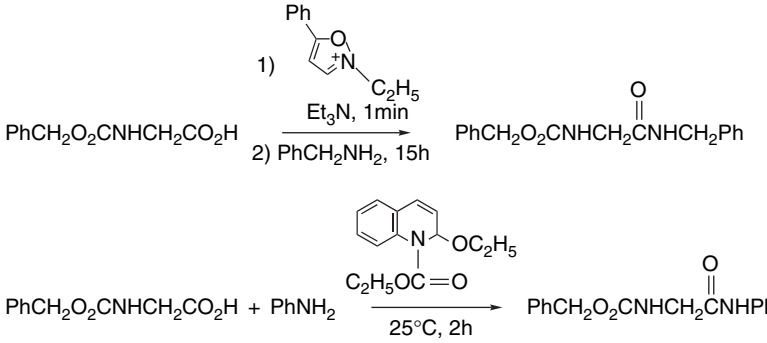


3.16. Two heterocyclic ring systems that have found some use in the formation of amides under mild conditions are *N*-alkyl-5-arylisoxazolium salts (**16A**) and *N*-acyloxy-2-alkoxydihydroquinolines (**16B**).



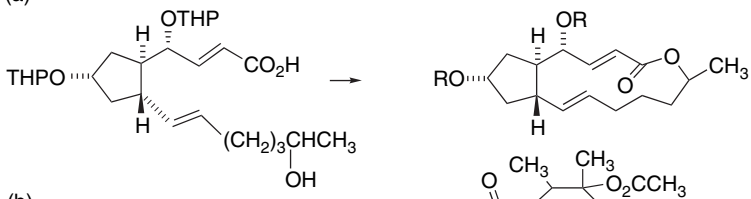

**16A** **16B**

Typical reaction conditions for these reagents are shown below. Propose mechanisms by which these heterocyclic molecules can function to activate carboxy groups under these conditions.

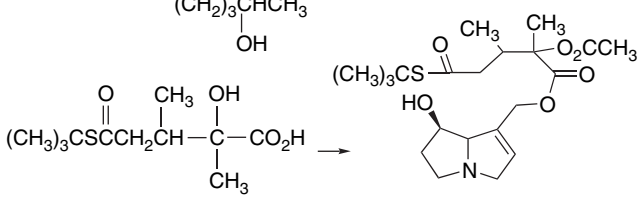



3.17. Either because of potential interference with other functional groups present in the molecule or because of special structural features, the following reactions require careful selection of reagents and reaction conditions. Identify the special requirements in each reactant and suggest appropriate reagents and reaction conditions for each transformation.

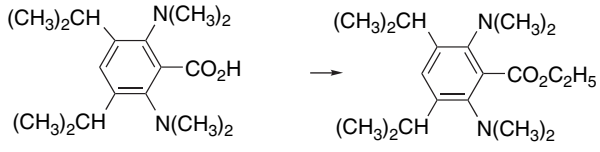
(a)




(b)

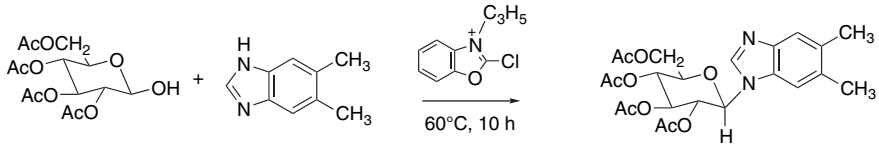



(c)

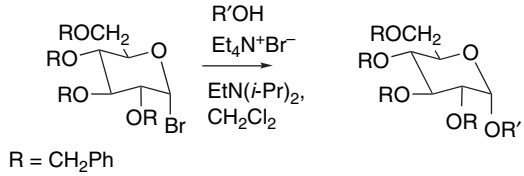



3.18. The preparation of nucleosides by reaction between carbohydrates and heterocyclic bases is fundamental to the study of the important biological activity

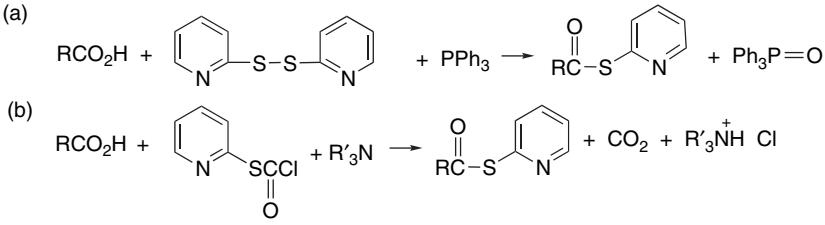
of these substances. Several methods exist for forming the nucleoside bonds. Application of 2-chloro-3-ethylbenzoxazolium chloride to this reaction was investigated using 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose. Good yields were observed and the reaction was stereospecific for the β-nucleoside. Suggest a mechanism to explain the retention of configuration.




3.19. A route to α-glycosides involves treatment of a 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl bromide with an alcohol, tetraethylammonium bromide, and diisopropylethylamine in $CH_2Cl_2$. Explain the stereoselectivity of this reaction.



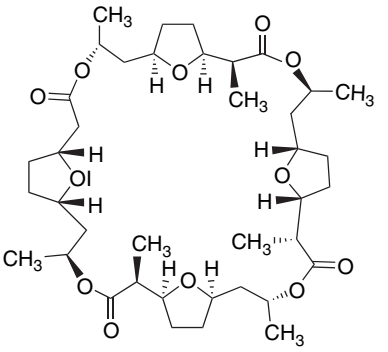

3.20. Write mechanisms for formation of 2-pyridylthio esters by the following methods:



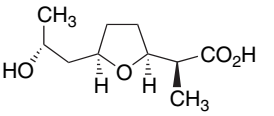

3.21. The ionophoric antibiotic nonactin is a 32-membered macrocycle that contains two units of (−)-nonactic acid and two units of (+)-nonactic acid in an alternating sequence.

a. Assuming that you have access to both (+)- and (−)-nonactic acid, devise a strategy and protecting group sequence that could provide the natural macromolecule in high stereochemical purity.

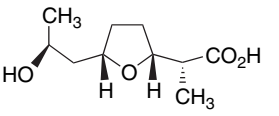
b. Suppose you had access to (+)-nonactic acid and the C(8) epimer of (−)-nonactic acid, how could you obtain nonactin?



Nonactin



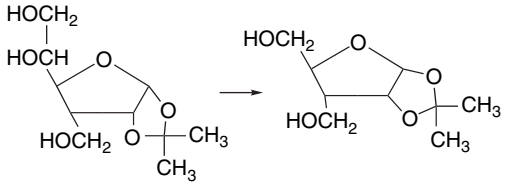
(+)-nonactic acid



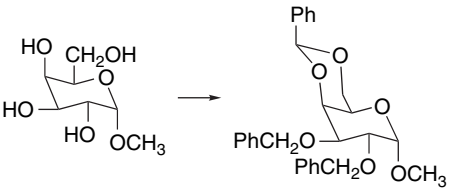
(–)-nonactic acid

3.22. Because they are readily available from natural sources in enantiomerically pure form, carbohydrates are very useful starting materials for the synthesis of other enantiomerically pure substances. However, the high number of similar functional groups present in the carbohydrates requires versatile techniques for protection and deprotection. Show how appropriate manipulation of protecting groups and other selective reactions could be employed to effect the following transformations.

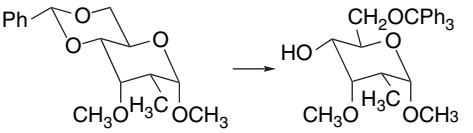
(a)



(b)



(c)



(d)