1

ALIPHATIC NUCLEOPHILIC SUBSTITUTION

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1.1 INTRODUCTION

Nucleophilic substitution reactions at an aliphatic center are among the most fundamental transformations in classical synthetic organic chemistry, and provide the practicing chemist with proven tools for simple functional group interconversion as well as complex target-oriented synthesis. Conventional S_N2 displacement reactions involving simple nucleophiles and electrophiles are well-studied transformations, are among the first concepts learned by chemistry students and provide a launching pad for more complex subject matter such as stereochemistry and physical organic chemistry.

A high level survey of the chemical literature provides an overwhelming mass of information regarding aliphatic nucleophilic substitution reactions. This chapter attempts to highlight those methods that stand out from the others in terms of scope, practicality, and scalability.

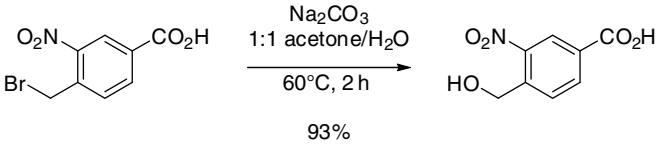
1.2 OXYGEN NUCLEOPHILES

1.2.1 Reactions with Water

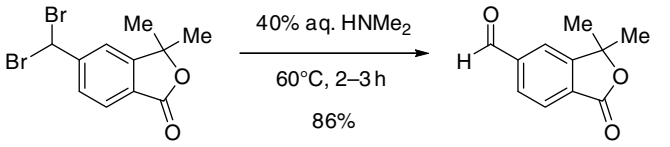
1.2.1.1 Hydrolysis of Alkyl Halides The reaction of water with an alkyl halide to form the corresponding alcohol is rarely utilized in target-oriented organic synthesis. Instead, conversion of alcohols to their corresponding halides is more common since methods for the synthesis of halides are less abundant. Nonetheless, alkyl halide hydrolysis can provide simple, efficient access to primary alcohols under certain circumstances. Namely, the hydrolysis of activated benzylic or allylic halides is a facile reaction, and following benzylic or allylic halogenation, provides a simple approach to the synthesis of this

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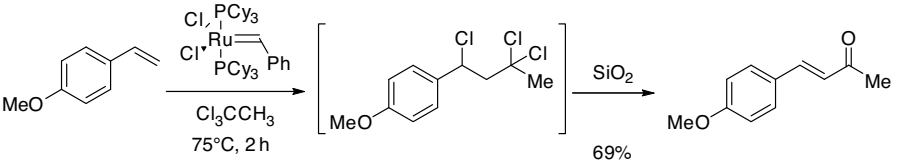
subset of alcohols. Typical conditions involve treatment of the alkyl halide with a mild base in an acetone-water or acetonitrile-water mixed solvent system. Moderate heating will accelerate the reaction, and is commonly employed.[1]



1.2.1.2 Hydrolysis of gem-Dihalides Geminal dihalides can be converted to aldehydes or ketones via direct hydrolysis. The desired conversion can be markedly accelerated by heating in the presence of an acid or a base, or by including a nucleophilic amine promoter such as dimethylamine.[2]

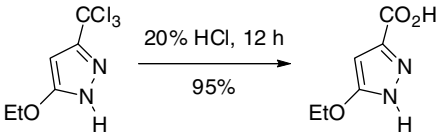


In the example below from Snapper and coworkers, a trichloro- intermediate was prepared from *p*-methoxystyrene via the Kharasch addition of 1,1,1-trichloroethane. Contact with silica gel effected elimination of the benzylic chloride as well as hydrolysis of the geminal dichloride moiety to yield the α,β-unsaturated methyl ketone in good overall yield.[3]

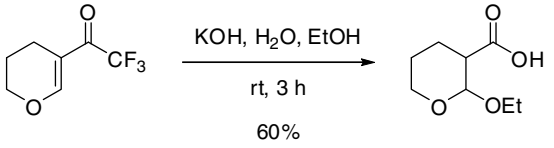


1.2.1.3 Hydrolysis of 1,1,1-Trihalides 1,1,1-Trihalides are at the appropriate oxidation state to serve as carboxylic acid precursors. These compounds react readily with water at acidic pH, providing the corresponding acids in high yield, and often at ambient temperature.[4] Trichloromethyl groups, rather than tribromo- or triiodo- analogs, are more often utilized due to superior access via nucleophilic displacement reactions by trichloromethyl anions.

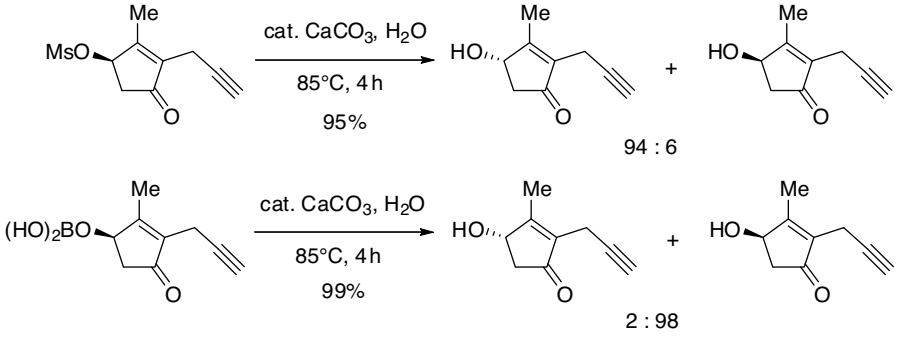
[1]Lee, H. B.; Zaccaro, M. C.; Pattarawarapan, M.; Roy, S.; Saragovi, H. U.; Burgess, K. *J. Org. Chem.* **2004**, *69*, 701–713.
[2]Bankston, D. *Synthesis* **2004**, 283–289.
[3]Lee, B. T.; Schrader, T. O.; Martin-Matute, B.; Kauffman, C. R.; Zhang, P.; Snapper, M. L. *Tetrahedron* **2004**, *60*, 7391–7396.
[4]Martins, M. A. P.; Pereira, C. M. P.; Zimmermann, N. E. K.; Moura, S.; Sinhorin, A. P.; Cunico, W.; Zanatta, N.; Bonacorso, H. G.; Flores, A. C. F. *Synthesis* **2003**, 2353–2357.



The trifluoromethyl group has seen increased application in the pharmaceutical industry in recent years due to its relative metabolic stability. Although trifluoromethyl groups are susceptible to vigorous hydrolytic conditions,[5] they are not frequently utilized as carboxylic acid precursors due to the relative expense of incorporating fluorine into building blocks. However, an increasingly common synthetic application of the CF_3 function is highlighted by the example below. Alkaline hydrolysis of a trifluoromethyl ketone provides the corresponding carboxylic acid in good yield. Here, the CF_3 group is not the point of nucleophilic attack by water. Instead, the strong inductive effect of the three highly electronegative fluorine atoms makes the trifluoromethyl anion an excellent leaving group, and attack occurs at the carbonyl carbon.[6]



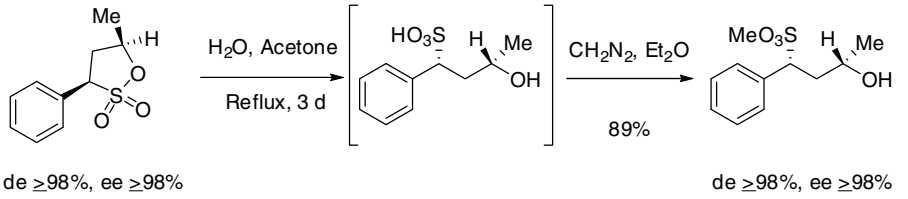
1.2.1.4 Hydrolysis of Alkyl Esters of Inorganic Acids Alkaline hydrolysis of inorganic esters may proceed through competing mechanisms, as illustrated by the mesylate and boric acid monoester in the following scheme. Sulfonate hydrolysis favors the product of stereochemical inversion, via direct S_N2 attack at the carbon bearing the sulfonate. In contrast, the corresponding boron derivative is hydrolyzed under identical reaction conditions with retention of configuration, which is the result of formal attack by hydroxide at boron.[7]



Enders and coworkers demonstrated that γ-sultone hydrolysis occurs exclusively via attack at carbon to provide γ-hydroxy sulfonates with a high degree of stereochemical

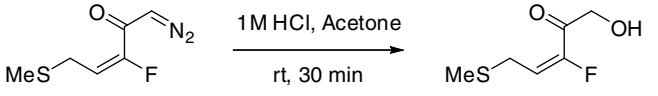
[5]Butler, D. E.; Poschel, B. P. H.; Marriott, J. G. *J. Med. Chem.* **1981**, *24*, 346–350.
[6]Hojo, M.; Masuda, R.; Sakaguchi, S.; Takagawa, M. *Synthesis* **1986**, 1016–1017.
[7]Danda, H.; Maehara, A.; Umemura, T. *Tetrahedron Lett*. **1991**, *32*, 5119–5122.

control.[8] In order to verify stereochemistry, the crude sulfonic acid was converted into the corresponding methyl sulfonate by treatment with diazomethane (see Section 1.2.3.5).

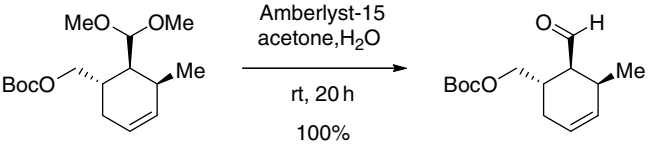


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1.2.1.5 Hydrolysis of Diazo Ketones Treatment of simple α-diazo ketones with hydrochloric acid in aqueous acetone provides direct access to the corresponding alcohols.[9] In their 1968 paper, Tillett and Aziz describe an investigation into the kinetics of this transformation that utilized a number of diazoketones and mineral acids.[10] Although the reaction can be run under mild conditions, and is often high yielding, the preparation and handling of diazo compounds is a safety concern that may preclude their use on large scale.

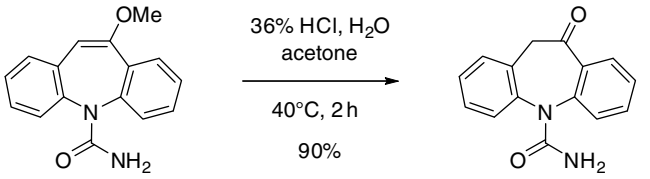


1.2.1.6 Hydrolysis of Acetals, Enol Ethers, and Related Compounds Acetals are highly susceptible to acid-catalyzed hydrolysis, typically providing the corresponding aldehydes under very mild conditions. Almost any acid catalyst can be employed, so the choice is usually dependent upon substrate compatibility. Solid-supported sulfonic acid catalysts such as Amberlyst-15[11] are an especially attractive option due to the relative ease of catalyst removal by simple filtration.[12]

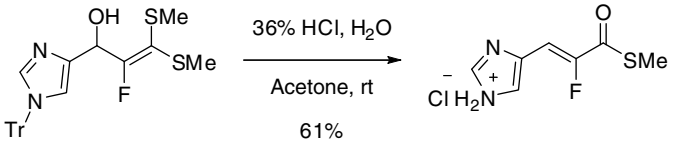


Enol ethers of simple ketones may be similarly hydrolyzed by treatment with aqueous acid. A water-miscible organic cosolvent such as acetone or acetonitrile is often included to improve substrate solubility.[13] Moderate heating increases the rate of hydrolysis, but high temperatures are seldom required.

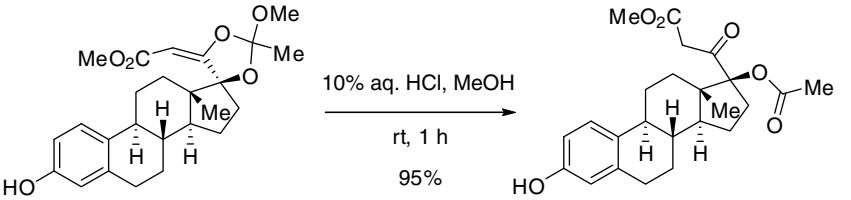
[8]Enders, D.; Harnying, W.; Raabe, G. *Synthesis* **2004**, 590–594.
[9]Pirrung, M. C.; Rowley, E. G.; Holmes, C. P. *J. Org. Chem.* **1993**, *58*, 5683–5689.
[10]Aziz, S.; Tillett, J. G. *J. Chem. Soc. B* **1968**, 1302–1307.
[11]Kunin, R.; Meitzner, E.; Bortnick, N. *J. Am. Chem. Soc.* **1962**, *84*, 305–306.
[12]Coppola, G. M. *Synthesis* **1984**, 1021–1023.
[13]Fuenfschilling, P. C.; Zaugg, W.; Beutler, U.; Kaufmann, D.; Lohse, O.; Mutz, J.-P.; Onken, U.; Reber, J.-L.; Shenton, D. *Org. Process Res. Dev.* **2005**, *9*, 272–277.



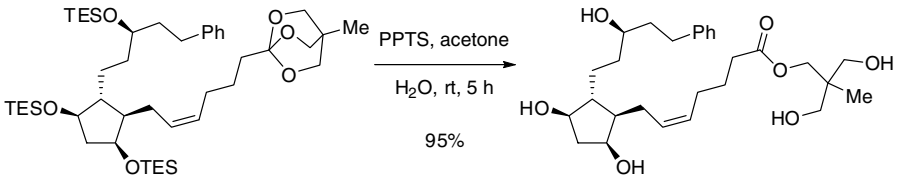
Dithioketene acetals may be hydrolyzed to thioesters under very mild conditions. Note that the strongly acidic reaction conditions employed in the example below resulted in concomitant β-dehydration and loss of the acid labile *N*-trityl protecting group.[9]



Orthoesters may also be hydrolyzed through treatment with aqueous acid, as exemplified in the scheme below.[14] Methanol is often included as a nucleophilic cosolvent that participates in the hydrolysis.



Under mildly acidic conditions, a terminal orthoester will provide the carboxylic acid ester.[15] However, prolonged exposure to aqueous acid will yield the carboxylic acid.

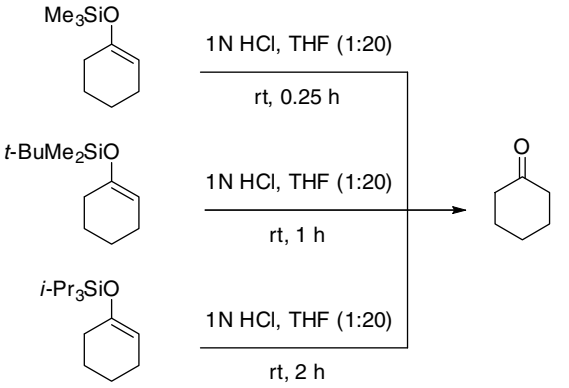


1.2.1.7 Hydrolysis of Silyl Enol Ethers Silyl enol ethers are prone to hydrolysis at a rate generally consistent with their relative steric bulk. Trimethylsilyl (TMS) enol ethers are particularly labile, and may by hydrolyzed in the absence of an acid catalyst in some

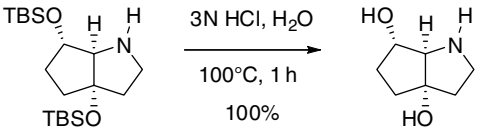
[14]Kato, K.; Nouchi, H.; Ishikura, K.; Takaishi, S.; Motodate, S.; Tanaka, H.; Okudaira, K.; Mochida, T.; Nishigaki, R.; Shigenobu, K.; Akita, H. *Tetrahedron* **2006**, *62*, 2545–2554.

[15]Martynow, J. G.; Jozwik, J.; Szelejewski, W.; Achmatowicz, O.; Kutner, A.; Wisniewski, K.; Winiarski, J.; Zegrocka-Stendel, O.; Golebiewski, P. *Eur. J. Org. Chem.* **2007**, 689–703.

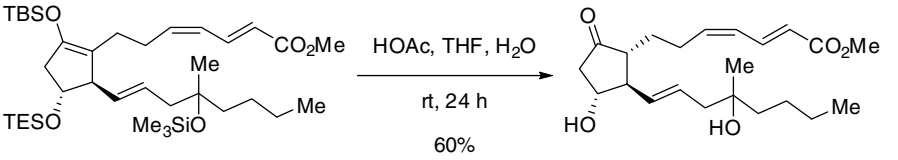
instances.[16] In contrast, bulky triisopropylsilyl (TIPS) enol ethers are generally stable enough to withstand an acidic aqueous workup and may even be purified via silica gel chromatography. In the scheme below, the TMS, *tert*-butyl dimethylsilyl (TBS) and TIPS enol ethers of cyclohexanone are desilylated by treatment with aqueous hydrochloric acid in tetrahydrofuran. The variation in reaction rate under these conditions is noteworthy.[17]



1.2.1.8 Hydrolysis of Silyl Ethers Silyl ethers are generally less susceptible to acid-catalyzed hydrolysis than their enol ether counterparts. However, increasing the reaction time, reaction temperature or acid concentration can provide a simple, high-yielding method for the removal of silicon-based hydroxyl protecting groups, provided that the rest of the molecule is stable to such treatment.[18]



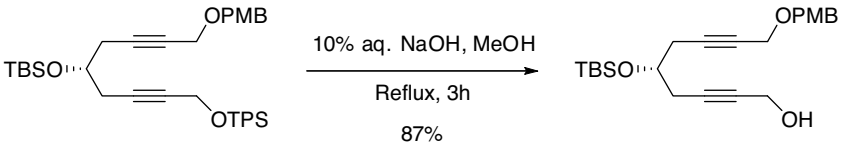
In the example below, the removal of two silyl ethers and one silyl enol ether was accomplished with aqueous acetic acid in THF at room temperature.[19] These milder conditions necessitated a longer reaction time, but conserved the acid sensitive methyl ester and tertiary alcohol functional groups.



[16]Keana, J. F. W.; Eckler, P. E. *J. Org. Chem.* **1976**, *41*, 2850–2854.
[17]Manis, P. A.; Rathke, M. W. *J. Org. Chem.* **1981**, *46*, 5348–5351.
[18]Sun, H.; Abboud, K. A.; Horenstein, N. A. *Tetrahedron* **2005**, *61*, 10462–10469.
[19]Collins, P. W.; Gasiecki, A. F.; Jones, P. H.; Bauer, R. F.; Gullikson, G. W.; Woods, E. M.; Bianchi, R. G. *J. Med. Chem.* **1986**, *29*, 1195–1201.

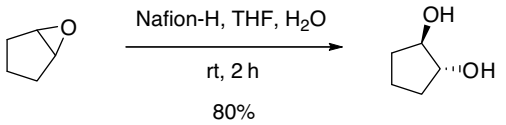
For acid-sensitive substrates, the use of fluoride ion (e.g., tetra-*n*-butylammonium fluoride, TBAF) provides an attractive alternative (see Section 1.5.1.7) and is increasingly employed as a first choice reagent.

Silyl ethers may be cleaved under aqueous alkaline conditions when the silicon center is less electron-rich. For example, *tert*-butyl diphenylsilyl (TBDPS or TPS) ethers are susceptible to base-promoted cleavage, despite their relative stability to acid. This reactivity is complementary to that of TBS ethers, allowing for selective silyl protection of similar functional groups.[20]



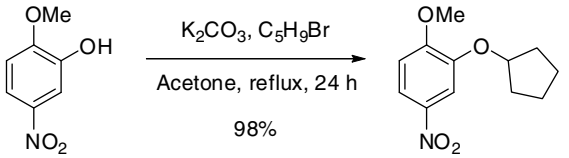
Silyl ethers may also be cleaved by nucleophilic alcohols in the presence of strong acid catalysts (see Section 1.2.2.6).

1.2.1.9 Hydrolysis of Epoxides Epoxides can be efficiently ring-opened under acid catalysis in an aqueous environment to afford 1,2-diol products. In cases where the regiochemistry of attack by water is inconsequential, or is directed by steric and/or electronic bias within the substrate, simple Brønsted acid catalysts are utilized. In the example below, hydrolysis is promoted by the sulfonated tetrafluoroethylene copolymer Nafion-H to provide the racemic 1,2-*anti*-diol product via backside attack on the epoxide.[21]



1.2.2 Reactions with Alcohols

1.2.2.1 Preparation of Ethers from Alkyl Halides The preparation of ethers from alcohols may be accomplished via treatment with an alkyl halide in the presence of a suitable base (the Williamson ether synthesis). For relatively acidic alcohols such as phenol derivatives, the use of potassium carbonate in acetone is a simple, low cost option.[22]



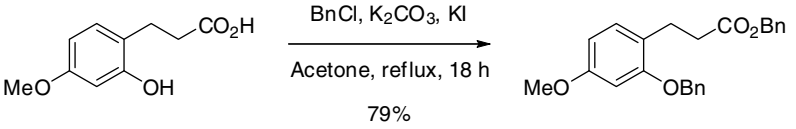
The rate of ether formation can be accelerated by increasing the reaction temperature, or more commonly by employing a more reactive alkyl halide. This is accomplished in the

[20]Hatakeyama, S.; Irie, H.; Shintani, T.; Noguchi, Y.; Yamada, H.; Nishizawa, M. *Tetrahedron* **1994**, *50*, 13369–13376.

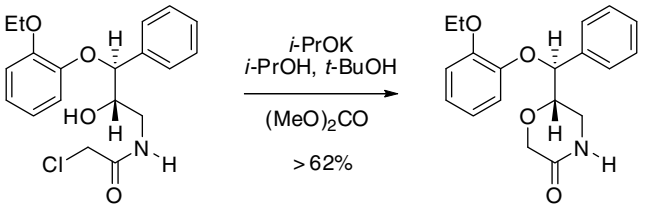
[21]Olah, G. A.; Fung, A. P.; Meidar, D. *Synthesis* **1981**, 280–282.

[22]Garcia, A. L. L.; Carpes, M. J. S.; de Oca, A. C. B. M.; dos Santos, M. A. G.; Santana, C. C.; Correia, C. R. D. *J. Org. Chem.* **2005**, *70*, 1050–1053.

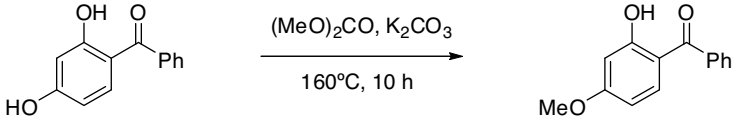
example below via conversion of benzyl chloride to benzyl iodide *in situ* by including potassium iodide in the reaction mixture (Finkelstein reaction; see Section 1.5.1.1).[23] Since the iodide ions are regenerated over the course of the reaction, a sub-stoichiometric quantity can often be used. However, a stoichiometric excess of iodide increases the concentration of the more reactive alkylating agent, and thus improves the kinetics of the alkylation reaction. Note that under the conditions utilized, the carboxylic acid is also converted to the corresponding benzyl ester. For more on the preparation of esters from carboxylic acids see Sections 1.2.3 and 2.29.



Henegar and coworkers reported the use of potassium isopropoxide in dimethyl carbonate for the large scale preparation of an ether intermediate in the synthesis of the commercial antidepressant (±)-reboxetine mesylate.[24]

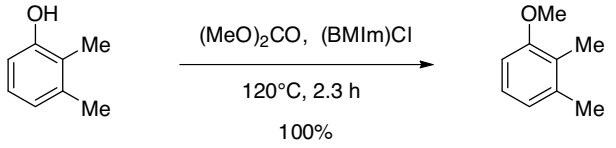


1.2.2.2 Preparation of Methyl Ethers from Dimethyl Carbonate or Dimethyl Sulfate Dimethyl carbonate is an ambident electrophile that typically reacts with soft nucleophiles at a methyl carbon and with hard nucleophiles at the central carbonyl. Via the former mechanism, dimethyl carbonate has been used for the methylation of phenols, leading to the formation of arylmethyl ethers. This is an especially attractive reagent for large scale applications, owing to the low cost, low toxicity and neglegible environmental impact of dimethyl carbonate,[25] however scope is limited due to the modest reactivity of the reagent. In the example below, Thiébaud and coworkers illustrate the selective methylation of a bis-phenol compound with dimethyl carbonate and potassium carbonate in the absence of solvent.[26]

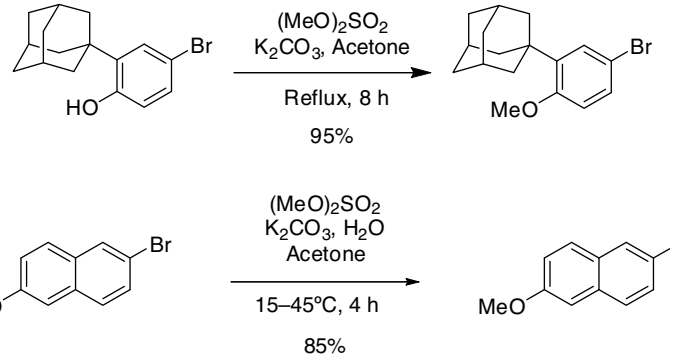


[23]Bourke, D. G.; Collins, D. J. *Tetrahedron* **1997**, *53*, 3863–3878.
[24]Henegar, K. E.; Ball, C. T.; Horvath, C. M.; Maisto, K. D.; Mancini, S. E. *Org. Process Res. Dev.* **2007**, *11*, 346–353.
[25]Tundo, P.; Rossi, L.; Loris, A. *J. Org. Chem.* **2005**, *70*, 2219–2224.
[26]Ouk, S.; Thiebaud, S.; Borredon, E.; Le Gars, P. *Green Chem.* **2002**, *4*, 431–435.

Shen and coworkers discussed the "greenness" of their protocol for the preparation of arylmethyl ethers from their phenol precursors.[27] Thus, treatment of various phenols with dimethyl carbonate at 120°C in the recyclable ionic liquid 1-*n*-butyl-3-methylimidazolium-chloride [(BMIm)Cl] provides quantitative yields of aryl methyl ethers. The use of ionic liquids has been heavily debated in recent years, as these materials are relatively expensive and current methods for their manufacture pose a significant environmental impact. Nevertheless, opportunities for reuse and recycle make continued development in this area a worthwhile venture.



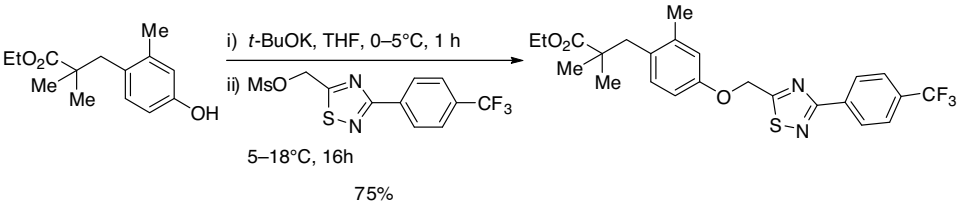
The preferred method for the preparation of methyl ethers via alkylation of alcohol precursors generally utilizes dimethyl sulfate $(MeO)_2SO_2$, rather than methyl iodide, due to the decreased worker-exposure risk that accompanies its lower volatility. Typically, the alcohol is treated with dimethyl sulfate and a suitable base in a polar aprotic solvent. Yields are generally high and product isolation relatively straightforward. The examples below are illustrative, and were both carried out on a large scale.[28,29] It should be noted that most alkylating agents—dimethylsulfate included—pose serious toxicological hazards and thus require cautious handling and environmental controls.



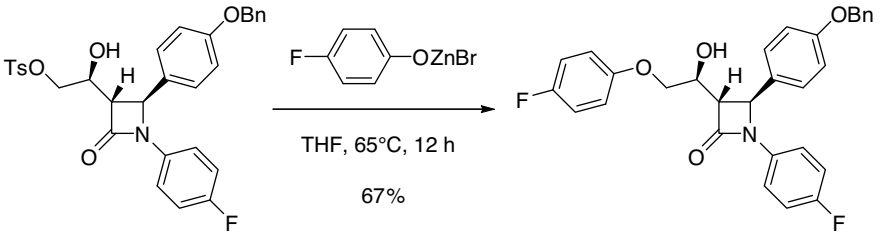
1.2.2.3 Preparation of Ethers from Alkyl Sulfonates A widespread and practical strategy for the synthesis of ethers, especially on large scale, is through the intermediacy of alkyl sulfonates. Broad access to alcohol precursors, coupled with the low cost and high efficiency in converting these alcohols to electrophilic sulfonates has contributed to the popularity of this method. Mesylates or tosylates are used most often, as MsCl and TsCl are considerably less expensive than other sulfonyl halides. However, for demanding nucleophilic substitution reactions, the 4-bromobenzenesulfonate (brosylate) or 4-nitrobenzenesulfonate

[27]Shen, Z. L.; Jiang, X. Z.; Mo, W. M.; Hu, B. X.; Sun, N. *Green Chem.* **2005**, *7*, 97–99.
[28]Liu, Z.; Xiang, J. *Org. Process Res. Dev.* **2006**, *10*, 285–288.
[29]Prabhakar, C.; Reddy, G. B.; Reddy, C. M.; Nageshwar, D.; Devi, A. S.; Babu, J. M.; Vyas, K.; Sarma, M. R.; Reddy, G. O. *Org. Process Res. Dev.* **1999**, *3*, 121–125.

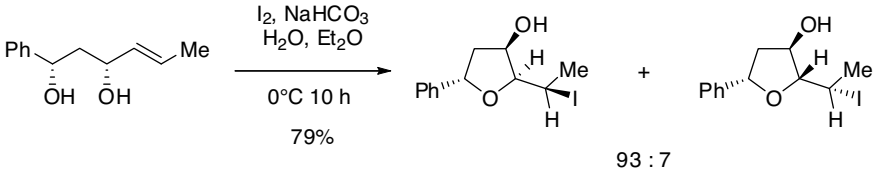
(nosylate, ONs) offer increased reactivity. In the following example, a substituted phenol was alkylated with a primary mesylate in good yield under representative conditions.[30]



In a second example, alkylation was shown to proceed through an epoxide intermediate formed via intramolecular displacement of the tosylate by the adjacent hydroxyl. The zinc alkoxide was superior to the lithium derivative in terms of yield and reaction rate.[31]

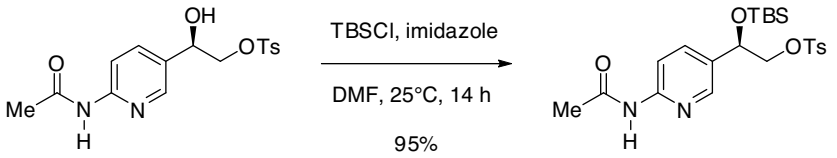


1.2.2.4 Iodoetherification Treatment of olefins with iodine provides an electrophilic iodonium species that can be trapped with oxygen nucleophiles to provide ethers. A base is included to quench the HI that gets generated during the reaction. The intramolecular nucleophilic displacement occurs at a much higher rate than intermolecular trapping, so cyclic ethers are formed in high yield. In the example below, two additional stereocenters are created with high selectivity through treatment of an unsaturated *cis*-1,3-diol with iodine and sodium bicarbonate in aqueous ether at 0°C.[32]

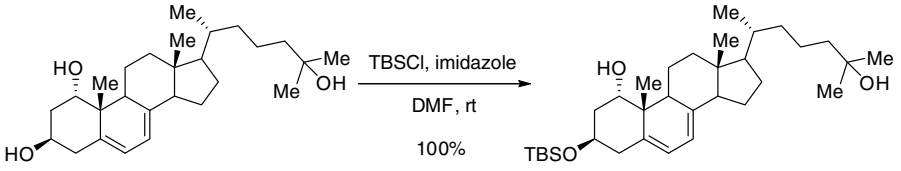


1.2.2.5 Preparation of Silyl Ethers Despite the relatively high molar expense of substituted silicon compounds such as TBSCl, silyl ethers are often utilized as alcohol-protecting groups in synthesis because of their excellent compatibility with a broad range of common processing conditions, coupled with their relative ease of removal. Vanderplas and coworkers prepared the TBS ether below in high yield as part of a multi-kilogram synthesis of a β-3 adrenergic receptor agonist.[33] The preferred conditions for TBS protection of this secondary alcohol included imidazole base in dimethylformamide.

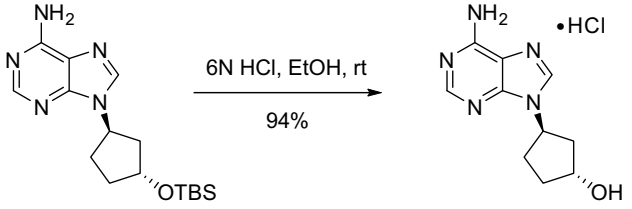
[30]Reuman, M.; Hu, Z.; Kuo, G.-H.; Li, X.; Russell, R. K.; Shen, L.; Youells, S.; Zhang, Y. *Org. Process Res. Dev.* **2007**, *11*, 1010–1014.
[31]Wu, G. G. *Org. Process Res. Dev.* **2000**, *4*, 298–300.
[32]Tamaru, Y.; Hojo, M.; Kawamura, S.; Sawada, S.; Yoshida, Z. *J. Org. Chem.* **1987**, *52*, 4062–4072.
[33]Vanderplas, B. C.; DeVries, K. M.; Fox, D. E.; Raggon, J. W.; Snyder, M. W.; Urban, F. *J. Org. Process Res. Dev.* **2004**, *8*, 583–586.



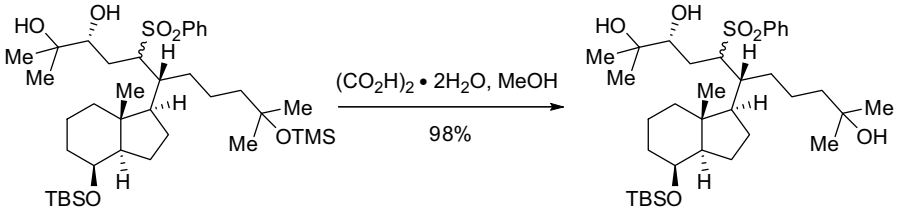
The example below highlights the strong steric bias of TBSCl toward reaction with the unhindered secondary alcohol over the more hindered secondary and tertiary alcohols.[34]



1.2.2.6 Cleavage of Silyl Ethers with Alcohols Although the most common methods utilize fluoride ion (see Section 1.5.1.7), silyl ethers can be cleaved with alcohols promoted by strong acids. Watson and coworkers reported a high-yielding example of the use of ethanolic hydrogen chloride in their large scale synthesis of the tumor necrosis factor-α inhibitor candidate MDL 201449A.[35]



Selective cleavage of a TMS ether in the presence of the more sterically encumbered TBS derivative has been accomplished via treatment with a methanolic solution of oxalic acid dihydrate.[36]



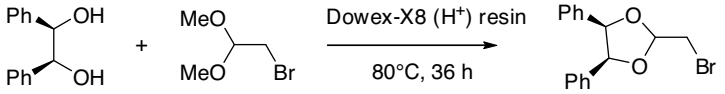
[34]Van Arnum, S. D.; Carpenter, B. K.; Moffet, H.; Parrish, D. R.; MacIntrye, A.; Cleary, T. P.; Fritch, P. *Org. Process Res. Dev.* **2005**, *9*, 306–310.

[35]Watson, T. J. N.; Curran, T. T.; Hay, D. A.; Shah, R. S.; Wenstrup, D. L.; Webster, M. E. *Org. Process Res. Dev.* **1998**, *2*, 357–365.

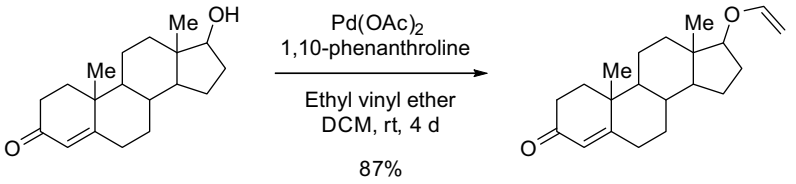
[36]Maehr, H.; Uskokovic, M. R.; Adorini, L.; Reddy, G. S. *J. Med. Chem.* **2004**, *47*, 6476–6484.

1.2.2.7 Transetherification The direct interconversion of ethers is not typically a practical transformation, and is thus rarely employed. The reaction can be accomplished, however, by treating the starting ether with an alcohol under the promotion of a strong mineral acid. The interconversion is an equilibrium process, so the alcohol is typically used as a cosolvent or in significant molar excess. A thorough study of the thermodynamics of interconversion of electronically diverse 1-phenylethyl ethers with aliphatic alcohols was reported by Jencks and coworkers.[37]

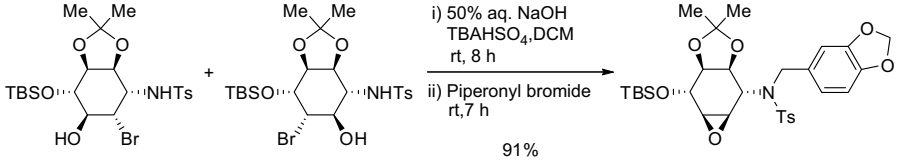
The following example from Pittman and coworkers highlights the efficiency of acetal exchange under Brønsted acid catalysis.[38] This reaction is formally a double transetherification, although it has the advantage of proceeding via an intermediate oxonium ion. In this instance, the reaction is rendered irreversible by running at a temperature where the liberated methanol is removed by distillation.



A wide variety of vinyl ethers can be prepared from ethyl vinyl ether via palladium-catalyzed transetherification, as exemplified below.[39] Additional substitution on the olefin, however, severely diminishes the efficiency of the transformation and limits scope. This reaction is not a nucleophilic aliphatic substitution, but is included here to illustrate this complementary, albeit limited methodology.

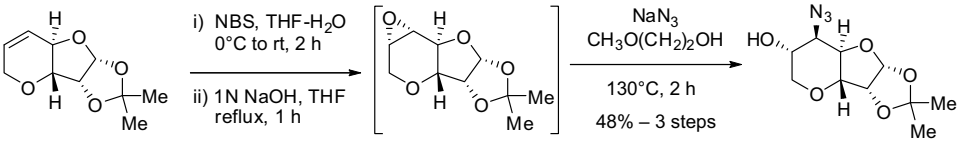


1.2.2.8 Preparation of Epoxides Epoxides can be prepared in high yield through intramolecular nucleophilic displacement of halides by vicinal hydroxyls. In the example below, concentrated aqueous sodium hydroxide is used as the base in dichloromethane.[40] This solvent choice, when used in combination with highly concentrated NaOH solution, minimizes water content within the organic phase to prevent competitive epoxide hydrolysis to the corresponding 1,2-diol. The addition of a phase transfer catalyst, as well as aggressive agitation, facilitates movement of hydroxide ions into the dichloromethane.

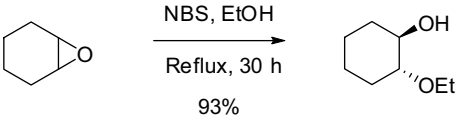


[37]Rothenberg, M. E.; Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1985**, *107*, 1340–1346.
[38]Zhu, P. C.; Lin, J.; Pittman, C. U., Jr., *J. Org. Chem.* **1995**, *60*, 5729–5731.
[39]Weintraub, P. M.; King, C.-H. R. *J. Org. Chem.* **1997**, *62*, 1560–1562.
[40]Elango, S.; Yan, T.-H. *Tetrahedron* **2002**, *58*, 7335–7338.

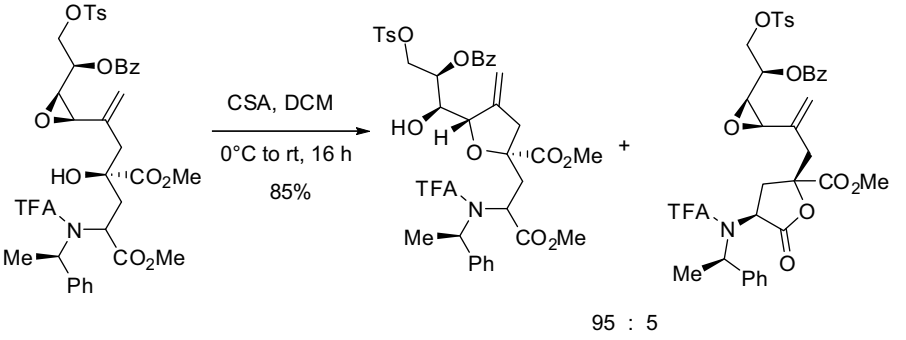
Epoxides are often prepared from olefin precursors by sequential reaction with *N*-bromosuccinimide (NBS) and hydroxide in an aqueous environment. The NBS initially forms an electrophilic bromonium species, which is quickly converted to a bromohydrin via nucleophilic attack by water. As described in the following example, the bromohydrin can be converted to an epoxide in the same reaction vessel by addition of sodium hydroxide.[41] In this instance, the epoxide was not purified, but was further reacted to the azidohydrin by reaction with sodium azide at an elevated temperature. The opening of epoxides with nitrogen nucleophiles is also discussed in Section 1.4.1.6. More on the preparation of epoxides from carbon-carbon double bonds can be found in Section 3.10.4.



1.2.2.9 Reaction of Alcohols with Epoxides Epoxides can be opened with nucleophilic alcohols in the presence of various activating agents. Despite a low degree of atom economy, *N*-bromosuccinimide (NBS) proved to be a very effective promoter in the example below.[42] A catalytic quantity of an acid catalyst is often sufficient, however.

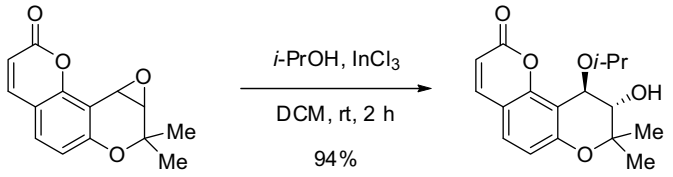


In the example below from Loh and coworkers, a late stage intramolecular epoxide opening by an alcohol is catalyzed by camphorsulfonic acid in dichloromethane to provide the desired furan as a single diastereomer in good yield.[43] The γ-lactone resulting from intramolecular transesterification was observed as a minor byproduct.

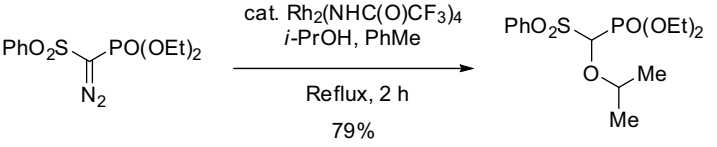


[41]Loiseleur, O.; Schneider, H.; Huang, G.; Machaalani, R.; Selles, P.; Crowley, P.; Hanessian, S. *Org. Process Res. Dev.* **2006**, *10*, 518–524.
[42]Iranpoor, N.; Firouzabadi, H.; Chitsazi, M.; Ali Jafari, A. *Tetrahedron* **2002**, *58*, 7037–7042.
[43]Huang, J.-M.; Xu, K.-C.; Loh, T.-P. *Synthesis* **2003**, 755–764.

The specific case involving interconversion of two α,β-epoxy alcohols under basic conditions is known as the Payne rearrangement,[44] and is discussed in Section 7.2.2.3. The intermolecular ring-opening of epoxides by alcohol nucleophiles may be catalyzed by Lewis acids. The use of indium(III) chloride has proven to be particularly effective, as exemplified by Lee and coworkers in the following example.[45] Here, both sterics (geminal methyls) and electronics (positive charge stabilization) direct the isopropanol nucleophile to the benzylic position.



1.2.2.10 The Reaction of Alcohols with Diazo Compounds In a series of publications, Moody and coworkers have demonstrated the utility of Rh(II)-catalyzed decomposition of α-diazo esters, sulfones, and phosphonates in the presence of various aliphatic and aromatic alcohols.[46,47] The intramolecular variant of this method has found utility in the synthesis of functionalized cyclic ethers. Widespread application of the intermolecular reaction, however, has been hindered by the need for a large stoichiometric excess of the alcohol component to limit competitive hydrogen abstraction that leads to reduced product.

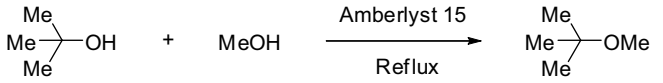


This example highlights the superiority of the Rh(II) trifluoroacetamide catalyst, as the more commonly employed $Rh_2(OAc)_4$ afforded desired O-H insertion product in an inferior yield of 67% after 72 hours at reflux. Interestingly, photochemical decomposition of this diazo compound in isopropanol provided the product of hydrogen abstraction (i.e., reduction) exclusively in 90% yield. Complementary oxidative methods for the synthesis of related compounds are discussed in Section 10.3.4.

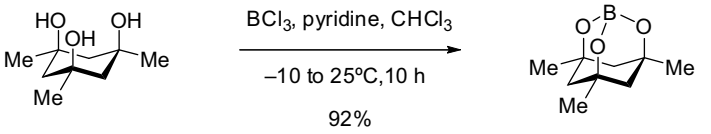
1.2.2.11 Preparation of Ethers via Dehydration of Alcohols The direct formation of ethers from alcohol precursors is typically limited to the preparation of symmetrical ethers, as dehydration under the strongly acidic conditions employed generally occurs indiscriminately. In the example below, Ziyang and coworkers optimized a method for the production of solvent and one-time fuel additive methyl *tert*-butyl ether. In this

[44]Payne, G. B. *J. Org. Chem.* **1962**, *27*, 3819–3822.
[45]Lee, Y. R.; Lee, W. K.; Noh, S. K.; Lyoo, W. S. *Synthesis* **2006**, 853–859.
[46]Moody, C. J.; Taylor, R. J. *J. Chem. Soc., Perkin Trans.* **1989**, *1*, 721–731.
[47]Cox, G. G.; Miller, D. J.; Moody, C. J.; Sie, E. R. H. B.; Kulagowski, J. J. *Tetrahedron* **1994**, *50*, 3195–3212.

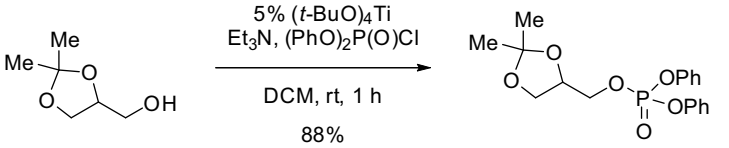
method, a heated stream of *tert*-butanol and methanol are passed through a column packed with the strongly acidic resin Amberlyst 15.[48]



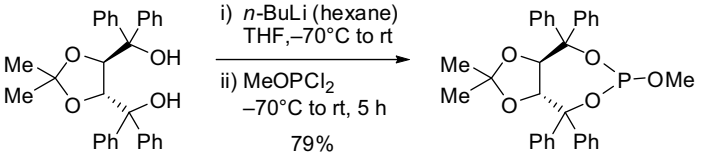
1.2.2.12 Addition of Alcohols to Boron, Phosphorous, and Titanium Borate esters can be prepared by direct reaction of alcohols with boron halides in the presence of a suitable base. In the following example, a 1,3,5-triol is reacted with boron trichloride and pyridine to yield a novel "tripod borate ester" in high yield. This compound is of particular interest due to the considerable distortion from planar geometry generally observed in borate esters.[49]



Phosphonate esters can be prepared in high yield by reaction of alcohols with diaryl halophosphates catalyzed by inorganic esters. As shown below, titanium(IV) *t*-butoxide was reported by Jones and coworkers to be the optimal catalyst.[50]



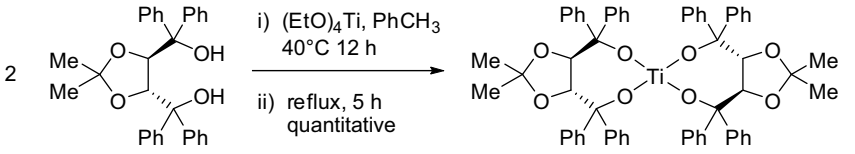
Phosphites and phosphonites are more commonly prepared by reaction of a metal alkoxide with a chlorophosphine derivative, as highlighted in the following example.[51] These reactions are exothermic, so cooling is generally required. Furthermore, most phosphites and phosphonites are air and moisture sensitive, so care must be taken to avoid degradation.



Due to the high oxophilicity of titanium(IV), titanates can be prepared through a process similar to the equilibrium driven ligand exchange observed with organometallic complexes. For example, heating titanium(IV) ethoxide in the presence of the TADDOL ligand shown

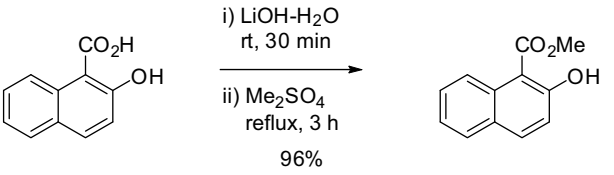
[48]Ziyang, Z.; Hidajat, K.; Ray, A. K. *J. Catal.* **2001**, *200*, 209–221.
[49]D'Accolti, L.; Fiorentino, M.; Fusco, C.; Capitelli, F.; Curci, R. *Tetrahedron Lett.* **2007**, *48*, 3575–3578.
[50]Jones, S.; Selitsianos, D.; Thompson, K. J.; Toms, S. M. *J. Org. Chem.* **2003**, *68*, 5211–5216.
[51]Seebach, D.; Hayakawa, M.; Sakaki, J.; Schweizer, W. B. *Tetrahedron* **1993**, *49*, 1711–1724.

below initially provides an equilibrium mixture of titanium alkoxides. Complete exchange can be achieved by removal of ethanol by distillation.[52]

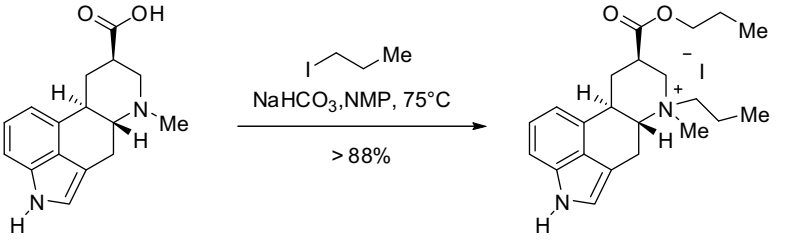


1.2.3 Reactions with Carboxylates

1.2.3.1 Alkylation of Carboxylic Acid Salts Carboxylic acids can serve as effective nucleophiles toward a variety of electrophilic reagents if first converted to their carboxylate salts via deprotonation with a suitable base. The relatively low pKa of carboxylic acids allows very mild bases to be employed. A reliable, scalable method for the preparation of methyl esters involves preparation of the lithium carboxylate with LiOH, followed by treatment with dimethyl sulfate, as exemplified below.[53] Note that methylation of the phenolic alcohol was avoided in this example through careful control of stoichiometry. Dimethyl sulfate may be replaced by iodomethane for most applications, however this is less preferred due to the increased volatility of the latter reagent (bp 42.4°C).



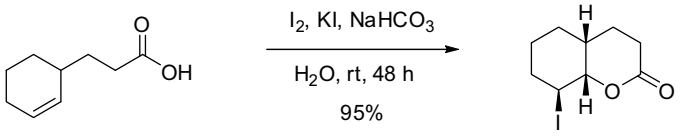
The most common method for the synthesis of esters from acids utilizes alkyl halides, owing to the relatively easy access to these electrophiles. Cabri and coworkers demonstrated a high-yielding *n*-propyl ester preparation via sodium carboxylate, which was obtained by treatment with $NaHCO_3$ in NMP.[54] Note that a tertiary amine was also quaternized under these conditions. For more on the alkylation of amines with alkyl halides, see Section 1.4.1.1.



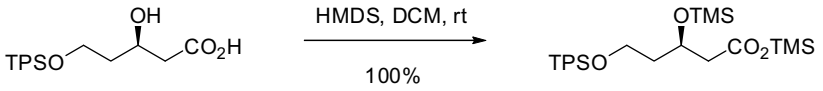
[52]Von dem Bussche-Huennefeld, J. L.; Seebach, D. *Tetrahedron* **1992**, *48*, 5719–5730.
[53]Chakraborti, A. K.; Nandi, A. B.; Grover, V. *J. Org. Chem.* **1999**, *64*, 8014–8017.
[54]Cabri, W.; Roletto, J.; Olmo, S.; Fonte, P.; Ghetti, P.; Songia, S.; Mapelli, E.; Alpegiani, M.; Paissoni, P. *Org. Process Res. Dev.* **2006**, *10*, 198–202.

This approach to the conversion of carboxylic acids to esters is complementary to the Fischer esterification, whereby the carboxylic acid is heated in an alcohol solvent in the presence of a strong acid with concomitant generation of water (see Section 2.29.1).

1.2.3.2 Iodolactonization Iodolactonization is a useful and practical method for the stereocontrolled preparation of lactones. In the example below from House and coworkers, the action of iodine upon the olefin provides an electrophilic intermediate iodonium ion. This highly reactive species is trapped in a stereospecific manner by the carboxylate nucleophile to provide a 1,2-anti relationship between the iodide and oxygen-bearing stereocenters.[55]

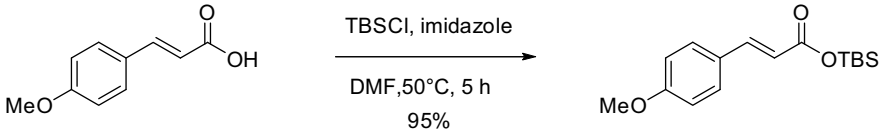


1.2.3.3 Preparation of Silyl Esters The use of silyl esters as carboxylic acid protecting groups is an increasingly popular methodology due to the simplicity of preparation and relative ease of removal during workup. An attractive large scale method for trimethylsilyl ester preparation utilizes hexamethyldisilazane (HMDS) as both a base and TMS donor.[56] This method also proved effective in forming a silyl ether from the secondary alcohol precursor. For more on the formation of silyl ethers, see Section 1.2.2.5.



TPS = *tert*-butyl diphenylsilyl

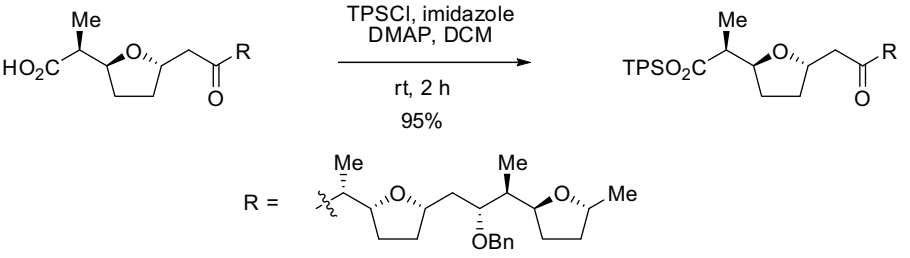
The HMDS method described above is clearly advantageous if a TMS ester is desired. Unfortunately, the corresponding TES, TBS, or TIPS analogs are inaccessible with this methodology. As a result, silyl esters are more generally prepared by treatment of carboxylate salts with silyl chlorides or triflates. In the example below, *p*-methoxy cinnamic acid is converted to its TBS ester in high yield via treatment with *tert*-butyl dimethysilyl chloride and imidazole in DMF.[57]



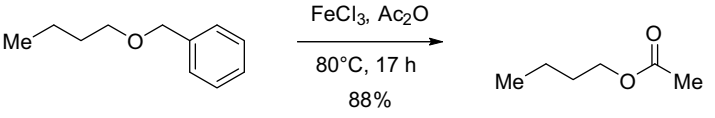
The solvent employed for this reaction is often determined by the solubility of the intermediate carboxylate salt. Dichloromethane[58] and tetrahydrofuran[59] have proven successful in many cases. Triethylamine is commonly used as a base in place of imidazole,

[55]House, H. O.; Carlson, R. G.; Babad, H. *J. Org. Chem.* **1963**, *28*, 3359–3361.
[56]Smith, A. B.; Safonov, I. G.; Corbett, R. M. *J. Am. Chem. Soc.* **2002**, *124*, 11102–11113.
[57]Ponticello, G. S.; Freedman, M. B.; Habecker, C. N.; Holloway, M. K.; Amato, J. S.; Conn, R. S.; Baldwin, J. J. *J. Org. Chem.* **1988**, *53*, 9–13.
[58]Fache, F.; Suzan, N.; Piva, O. *Tetrahedron* **2005**, *61*, 5261–5266.
[59]McNamara, L. M. A.; Andrews, M. J. I.; Mitzel, F.; Siligardi, G.; Tabor, A. B. *J. Org. Chem.* **2001**, *66*, 4585–4594.

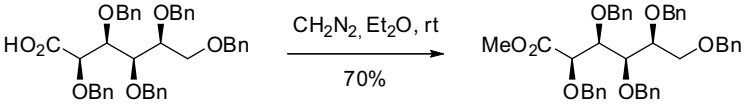
and 4-dimethylaminopyridine (DMAP) may be added as a nucleophilic catalyst to activate the silyl electrophile in case of a sluggish reaction. In the example below, a *tert*-butyldiphenylsilyl (TPS) ester was prepared in high yield.[60]



1.2.3.4 Cleavage of Ethers with Acetic Anhydride The cleavage of ethers with acetic anhydride in the presence of ferric chloride was first reported by Knoevenagel in 1914 for the conversion of diethyl ether to ethyl acetate.[61] Ganem and coworkers followed years later with mechanistic studies and an examination of substrate scope for the method.[62] In the example below, benzyl-*n*-butyl ether is converted to *n*-butyl acetate in high yield after several hours at 80°C. The benzyl acetate byproduct was not quantified.



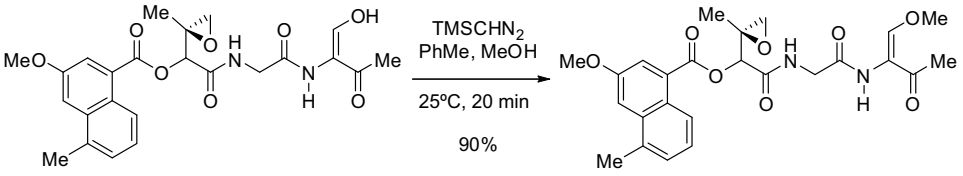
1.2.3.5 Alkylation of Carboxylic Acids and Enols with Diazo Compounds One of the most efficient methods for the preparation of methyl esters from carboxylic acids involves reaction with a solution of diazomethane in ether.[63] Esterification is generally rapid and highly chemoselective. Therefore, products can typically be isolated by simple evaporation of the volatile ether solvent. This method is not typically applied on large scale due to the serious hazards associated with the preparation and handling of diazomethane. However, with specialized equipment and proper engineering controls in place, methyl ester formation via treatment with diazomethane is sometimes the method of choice, as exemplified by the example below.[64] These conditions are also effective for the methylation of sulfonic acids, as described in Section 1.2.1.4.



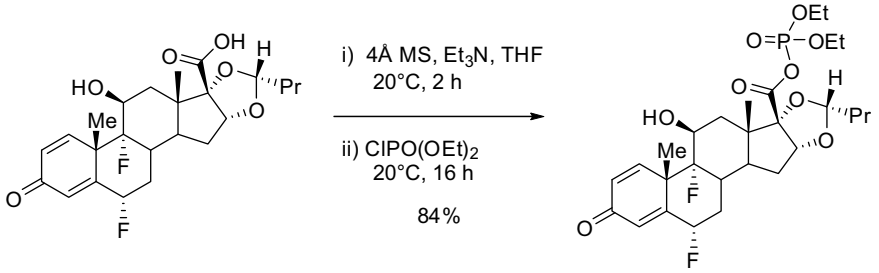
A safer, more practical alternative to the use of toxic and volatile diazomethane is provided by the commercially available reagent trimethylsilyl diazomethane. In the example

[60]Kim, W. H.; Hong, S. K.; Lim, S. M.; Ju, M.-A.; Jung, S. K.; Kim, Y. W.; Jung, J. H.; Kwon, M. S.; Lee, E. *Tetrahedron* **2007**, *63*, 9784–9801.
[61]Knoevenagel, E. *Justus Liebigs Ann. Chem.* **1914**, *402*, 111–148.
[62]Ganem, B.; Small, V. R., Jr., *J. Org. Chem.* **1974**, *39*, 3728–3730.
[63]Arndt, F. *Org. Synth.* **1935**, *15*, 3–5.
[64]Schmidt, R. R.; Frick, W. *Tetrahedron* **1988**, *44*, 7163–7169.

below, the enol form of a β-ketoaldehyde is converted to its methyl enol ether derivative in high yield and with excellent regioselectivity.[65] A discussion of the mechanism of this interesting transformation has been published.[66] For more on nucleophilic substitution reactions of enols and carbonyls, see Section 1.2.4.



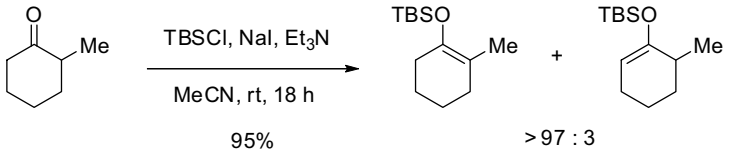
1.2.3.6 Preparation of Mixed Organic-Inorganic Anhydrides The reaction of carboxylic acid salts with phosphonic acid halides can provide the corresponding carboxylic acid-phosphonic acid mixed anhydrides in good yield. In the example below, a diethylphosphonate ester was prepared from a triethylammonium carboxylate under very mild conditions.[67]



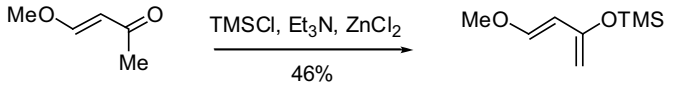
1.2.4 Reactions with Other Oxygen Nucleophiles

1.2.4.1 Formation of Silyl Enol Ethers and Silyl Ketene Acetals The formation of silyl enol ethers has been a topic of considerable study, due to the broad utility of these compounds in carbon−carbon bond forming reactions. Silyl enol ethers are typically prepared by treatment of an enolizable carbonyl compound with a silyl halide or triflate in the presence of a suitable base. For unsymmetrical ketones, such as 2-methylcyclohexanone (shown below), regioisomeric enol ether products are possible, and methods for the selective preparation of both the kinetically favored and thermodynamically favored isomers have been developed.[68,69] Treatment of ketones with a silyl chloride in the presence of a weak nitrogen base such as triethylamine provides the thermodynamically favored silyl enol ether (more substituted olefin) at or near room temperature in excellent yield.[70]

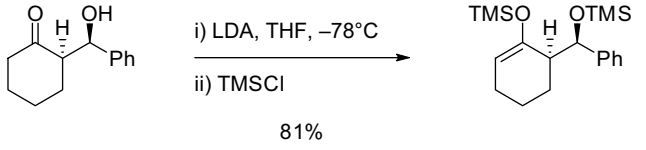
[65]Coleman, R. S.; Tierney, M. T.; Cortright, S. B.; Carper, D. J. *J. Org. Chem.* **2007**, *72*, 7726–7735.
[66]Kuehnel, E.; Laffan, D. D. P.; Lloyd-Jones, G. C.; Martinez del Campo, T.; Shepperson, I. R.; Slaughter, J. L. *Angew. Chem., Int. Ed. Engl.* **2007**, *46*, 7075–7078.
[67]Procopiou, P. A.; Biggadike, K.; English, A. F.; Farrell, R. M.; Hagger, G. N.; Hancock, A. P.; Haase, M. V.; Irving, W. R.; Sareen, M.; Snowden, M. A.; Solanke, Y. E.; Tralau-Stewart, C. J.; Walton, S. E.; Wood, J. A. *J. Med. Chem.* **2001**, *44*, 602–612.
[68]D'Angelo, J. *Tetrahedron* **1976**, *32*, 2979–2990.
[69]Heathcock, C. H. *Modern Synthetic Methods* **1992**, *6*, 1–102.
[70]Takasu, K.; Ishii, T.; Inanaga, K.; Ihara, M. *Org. Synth.* **2006**, *83*, 193–199.



The use of anhydrous zinc dichloride is key to formation of Danishefsky's diene.[71] The zinc additive plays a dual role of Lewis acid and dehydrative agent in this enol ether formation. The use of freshly fused $ZnCl_2$ is preferred and ensures a more robust outcome.



In contrast to the conditions described above, enolization with a strong, bulky base at low temperature favors removal of the most sterically accessible α-proton to provide the kinetically favored enol ether upon silylation (less substituted olefin).[72] In the following example, the dianion of a β-hydroxy ketone was formed with 2.2 equivalents of LDA at −78°C. Silylation occurred with complete selectivity for the enol ether shown.

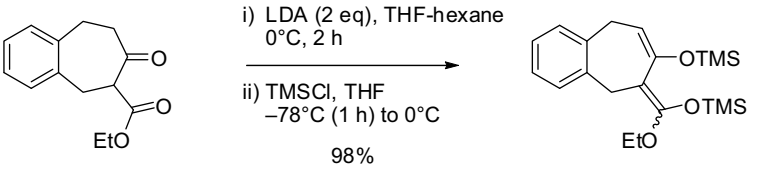


In the following example from Aventis, a trimethylsilyl enol ether was prepared in good yield despite the presence of a rather labile epoxide. Slow addition of the starting ketone into a cold solution of LDA and a careful isolation protocol proved to be important.[73]

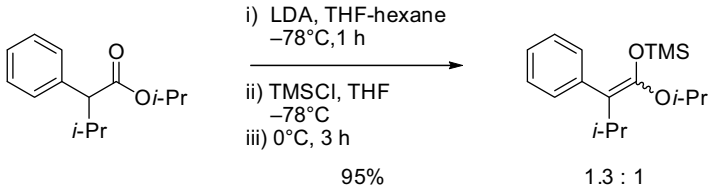


As exemplified by Albrecht and coworkers, treatment of a β-ketoester with two equivalents of LDA yields a dienolate intermediate. Quenching the dienolate with two molar equivalents of chlorotrimethylsilane provides the silyl enol ether as well as a silyl ketene acetal in excellent yield.[74]

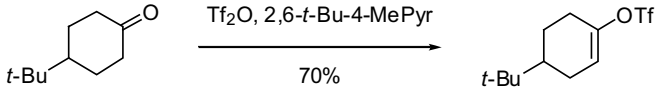
[71]Danishefsky, S.; Kitahara, T.; Schuda, P. F. *Org. Synth.* **1983**, *61*, 147–151.
[72]Martin, V. A.; Albizati, K. F. *J. Org. Chem.* **1988**, *53*, 5986–5988.
[73]Larkin, J. P.; Wehrey, C.; Boffelli, P.; Lagraulet, H.; Lemaitre, G.; Nedelec, A.; Prat, D. *Org. Process Res. Dev.* **2002**, *6*, 20–27.
[74]Albrecht, U.; Nguyen, T. H. V.; Langer, P. *J. Org. Chem.* **2004**, *69*, 3417–3424.



A second example of the preparation of a silyl ketene acetal from an enolizable ester is included below.[75] Note that the geometry of the newly formed double bond is not controlled, and a mixture of products is obtained.



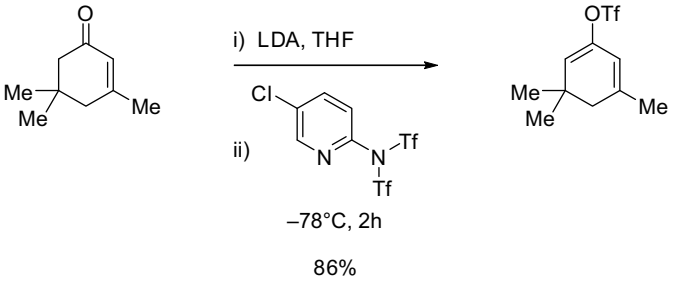
1.2.4.2 Formation of Enol Triflates The increasing utility of enol trifluoromethanesulfonates (triflates) in metal-catalyzed cross-coupling reactions has fueled the development of practical methods for their preparation. The synthesis of enol triflates is analogous to silyl enol ether formation. When the regioselectively of enolization is not a concern, enol triflates may be prepared by trapping the enol tautomers of carbonyl compounds with triflic anhydride (Tf_2O) in the presence of a mild nitrogen base. These reactions are commonly carried out in dichloromethane to avoid interactions between the strongly electrophilic Tf_2O and the solvent, although other non-Lewis basic media may be used. Due to the relative instability of enol triflates toward hydrolysis, manipulation during isolation and/or purification should be minimized and cold storage is recommended. In the following example, the enol triflate is prepared in good yield by treatment of the ketone with triflic anhydride and a bulky pyridine base.[76,77]



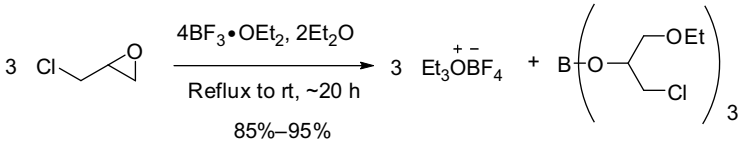
The use of phenyl- or *N*-(2-pyridyl)-triflimide in place of Tf_2O can be advantageous, as described by Comins and coworkers.[78] In general, triflimides may be used to trap metallo enolates with excellent regiospecificity. Therefore, careful choice of enolization conditions can provide a vinyl triflate with a high degree of regioselection. The Comins pyridyl triflimide, which is more reactive than its phenyl variant, is a solid at ambient temperature and the byproducts are more easily removed from reaction mixtures.[79,80] In the example

[75]Mermerian, A. H.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 5604–5607.
[76]Scott, W. J.; Crisp, G. T.; Stille, J. K. *Org. Synth.* **1990**, *68*, 116–129.
[77]Cacchi, S.; Morera, E.; Ortar, G. *Org. Synth.* **1990**, *68*, 138–147.
[78]McMurry, J. E.; Scott, W. J. *Tetrahedron Lett*. **1983**, *24*, 979–982.
[79]Comins, D. L.; Dehghani, A. *Tetrahedron Lett*. **1992**, *33*, 6299–6302.
[80]Comins, D. L.; Dehghani, A.; Foti, C. J.; Joseph, S. P. *Org. Synth.* **1997**, *74*, 77–83.

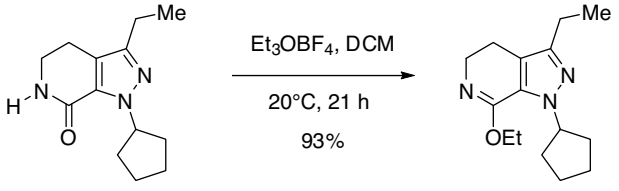
below, an LDA-derived lithium enolate was trapped with Comins' chloropyridyl triflimide reagent to yield the vinyl triflate shown in high yield. It is notable that γ-deprotonation, leading to formation of the regioisomeric 1,3-diene, was not observed.



1.2.4.3 Formation of Oxonium Salts Trialkyloxonium salts are powerful alkylating agents with broad utility. These reagents are generally effective under very mild reaction conditions, and often alkylate modest nucleophiles when others fail; alkylation of over fifty functional groups has been reported with trialkyloxonium salts.[81] First reported by Meerwein (who was also responsible for the development of numerous applications), triethylammonium tetrafluoroborate provides access to ethyl enol ethers from carbonyl compounds (see Section 1.2.4.3). The synthesis of this reagent utilizes epichlorohydrin, boron trifluoride diethyletherate, and diethyl ether.[82] In an analogous manner, trimethylammonium tetrafluoroborate is prepared from dimethyl ether.[81]

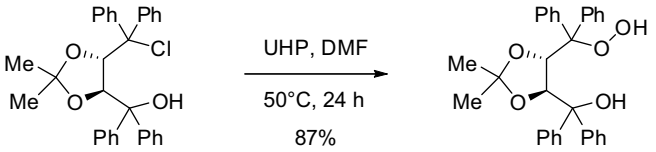


1.2.4.4 Reactions of Carbonyl Compounds with Oxonium Salts Triethyloxonium tetrafluoroborate (Meerwein salt) is generally effective for the conversion of carbonyl compounds to their corresponding ethyl enol ether variants. For additional information regarding the synthesis of Meerwein salts, see Section 1.2.4.2. The reagent is an extremely powerful electrophile and care must be taken to ensure worker safety and minimize environmental impact during its use. That said, the example below illustrates the high yields that are achievable with Et_3OBF_4 under very mild conditions.[83]

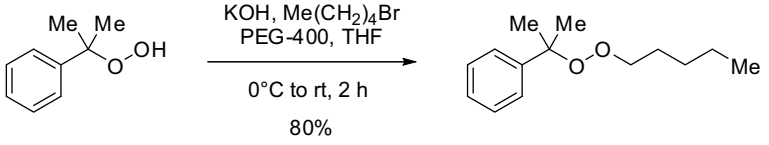


[81]Curphey, T. J. *Org. Synth.* **1971**, *51*, 142–147.
[82]Meerwein, H. *Org. Synth.* **1966**, *46*, 113–115.
[83]Urban, F. J.; Anderson, B. G.; Orrill, S. L.; Daniels, P. J. *Org. Process Res. Dev.* **2001**, *5*, 575–580.

1.2.4.5 Preparation of Hydroperoxides and Peroxyethers Care should be taken in handling all peroxides due to their propensity to decompose violently when exposed to shock or heat. As a result, peroxy compounds are rarely utilized as synthetic intermediates on large scale. However, well-studied hydroperoxide reagents are sometimes employed. A common method for hydroperoxide synthesis involves reaction of an electrophile with hydrogen peroxide under acidic or basic catalysis. Although most commonly utilized in oxidation reactions, urea hydrogen peroxide (UHP) is an alternative form of H_2O_2 that has proven useful in hydroperoxide synthesis. In the following example, moderate heating of an activated alkyl halide with UHP in DMF provides the hydroperoxide in excellent yield.[84] Some of the practical advantages of UHP include the fact that it is a relatively stable, inexpensive, and easily-handled solid.

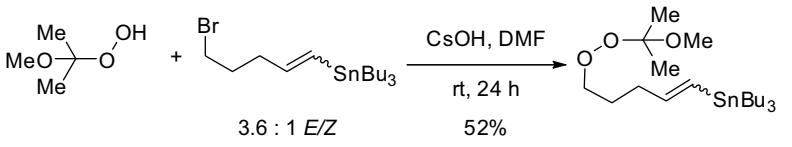


In a manner analogous to the preparation of ethers from alcohols, peroxyethers can be prepared via treatment of hydroperoxides with a base in the presence of an alkyl halide or sulfonic acid ester (e.g., mesylate). These conditions are not always applicable however, as aliphatic peroxides containing α-hydrogens are prone to degradation under basic conditions. Nevertheless, when reactive electrophiles are used, appreciable yields and reaction rates can be seen at or near ambient temperature for many substrates. Reported methods involve the use of primary alkyl iodides in the presence of silver oxide[85,86] or, preferably, bromides or sulfonates with potassium hydroxide base. In the latter method, polyethylene glycol is a recommended cosolvent. The addition of crown ethers or PEG-400 is thought to promote nucleophilicity through chelation to potassium ions and sometimes leads to superior yields.[87]

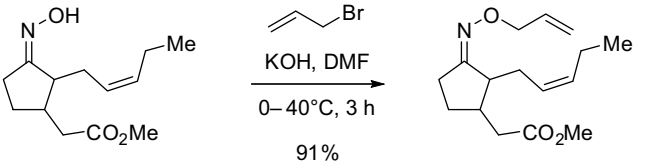


For less reactive or sterically hindered peroxides, cesium hydroxide has been shown to provide acceptable reaction rates in peroxyether formation at ambient temperature, thus avoiding a thermal degradation threat.[88]

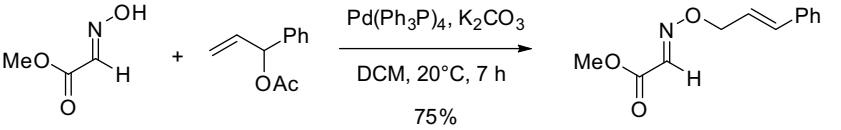
[84]Aoki, M.; Seebach, D. *Helv. Chim. Acta* **2001**, *84*, 187–207.
[85]Ito, T.; Tokuyasu, T.; Masuyama, A.; Nojima, M.; McCullough, K. J. *Tetrahedron* **2003**, *59*, 525–536.
[86]Hamada, Y.; Tokuhara, H.; Masuyama, A.; Nojima, M.; Kim, H.-S.; Ono, K.; Ogura, N.; Wataya, Y. *J. Med. Chem.* **2002**, *45*, 1374–1378.
[87]Bourgeois, M. J.; Montaudon, E.; Maillard, B. *Synthesis* **1989**, 700–701.
[88]Dussault, P. H.; Eary, C. T. *J. Am. Chem. Soc.* **1998**, *120*, 7133–7134.



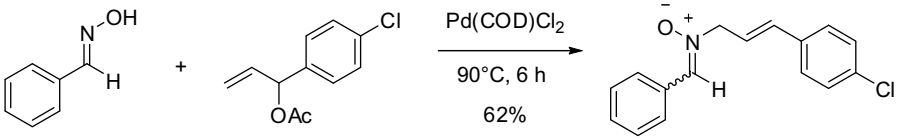
1.2.4.6 Alkylation of Oximes In most instances, oximes react with electrophiles such as aliphatic halides in a manner analogous to the corresponding reactions of alcohols. The example below outlines a typical procedure, in which an oxime is treated with an alkyl bromide and an inorganic base in a polar aprotic solvent.[89]



Takemoto and coworkers have employed oxime nucleophiles in palladium-catalyzed allylic substitution reactions. Here, the electrophile is an intermediate palladium(II) π-allyl complex, and the base is potassium carbonate.[90] The reaction proceeds in good yield to give the product of O-alkylation near ambient temperature, and at a reasonable rate, despite the poor solubility of K_2CO_3 in dichloromethane. For more on metal-catalyzed allylic substitution with oxygen nucleophiles, see Section 6.8.3.



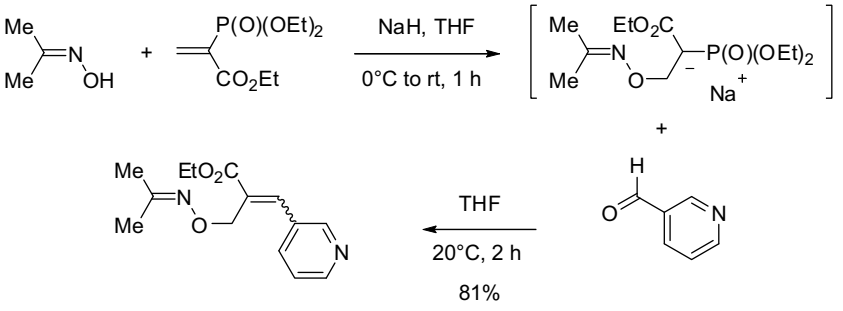
The example below highlights the ambiguous nature of an oxime's ability to react at nitrogen, as opposed to oxygen, under certain conditions. In this instance, palladium(II) catalysis under solvent-free conditions provided the N-alkylated oxime as a mixture of geometrical isomers in moderate yield.



In the example below, the oxygen atom of an oxime adds in a conjugate fashion to provide a stabilized anion for subsequent Horner-Wadsworth-Emmons reaction with nicotinaldehyde. Sodium hydride, which requires some additional handling precautions for large scale applications, is employed as the base in this instance.[91] This example is included to further

[89]Yamada, T.; Goto, K.; Mitsuda, Y.; Tsuji, J. *Tetrahedron Lett.* **1987**, *28*, 4557–4560.
[90]Miyabe, H.; Yoshida, K.; Reddy, V. K.; Matsumura, A.; Takemoto, Y. *J. Org. Chem.* **2005**, *70*, 5630–5635.
[91]Shen, Y.; Jiang, G.-F. *Synthesis* **2000**, 502–504.

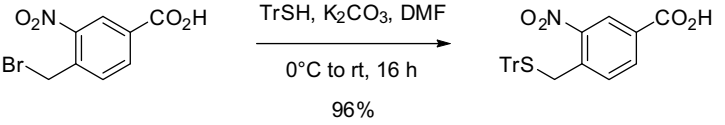
illustrate the useful application of oxime nucleophiles. For more on nucleophilic addition of ROH to polarized carbon–carbon multiple bonds, see Section 3.2.2.



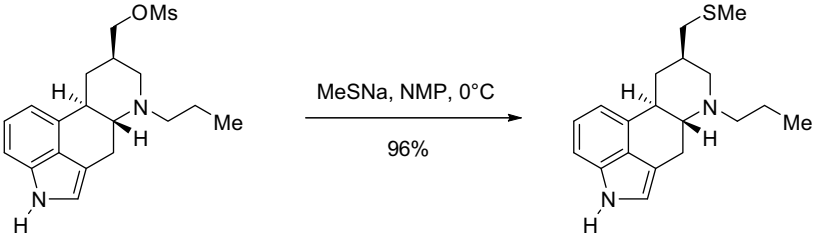
1.3 SULFUR NUCLEOPHILES

1.3.1 Reactions with Thiols

1.3.1.1 Preparation of Thioethers Thioethers are generally prepared via reaction of thiols with electrophiles such as alkyl halides in the presence of an appropriate base. Thiols are not potent nucleophiles; however, S_N2 displacement reactions may frequently be accomplished near ambient temperature, as illustrated in the example below.[1] In this instance, sterically encumbered trityl thiol is alkylated in high yield and at a reasonable rate with a reactive benzylic bromide.

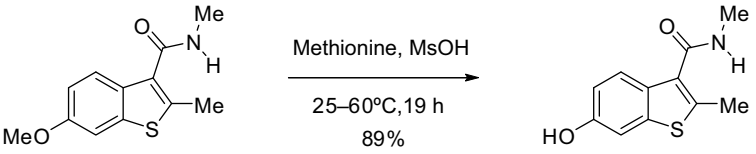


Cabri and coworkers described a highly efficient thioether formation in the synthesis of the ergot alkaloid derivative pergolide mesylate.[54] Direct S_N2 displacement of the primary mesylate shown below was accomplished with commercially available sodium methanethiolate, which can also be generated *in situ* from methanethiol and sodium hydroxide. The latter method is generally not preferred due to the challenges associated with handling toxic, malodorous methanethiol gas (bp 6°C).



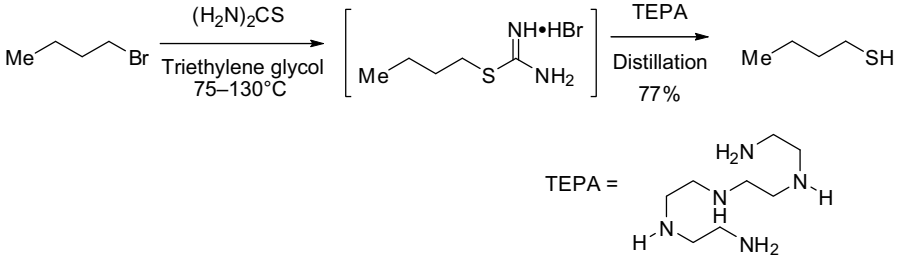
1.3.1.2 Cleavage of Arylmethyl Ethers Another useful application of nucleophilic sulfur reagents involves the cleavage of arylmethyl ethers to afford the corresponding

phenols.[92] In the example below, an intermediate in the synthesis of a VEGFR inhibitor candidate was prepared in high yield by treatment of a methoxybenzothiophene derivative with four equivalents of methionine in methanesulfonic acid.[93]

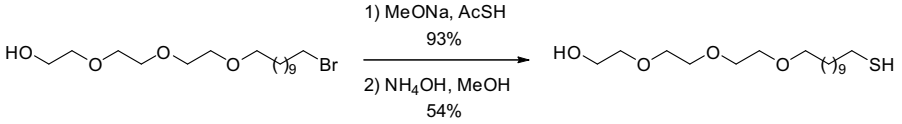


1.3.2 Reactions with Other Sulfur Nucleophiles

1.3.2.1 Preparation of Thiols The preparation of thiols via direct displacement of alkyl halides with sodium sulfide is not straightforward due to low solubility of this sulfur reagent in most organic solvents. As a result, simple aliphatic thiols are most often prepared via the intermediacy of somewhat more elaborate precursors. In the example below an isothiuronium salt is prepared via reaction of an alkyl bromide with thiourea, followed by reaction with a nucleophilic amine.[94] This method relies on distillation of the thiol product for isolation and purification, and is therefore most applicable to the preparation of low molecular weight derivatives.

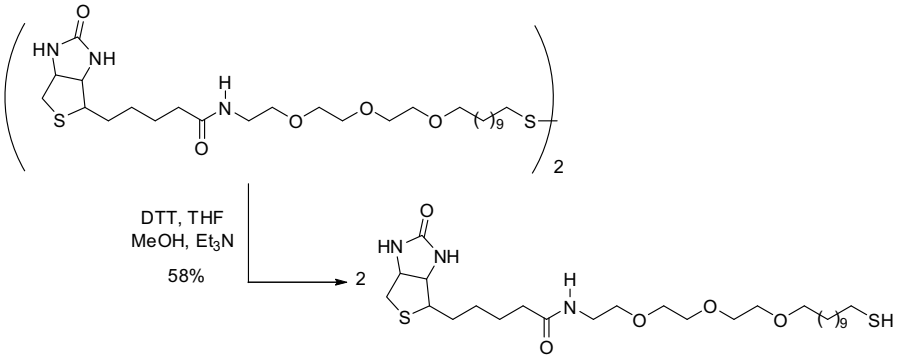


Perhaps more generally, aliphatic thiols are prepared by reaction of alkyl halides with thioacetic acid salts, followed by thioester cleavage under alkaline conditions.[95] The example below is representative, although use of commercially available thioacetic acid sodium salt would be preferred due to the obnoxious odor associated with free thioacids.

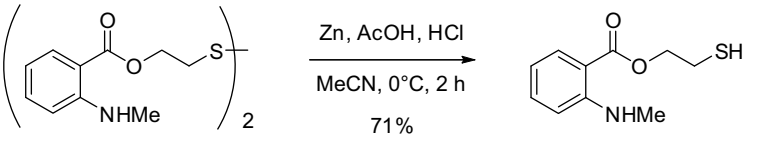


[92]Linderberg, M. T.; Moge, M.; Sivadasan, S. *Org. Process Res. Dev.* **2004**, *8*, 838–845.
[93]Scott, R. W.; Neville, S. N.; Urbina, A.; Camp, D.; Stankovic, N. *Org. Process Res. Dev.* **2006**, *10*, 296–303.
[94]Cossar, B. C.; Fournier, J. O.; Fields, D. L. *J. Org. Chem.* **1962**, *27*, 93–95.
[95]Canaria, C. A.; Smith, J. O.; Yu, C. J.; Fraser, S. E.; Lansford, R. *Tetrahedron Lett.* **2005**, *46*, 4813–4816.

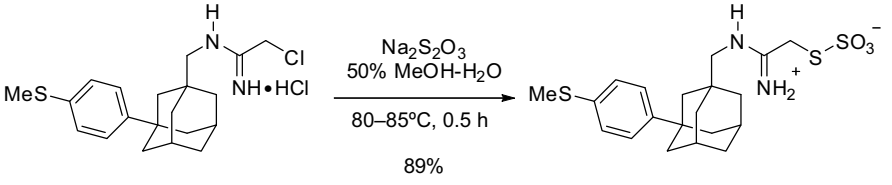
Independent of the method employed for their construction, thiols are a challenge to store and manipulate due to their stench and propensity to form disulfides in a mildly oxidizing environment such as air. As a result, the more stable disulfide dimers are sometimes targeted as thiol precursors. An attractive method for nucleophilic disulfide cleavage involves treatment with Cleland's reagent (dithiothreitol, DTT), which liberates the thiol under mild aqueous conditions.[95] Although this method would undoubtedly apply to a broad range of synthetic organic challenges, the use of DTT is dominated by its applications in biochemistry as a means to reduce thiolated DNA.



A number of other chemical methods have been developed for disulfide cleavage, including the use of mild reducing agents such as phosphines, sodium borohydride, or zinc in acetic acid.[96] A single example is included here, but for more on the preparation of thiols via reductive cleavage of disulfides, see Section 9.7.5.

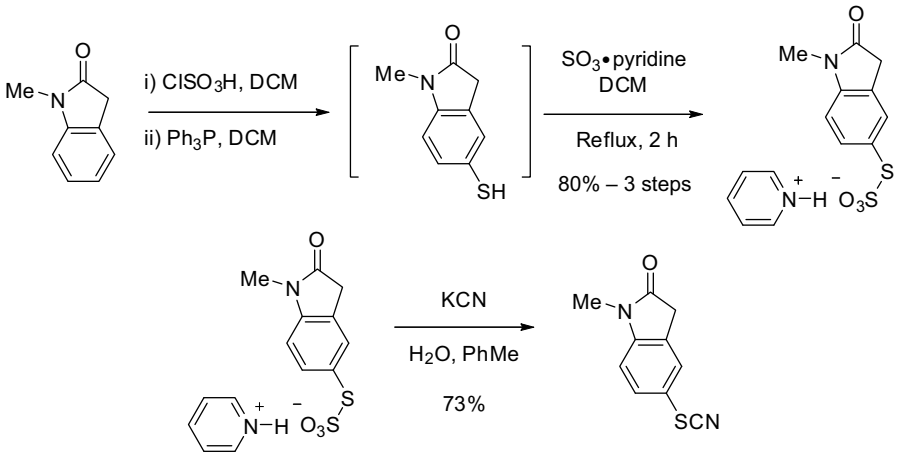


1.3.2.2 Formation of Bunte Salts Salts of S-alkyl or S-aryl hydrogen thiosulfates are known as Bunte salts. They are frequently prepared as precursors to thiols or disulfides. Most commonly, Bunte salts are prepared from alkyl halides and sodium thiosulfate by heating in aqueous methanol.[97]

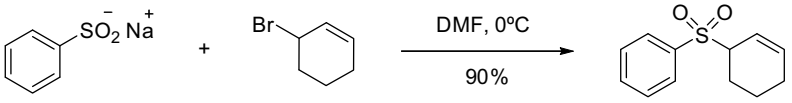


[96]Hartman, R. F.; Rose, S. D. *J. Org. Chem.* **2006**, *71*, 6342–6350.
[97]Tseng, C. C.; Handa, I.; Abdel-Sayed, A. N.; Bauer, L. *Tetrahedron* **1988**, *44*, 1893–1904.

In the example below, a pyridinium Bunte salt was prepared from the aryl thiol, then converted into the corresponding thiocyanate in good yield.[98] For a discussion on the preparation of aryl thiocyanates via electrophilic aromatic substitution, see Section 5.3.6.

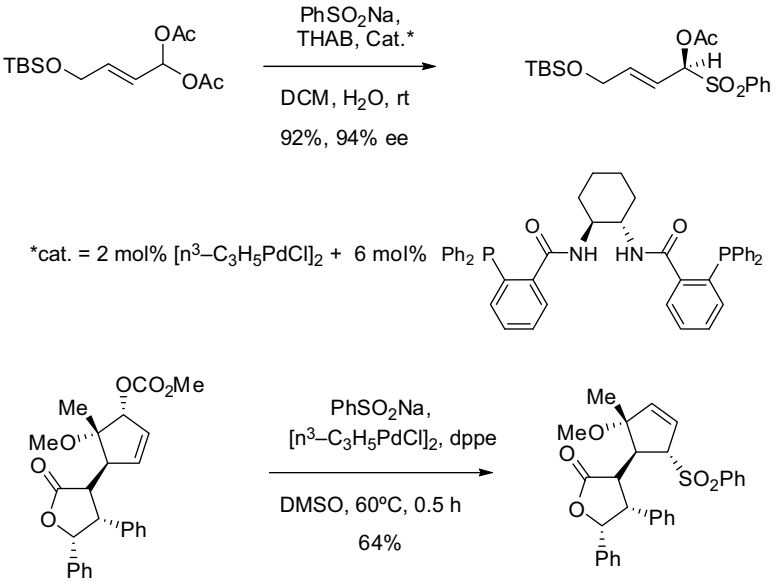


1.3.2.3 Alkylation of Sulfinic Acid Salts Sulfinic acids react with common electrophiles upon treatment with a mild base. Various arene sulfinic acid derivatives are commercially available as their stable, crystalline salts, in contrast to the parent acids, which are somewhat prone to decomposition and dimerization. Sulfinic acid salts are generally nucleophilic at sulfur, as opposed to oxygen, although exceptions have been reported. In the example below, commercially available sodium benzenesulfinate is reacted with an allylic bromide in dimethylformamide to provide the sulfone in high yield.[99,100]

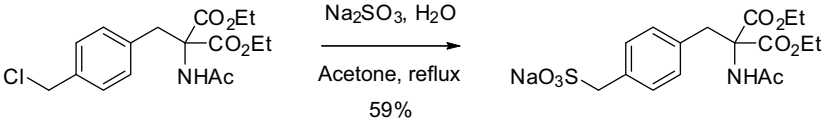


Another useful application of sulfinic acid nucleophiles is seen in palladium-catalyzed allylic substitution reactions. This mild methodology is useful for deprotection of allyl esters where standard acidic or alkaline hydrolysis would be incompatible with sensitive functionality, and is generally amenable to large scale. The following examples, from the research groups of Trost[101] and Hegedus[102] illustrate this reactivity toward π-allyl electrophiles. For more on metal-catalyzed allylic substitution, see Section 6.8.

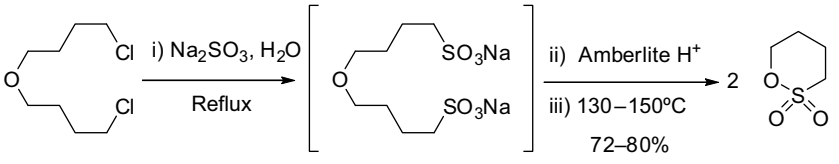
[98]Alcaraz, M.-L.; Atkinson, S.; Cornwall, P.; Foster, A. C.; Gill, D. M.; Humphries, L. A.; Keegan, P. S.; Kemp, R.; Merifield, E.; Nixon, R. A.; Noble, A. J.; O'Beirne, D.; Patel, Z. M.; Perkins, J.; Rowan, P.; Sadler, P.; Singleton, J. T.; Tornos, J.; Watts, A. J.; Woodland, I. A. *Org. Process Res. Dev.* **2005**, *9*, 555–569.
[99]Nilsson, Y. I. M.; Andersson, P. G.; Baeckvall, J. E. *J. Am. Chem. Soc.* **1993**, *115*, 6609–6613.
[100]Sellen, M.; Baeckvall, J. E.; Helquist, P. *J. Org. Chem.* **1991**, *56*, 835–839.
[101]Trost, B. M.; Crawley, M. L.; Lee, C. B. *J. Am. Chem. Soc.* **2000**, *122*, 6120–6121.
[102]Sebahar, H. L.; Yoshida, K.; Hegedus, L. S. *J. Org. Chem.* **2002**, *67*, 3788–3795.



1.3.2.4 Attack by Sulfite Ion Sulfite ion (SO_3^{2-}) is sufficiently nucleophilic to participate in S_N2 displacement reactions with aliphatic alkyl halides to provide the corresponding sulfonic acids after an acidic workup. The following example from Chen and coworkers is representative of typical reaction conditions and yields.[103]

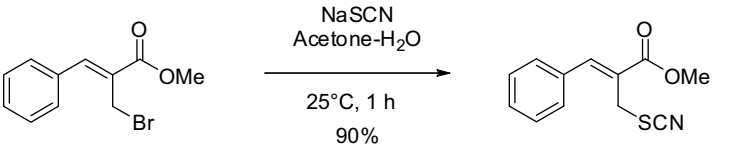


In the following example, the reaction of sodium sulfite with a symmetrical dichloride yielded the corresponding disulfonate intermediate. This was not isolated, but rather converted into a sultone by treatment with acidic Amberlite resin at an elevated temperature.[104]

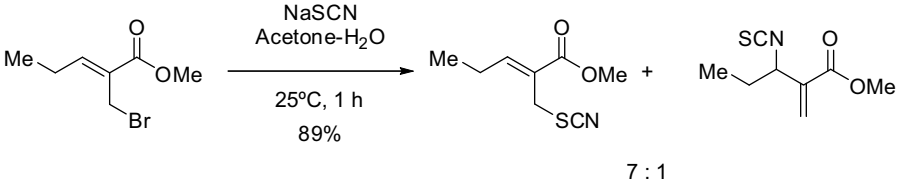


1.3.2.5 Preparation of Alkyl Thiocyanates Thiocyanate salts (typically sodium or potassium) are ambident nucleophiles, capable of either sulfur- or nitrogen-centered S_N2 attack on electrophiles. Reaction at sulfur is more frequently observed, providing thiocyanate products (vs. isothiocyanates). In the following example, Sa and coworkers report on a high-yielding preparation of allylic thiocyanates from allylic bromide precursors.[105]

[103]Chen, Y. T.; Xie, J.; Seto, C. T. *J. Org. Chem.* **2003**, *68*, 4123–4125.
[104]Snoddy, A. O. *Org. Synth.* **1957**, *37*, 55–57.
[105]Sa, M. M.; Fernandes, L.; Ferreira, M.; Bortoluzzi, A. J. *Tetrahedron Lett.* **2008**, *49*, 1228–1232.



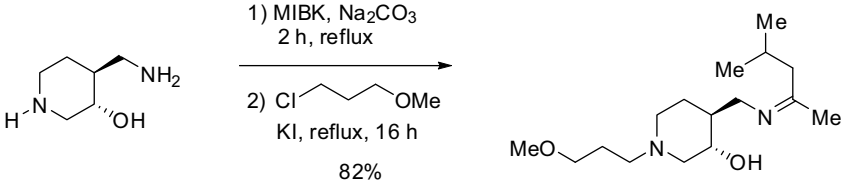
In addition to the primary reactivity described above, the authors also report measurable quantities of isothiocyanate products when the acrylate starting materials were alkyl substituted. Perhaps most interesting, the initially observed thiocyanate:isothiocyanate mixture (7:1) equilibrated to favor the latter compound (1:6) after prolonged periods at ambient temperature.



1.4 NITROGEN NUCLEOPHILES

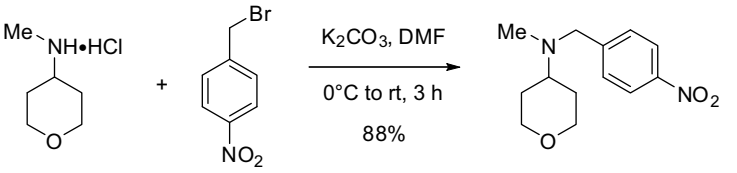
1.4.1 Amine Alkylation

1.4.1.1 Amine Alkylation with Alkyl Halides and Onium Salts The alkylation of nitrogen with alkyl halides is one of the most commonly utilized transformations in target-oriented synthetic chemistry. The inherently strong nucleophilicity of amines provides reliable, generally predictable reaction rates under mild conditions and in a variety of solvents. The nucleophilicity of an amine is strongly influenced by steric and inductive influences from substituents. A helpful discussion regarding the nucleophilicities of various primary and secondary amines has been published.[106] In the example below, the primary amine is first protected as a ketimine derivative through dehydrative condensation with methyl isobutylketone before introduction of the alkyl chloride. This process prevents the formation of a mixture of N-alkylation products. To enhance the alkylation rate, the chloride is converted to its corresponding iodide *in situ* via reaction with potassium iodide (Finkelstein reaction; see Section 1.5.1.1).[107] For further examples of ketimine formation, see Section 2.7.1).

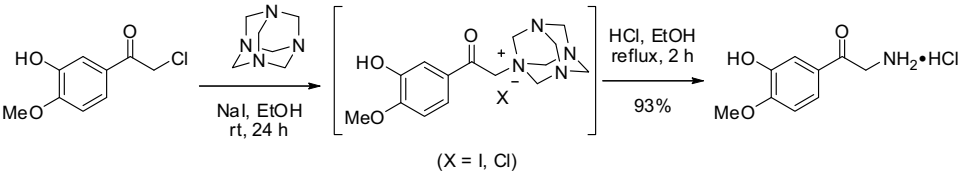


[106]Brotzel, F.; Chu, Y. C.; Mayr, H. *J. Org. Chem.* **2007**, *72*, 3679–3688.
[107]Laduron, F.; Tamborowski, V.; Moens, L.; Horvath, A.; De Smaele, D.; Leurs, S. *Org. Process Res. Dev.* **2005**, *9*, 102–104.

For ease of handling, amines are often prepared and stored as crystalline, non-volatile salts of a mineral acid. In most instances, these salts may be utilized directly in alkylation processes by introducing of a stoichiometric quantity of a base. The salt is first broken to provide the corresponding "free base", which then undergoes alkylation.[108] These reactions are generally facile and efficient, providing the starting salt is sufficiently soluble in the reaction medium, and overalkylation is controlled through proper stoichiometry and reaction temperature.

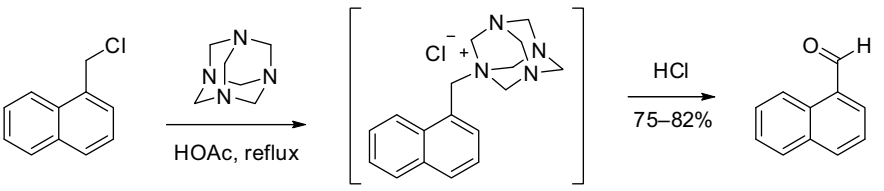


The tendency of tertiary amines to react further with alkylating agents to provide quaternary ammonium salts is occasionally a complicating factor. There are examples, however, where tertiary amine quaternization has been utilized in a productive manner. In the Delépine reaction,[109,110] primary alkyl halides are converted to the corresponding primary amines via treatment with hexamethylenetetramine, followed by hydrolysis. This sequence provides an inexpensive and reliable entry into aliphatic amines that can be conveniently isolated and handled as hydrochloride salts. The example below is representative.[111]

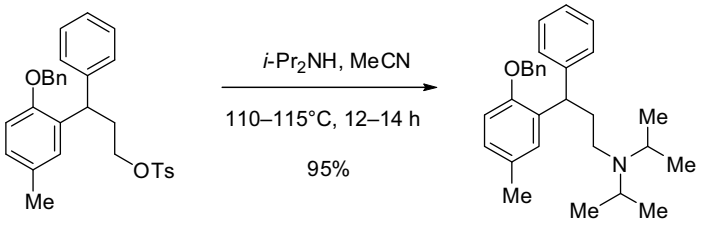


When benzylic alkyl halides are treated in a similar fashion with excess hexamethylenetetramine, the product of hydrolysis is the aldehyde. This useful variation, known as the Sommelet reaction,[112] provides fairly general access to aromatic aldehydes from benzylic halide precursors.[113–118] For additional discussion on benzylic oxidation, see Section 10.3.8.1 and 10.4.1.5.

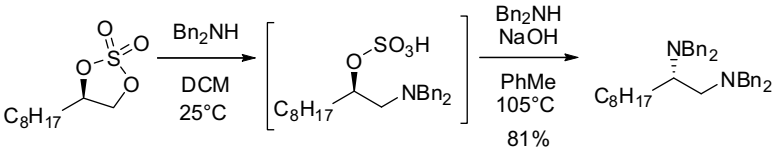
[108]Hashimoto, H.; Ikemoto, T.; Itoh, T.; Maruyama, H.; Hanaoka, T.; Wakimasu, M.; Mitsudera, H.; Tomimatsu, K. *Org. Process Res. Dev.* **2002**, *6*, 70–73.
[109]Delepine, M. *Bull. Soc. Chim. Fr.* **1895**, *13*, 352–355.
[110]Blazevic, N.; Kolbah, D.; Belin, B.; Sunjic, V.; Kajfez, F. *Synthesis* **1979**, 161–176.
[111]Nodiff, E. A.; Hulsizer, J. M.; Tanabe, K. *Chem. Ind.* **1974**, 962–963.
[112]Sommelet, M. *C. R. Acad. Sci. IIc* **1914**, *157*, 852–854.
[113]Angyal, S. J.; Morris, P. J.; Rassack, R. C.; Waterer, J. A. *J. Chem. Soc.* **1949**, 2704–2706.
[114]Angyal, S. J.; Rassack, R. C. *J. Chem. Soc.* **1949**, 2700–2704.
[115]Angyal, S. J.; Morris, P. J.; Tetaz, J. R.; Wilson, J. G. *J. Chem. Soc.* **1950**, 2141–2145.
[116]Angyal, S. J.; Barlin, G. B.; Wailes, P. C. *J. Chem. Soc.* **1953**, 1740–1741.
[117]Angyal, S. J.; Penman, D. R.; Warwick, G. P. *J. Chem. Soc.* **1953**, 1742–1747.
[118]Angyal, S. J.; Penman, D. R.; Warwick, G. P. *J. Chem. Soc.* **1953**, 1737–1739.



1.4.1.2 Amine Alkylation with Inorganic Esters Amines typically react with inorganic esters in a manner analogous to their interaction with alkyl halides. As exemplified by the following scheme, reaction of an amine with an alkyl sulfonate (e.g., mesylate, tosylate, etc.) proceeds smoothly in a polar aprotic solvent to provide the substituted amine.[119] Mild to moderate heating is often employed to decrease reaction time. One equivalent of a sulfonic acid is generated over the course of the reaction, so the product will require neutralization unless another base is included in the reaction.



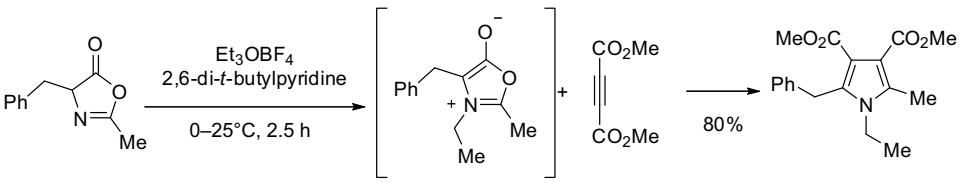
When cyclic sulfates are employed, initial attack typically occurs at the less sterically encumbered carbon center to provide the intermediate amino sulfate. In the example below, a second equivalent of amine is introduced to promote a second displacement at the more substituted carbon center. Note that considerably more forcing conditions are required for the second alkylation, and that this attack results in inversion of the stereocenter. The more sluggish reaction rate for the second addition often allows the use of two distinct amines in this stepwise reaction sequence.



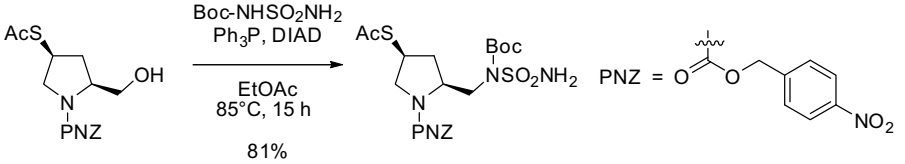
Trialkyloxonium tetrafluoroborate (Meerwein salts) have been used in the preparation of N-substituted pyrroles for pharmaceutical applications.[120] In the example below, the 2-oxazoline-5-one derived from phenylalanine is N-ethylated to produce the reactive dipole 1,3-oxazolium-5-oxide (munchnone). In the presence of dimethyl acetylenedicarboxylate, a [3 + 2] cycloaddition takes place to provide the *N*-ethyl pyrrole after carbon dioxide is lost via retro [4 + 2]. The authors note that extremely reactive alkylating agents

[119]Srinivas, K.; Srinivasan, N.; Reddy, K. S.; Ramakrishna, M.; Reddy, C. R.; Arunagiri, M.; Kumari, R. L.; Venkataraman, S.; Mathad, V. T. *Org. Process Res. Dev.* **2005**, *9*, 314–318.
[120]Hershenson, F. M.; Pavia, M. R. *Synthesis* **1988**, 999–1001.

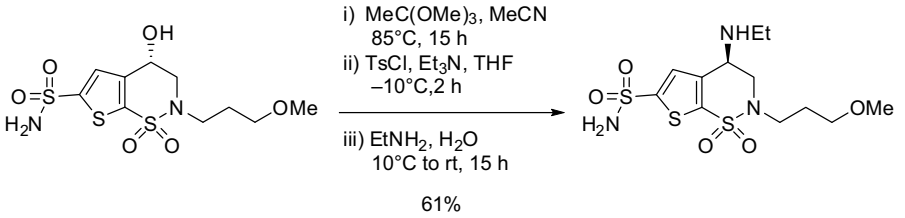
are required for this transformation; methyl iodide, dimethyl sulfate, and benzyl bromide are ineffective.



1.4.1.3 Amine Alkylation with Alcohols Alcohols may serve as useful precursors to amines, although an activation step is required. Unfortunately, the activation step often involves the use of reagents that add considerable expense and/or waste to the process. For instance, if the amine nucleophile is suitably acidic, as is the case for the Boc-protected sulfonamide below, Mitsunobu conditions may be employed.[121] Although this method can be effective for small scale applications, there is general agreement among process chemists that the phosphine, azodicarboxylate reagents and the byproducts they produce in the reaction decrease the utility of this method for large scale.



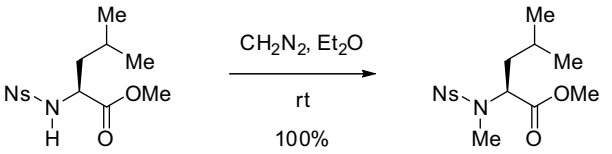
For more typical amine nucleophiles, such as simple unactivated primary amines, preactivation of the alcohol as its sulfonate ester (e.g., mesylate, tosylate, brosylate, etc.) is necessary.[122] This method is preferable for bulk production, due to the lower expense of sulfonyl ester halides, and the ease of removal of sulfonic acid byproducts via alkaline aqueous extraction. For more on the use of sulfonates in amine alkylation, see Section 1.4.1.2.



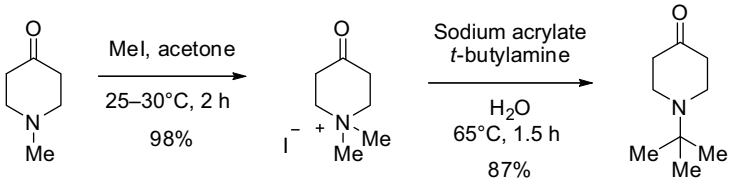
1.4.1.4 Amine Alkylation with Diazo Compounds As discussed in Section 1.2.3.5, the use of diazo compounds of low molecular weight is not preferred for large scale applications. However, the reaction of activated amines with diazomethane to provide N-methylated

[121]Nishino, Y.; Komurasaki, T.; Yuasa, T.; Kakinuma, M.; Izumi, K.; Kobayashi, M.; Fujiie, S.; Gotoh, T.; Masui, Y.; Hajima, M.; Takahira, M.; Okuyama, A.; Kataoka, T. *Org. Process Res. Dev.* **2003**, *7*, 649–654.
[122]Conrow, R. E.; Dean, W. D.; Zinke, P. W.; Deason, M. E.; Sproull, S. J.; Dantanarayana, A. P.; DuPriest, M. T. *Org. Process Res. Dev.* **1999**, *3*, 114–120.

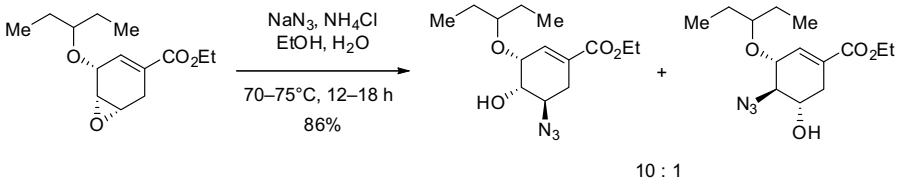
products is a clean, high-yielding transformation that can be carried out quite reliably on laboratory scale in fit-for-purpose glassware.[123]



1.4.1.5 Transamination The direct nucleophilic displacement of one aliphatic amine by another is not a widely employed transformation. The formal product of transamination can be obtained, however, under a range of reaction conditions. Although not technically a nucleophilic aliphatic substitution reaction, the example below highlights a formal transamination reaction. In this case, a series of elimination/conjugate addition reactions provide an efficient exchange of methylamine for *tert*-butylamine. Achieving a comparable transamination via direct S_N2 displacement with *tert*-butylamine would be very unlikely.[124]



1.4.1.6 Amine Alkylation with Epoxides The ring-opening of epoxides with nitrogen nucleophiles is a facile, well-established transformation. The reaction will often proceed thermally, although the use of Lewis or Brønsted acid catalysis is common. In their kilogram-scale synthesis of the anti-influenza drug oseltamivir (active pharmaceutical ingredient in Tamiflu®), Rohloff and coworkers described a regioselective ring-opening of a key epoxide intermediate with sodium azide and ammonium chloride in aqueous ethanol. Although this reaction was run at an elevated temperature, the authors warned against exceeding 80°C due to the potential explosivity of azides.[125]

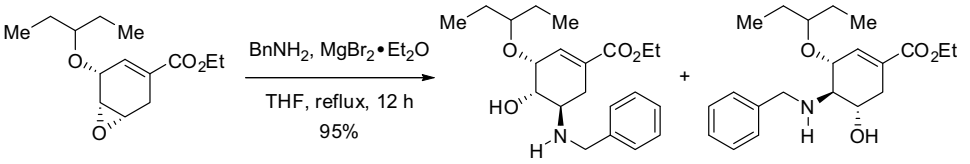


[123]Di Gioia, M. L.; Leggio, A.; Le Pera, A.; Liguori, A.; Napoli, A.; Siciliano, C.; Sindona, G. *J. Org. Chem.* **2003**, *68*, 7416–7421.

[124]Amato, J. S.; Chung, J. Y. L.; Cvetovich, R. J.; Reamer, R. A.; Zhao, D.; Zhou, G.; Gong, X. *Org. Process Res. Dev.* **2004**, *8*, 939–941.

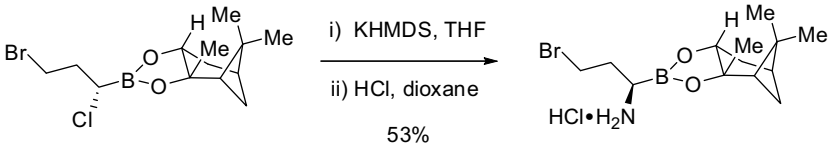
[125]Rohloff, J. C.; Kent, K. M.; Postich, M. J.; Becker, M. W.; Chapman, H. H.; Kelly, D. E.; Lew, W.; Louie, M. S.; McGee, L. R.; Prisbe, E. J.; Schultze, L. M.; Yu, R. H.; Zhang, L. *J. Org. Chem.* **1998**, *63*, 4545–4550.

The thermal and shock sensitivity of some azide-containing compounds has limited their use in large scale synthesis. To address these issues for bulk production, Karpf and Trussardi have developed alternative conditions for the regioselective introduction of nitrogen to their substrate. The use of benzylamine, with magnesium bromide as a Lewis acid catalyst, provided the desired 1,2-amino alcohol in comparable yield and regioselectivity.[126]



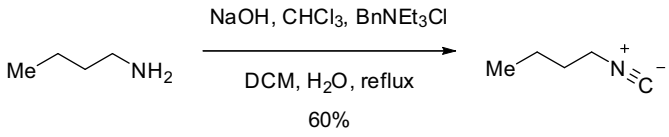
For additional discussion on the use of azide nucleophiles, see Section 1.4.3.2. For another example of the reaction of an epoxide with sodium azide see, Section 1.2.2.8.

1.4.1.7 Preparation of 1° Amines via Hexamethyldisilazane The direct nucleophilic displacement of aliphatic halides by hexamethyldisilazane (HMDS) has been demonstrated.[127] The main advantages of this method for the synthesis of amines are the elimination of multi-alkylation issues and that TMS groups are easily removed by an acidic workup to liberate an ammonium salt. The method has not been widely adopted, however, due to the poor nucleophilicity of the sterically bulky HMDS. In most cases, reaction rates are slow and yields are modest. In the example below, the displacement of a secondary chloride is assisted via participation by the neighboring boron atom, thus accelerating the reaction rate significantly.[128] Note that participation by boron offsets the normal rate advantage offered by the primary bromide (vs. secondary chloride) and also provides a steric bias that influences the stereochemical course of the reaction.[129]

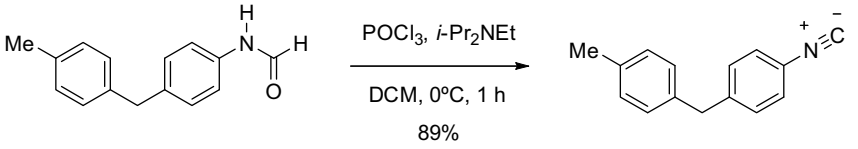


1.4.1.8 Preparation of Isocyanides ("Isonitriles") The first synthesis of an isocyanide was reported by Lieke in 1859; allyl iodide was reacted with silver cyanide to yield allyl isocyanide. A second method involves reaction of a primary amine with dichlorocarbene (generated by treatment of chloroform with a strong base), and is known as the Hofmann carbylamine reaction. Weber and coworkers reported an improvement to the latter method, wherein the use of phase transfer catalysis in dichloromethane-water solvent systems provides superior yields under milder conditions.[130,131]

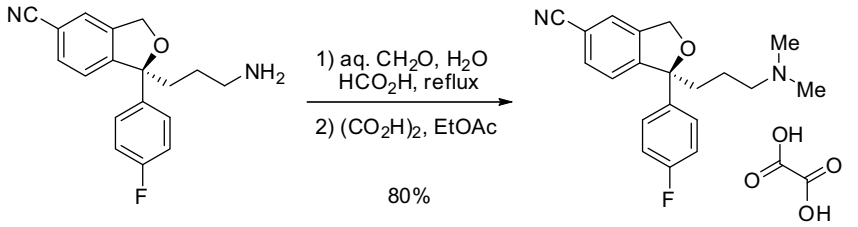
[126]Karpf, M.; Trussardi, R. *J. Org. Chem.* **2001**, *66*, 2044–2051.
[127]Bestmann, H. J.; Woelfel, G. *Chem. Ber.* **1984**, *117*, 1250–1254.
[128]Matteson, D. S.; Schaumberg, G. D. *J. Org. Chem.* **1966**, *31*, 726–731.
[129]Wityak, J.; Earl, R. A.; Abelman, M. M.; Bethel, Y. B.; Fisher, B. N.; Kauffman, G. S.; Kettner, C. A.; Ma, P.; McMillan, J. L.;et al. *J. Org. Chem.* **1995**, *60*, 3717–3722.
[130]Weber, W. P.; Gokel, G. W. *Tetrahedron Lett*. **1972**, 1637–1640.
[131]Weber, W. P.; Gokel, G. W.; Ugi, I. K. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 530–531.



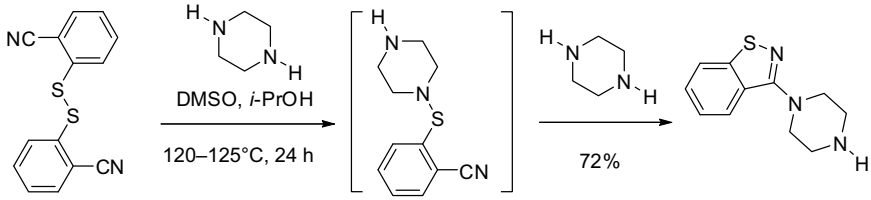
However, isocyanides can be more generally prepared via dehydration of *N*-formyl precursors.[132] A range of dehydrating agents is effective in the reaction, with phosphorous oxychloride ($POCl_3$) used in the representative example below.[133]



1.4.1.9 Methylation of Amines, the Eschweiler-Clarke reaction A special case of imine reduction is demonstrated in the Eschweiler-Clarke reaction, in which an amine is condensed with formaldehyde in the presence of formic acid to yield the N-methylated product. The reaction is most simply carried out in water at reflux, as demonstrated in the synthesis of citalopram.[134]



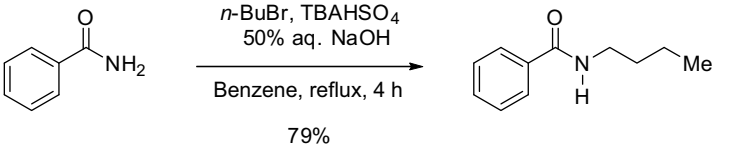
1.4.1.10 Preparation Sulfenamides As illustrated by Walinsky and coworkers in their work toward the atypical antipsychotic drug ziprasidone, nucleophilic secondary amines react with disulfides via attack at sulfur to liberate sulfenamide products.[135] These hydrolytically labile compounds may serve as amine precursors[136] or intermediates in the preparation of heterocycles[137] such the benzisothiazole shown below.



[132]Ugi, I.; Meyr, R. *Angew. Chem., Int. Ed. Engl.* **1958**, *70*, 702–703.
[133]Obrecht, R.; Herrmann, R.; Ugi, I. *Synthesis* **1985**, 400–402.
[134]Elati, C. R.; Kolla, N.; Vankawala, P. J.; Gangula, S.; Chalamala, S.; Sundaram, V.; Bhattacharya, A.; Vurimidi, H.; Mathad, V. T. *Org. Process Res. Dev.* **2007**, *11*, 289–292.
[135]Walinsky, S. W.; Fox, D. E.; Lambert, J. F.; Sinay, T. G. *Org. Process Res. Dev.* **1999**, *3*, 126–130.
[136]Wuts, P. G. M.; Jung, Y. W. *Tetrahedron Lett*. **1986**, *27*, 2079–2082.
[137]Davis, F. A. *Int. J. Sulfur Chem.* **1973**, *8*, 71–81.

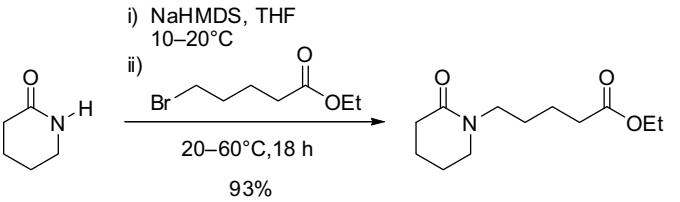
1.4.2 N-Alkylation of Amides, Lactams, Imides, and Carbamates

1.4.2.1 Alkylation with Alkyl Halides The alkylation of aryl amides with alkyl halides can be achieved under mild phase transfer conditions.[138] In the example below, benzamide is converted to its *N*-butyl derivative through reaction with *n*-butyl bromide in the presence of tetra-*n*-butylammonium hydrogensulfate. The high concentration of sodium hydroxide prevents hydrolytic side reactions from occurring by promoting clear separation between aqueous and organic phases. Benzene can typically be replaced by toluene or dichloromethane to provide secondary amides with equal efficiency. The primary concern with this protocol is competing formation of tertiary amides via double alkylation. However, this issue can be addressed by careful control of stoichiometry, as the second alkylation is generally much slower than the first.



Unfortunately, yields drop off somewhat when aliphatic amides are reacted under these conditions, and attempted introduction of a second alkyl group is generally unsuccessful. Primary sulfonamides can also be alkylated with these conditions, although doubly alkylated products are primarily obtained due to the increased acidity of this substrate class.

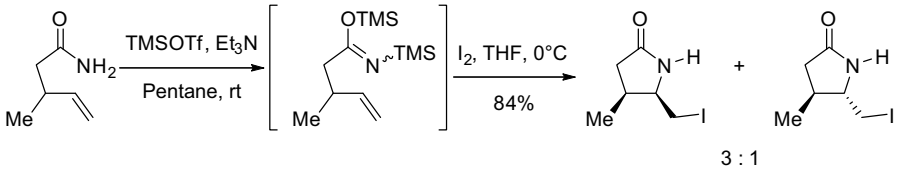
In cases where the mild biphasic conditions described above are ineffective, amides can typically be alkylated by deprotonation with a strong base under anhydrous conditions, followed by combination with an alkyl halide. In the alkylation of δ-valerolactam below, sodium hexamethyldisilazide in THF is utilized.[139] The amide salts often exhibit poor solubility in solvents such as THF, however, so proper agitation, along with moderate heating may be required for successful reactions.



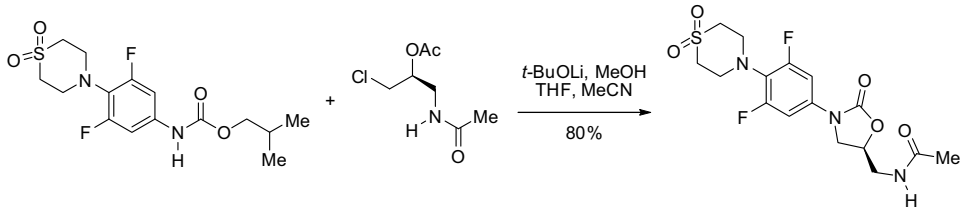
Primary amides may be converted to iodo lactams via intramolecular alkylation of electrophilic iodonium species.[140,141] The nucleophilic component in the example below is not the primary amide itself, but rather the *N,O*-bis(trimethylsilyl)imidate derivative shown in brackets. Silylation of the starting amide promotes the N-alkylation pathway

[138]Gajda, T.; Zwierzak, A. *Synthesis* **1981**, 1005–1008.
[139]Roenn, M.; McCubbin, Q.; Winter, S.; Veige, M. K.; Grimster, N.; Alorati, T.; Plamondon, L. *Org. Process Res. Dev.* **2007**, *11*, 241–245.
[140]Knapp, S.; Levorse, A. T. *J. Org. Chem.* **1988**, *53*, 4006–4014.
[141]Knapp, S.; Rodriques, K. E.; Levorse, A. T.; Ornaf, R. M. *Tetrahedron Lett.* **1985**, *26*, 1803–1806.

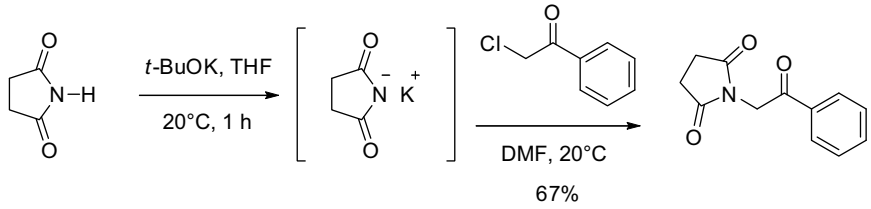
and prevents competitive iodolactone formation, as originally reported by Ganem and coworkers.[142]



During their pilot scale synthesis of an oxazolidinone antibacterial candidate, Lu and coworkers carried out a multi-kilogram carbamate alkylation as the first operation in a highly efficient three step sequence.[143] In this example, an *N*-aryl carbamate was reacted with a primary alkyl chloride in the presence of lithium *t*-butoxide. The desired alkylation product was obtained in high yield under these conditions, which also lead to subsequent acetate cleavage and oxazolidinone formation. The use of lithium-derived bases was critical, as sodium and potassium counterions gave rise to isomeric byproducts, as reported by Perrault during the development of structurally similar linezolid.[144]

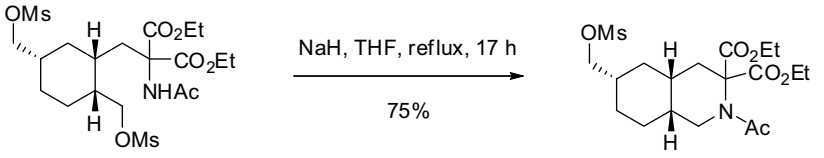


In the example below from Augustine and coworkers, potassium succinimide is reacted with α-chloroacetophenone in DMF to provide an *N*-alkyl succinimide that served as a precursor to enantiomerically enriched 2-amino-1-phenylethanol.[145] Consistent with their amide relatives, alkylation of imides most commonly occurs on nitrogen in the presence of a base, although O-alkylation can be a complicating side reaction. The use of a potassium counterion is generally effective for promoting nitrogen-centered attack.

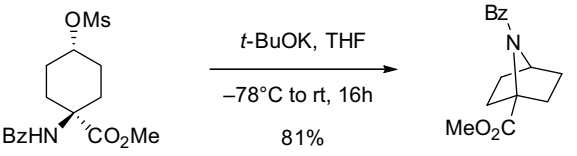


[142]Biloski, A. J.; Wood, R. D.; Ganem, B. *J. Am. Chem. Soc.* **1982**, *104*, 3233–3235.
[143]Lu, C. V.; Chen, J. J.; Perrault, W. R.; Conway, B. G.; Maloney, M. T.; Wang, Y. *Org. Process Res. Dev.* **2006**, *10*, 272–277.
[144]Perrault, W. R.; Pearlman, B. A.; Godrej, D. B.; Jeganathan, A.; Yamagata, K.; Chen, J. J.; Lu, C. V.; Herrinton, P. M.; Gadwood, R. C.; Chan, L.; Lyster, M. A.; Maloney, M. T.; Moeslein, J. A.; Greene, M. L.; Barbachyn, M. R. *Org. Process Res. Dev.* **2003**, *7*, 533–546.
[145]Tanielyan, S. K.; Marin, N.; Alvez, G.; Augustine, R. L. *Org. Process Res. Dev.* **2006**, *10*, 893–898.

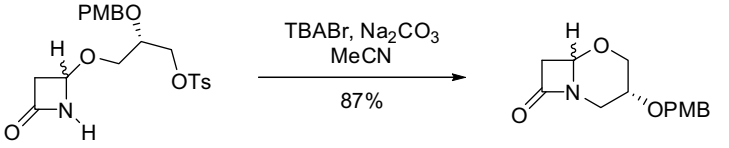
1.4.2.2 Alkylation with Alkyl Sulfonates Acetamide derivatives undergo intramolecular N-alkylation reactions with alkyl sulfonates (e.g., mesylates, tosylates, etc.) in good yield.[146] Sodium hydride in tetrahydrofuran was employed in this example, and is a common first choice for laboratory scale since the gaseous hydrogen byproduct is easily removed and relatively inert. Sodium hexamethyldisilazide (NaHMDS), which is safer and easier to handle on large scale, has also proven effective in some cases and should be considered.



Potassium *tert*-butoxide has also been successfully employed in amide alkylation reactions. In the example below, high yield of a bicyclic benzamide product was obtained via intramolecular mesylate displacement in THF.[147]



During development of synthetic methodology for the synthesis of oxacephem antibiotics, Chmielewski and coworkers reported an efficient intramolecular β-lactam alkylation with a primary tosylate.[148] In this instance, a very mild base (sodium carbonate) was sufficient to promote the alkylation, so long as tetra–*n*–butylammonium bromide was included.



1.4.3 Other Nitrogen Nucleophiles

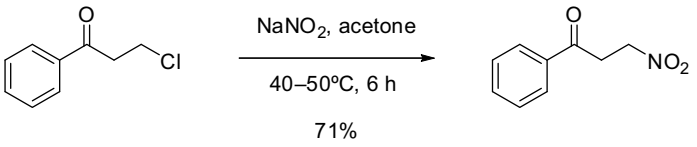
1.4.3.1 Nitrite Nucleophiles: Preparation of Nitro Compounds The preparation of aliphatic nitro compounds can be accomplished by treatment of alkyl halides with sodium or potassium nitrite. Moderate heating in a polar solvent such as acetone, acetonitrile, dimethylformamide or dimethylsulfoxide is generally required, and the formation of isomeric alkyl nitrites is competitive.[149]

[146]Hansen, M. M.; Bertsch, C. F.; Harkness, A. R.; Huff, B. E.; Hutchison, D. R.; Khau, V. V.; LeTourneau, M. E.; Martinelli, M. J.; Misner, J. W.; Peterson, B. C.; Rieck, J. A.; Sullivan, K. A.; Wright, I. G. *J. Org. Chem.* **1998**, *63*, 775–785.

[147]Avenoza, A.; Cativiela, C.; Busto, J. H.; Fernandez-Recio, M. A.; Peregrina, J. M.; Rodriguez, F. *Tetrahedron* **2001**, *57*, 545–548.

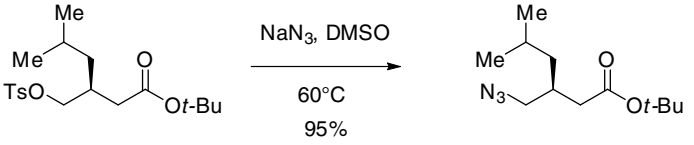
[148]Kaluza, Z.; Furman, B.; Krajewski, P.; Chmielewski, M. *Tetrahedron* **2000**, *56*, 5553–5562.

[149]Singh, P. N. D.; Mandel, S. M.; Sankaranarayanan, J.; Muthukrishnan, S.; Chang, M.; Robinson, R. M.; Lahti, P. M.; Ault, B. S.; Gudmundsdottir, A. D. *J. Am. Chem. Soc.* **2007**, *129*, 16263–16272.



Silver nitrite is superior to its sodium relative in many cases, affording moderate to good yields of nitro compounds in an aqueous environment.[150] However, a significant excess of this expensive reagent is required to minimize competitive formation of alcohols.

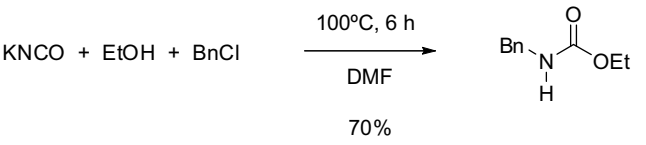
1.4.3.2 Azide Nucleophiles Due to a linear geometry that minimizes steric hindrance, azide ion is a highly effective nitrogen nucleophile. Azide has a nucleophilic constant (n)[151] that is approximately equivalent to that of NH_3, while possessing a basicity closer to that of acetate ion.[152] Furthermore, alkyl azides can be converted in a highly efficient manner to the corresponding amines via hydrogenolysis or via Staudinger reduction with a phosphine as the reducing agent (see Section 9.7.1.1). For these reasons, the use of azide ion as a nucleophile in organic synthesis is prevalent. In the example below, a primary alkyl tosylate is displaced by sodium azide in dimethylsulfoxide at 60°C to provide the primary alkyl azide in 95% yield.[153]



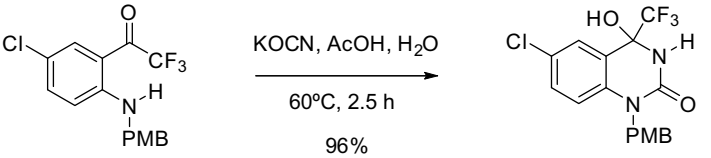
It should be noted that sodium azide and many related compounds are toxic substances and extreme care should be taken to minimize exposure while handling these reagents, reaction mixtures, and products. Furthermore, many azide compounds present an additional safety concern due to their tendency to aggressively decompose with concomitant nitrogen gas liberation. Many heavy metal azides are exceedingly shock sensitive, so handling of these compounds should be avoided. Finally, care must be taken during waste storage and disposal due to the propensity of azide ion to form explosive metal complexes with materials found in standard copper water pipes. For additional examples of C–N bond formation with azide nucleophiles, see Sections 1.2.2.8 and 1.4.1.6.

1.4.3.3 Isocyanates and Isothiocyanates as Nucleophiles Isocyanate salts are commonly employed reagents for the introduction of urea or carbamate functionalities. Isocyanate ions are reasonably nucleophilic at nitrogen, but upon alkylation, the resulting N-substituted isocyanates are electrophilic at the central carbon atom. The example below illustrates how this dual reactivity can be utilized for the preparation of carbamates in a single reaction from potassium isocyanate, an alcohol, and an alkyl halide.[154]

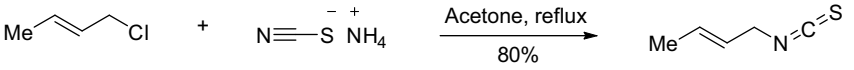
[150]Ballini, R.; Barboni, L.; Giarlo, G. *J. Org. Chem.* **2004**, *69*, 6907–6908.
[151]Swain, C. G.; Scott, C. B. *J. Am. Chem. Soc.* **1953**, *75*, 141–147.
[152]Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry, Part A: Structure and Mechanisms*. 4th ed.; Kluwer Academic/Plenum Publishers: Dordrecht, Netherlands, **2000**.
[153]Hoekstra, M. S.; Sobieray, D. M.; Schwindt, M. A.; Mulhern, T. A.; Grote, T. M.; Huckabee, B. K.; Hendrickson, V. S.; Franklin, L. C.; Granger, E. J.; Karrick, G. L. *Org. Process Res. Dev.* **1997**, *1*, 26–38.
[154]Argabright, P. A.; Rider, H. D.; Sieck, R. *J. Org. Chem.* **1965**, *30*, 3317–3321.



Magnus and coworkers reported a similar use of potassium isocyanate in their synthesis of NNRTI candidates for the treatment of HIV,[155] although in this case the carbonyl electrophile technically moves this example out of the scope of this chapter. For more on the addition of nitrogen nucleophiles to carbonyl carbon centers, see Chapter 2.



Isothiocyanate ions afford the same general reactivity, although competitive S-alkylation may be a minor complication. In the following example, the authors we able to isolate methallyl isothiocyanate prepared by refluxing an acetone solution of ammonium isothiocyanate with methallyl chloride in 80% yield. This product was converted to a thiourea derivative via treatment with alcoholic ammonia, and to 2–butenamine via acidic hydrolysis.[156]

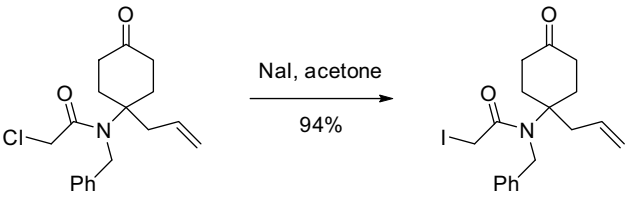


1.5 HALOGEN NUCLEOPHILES

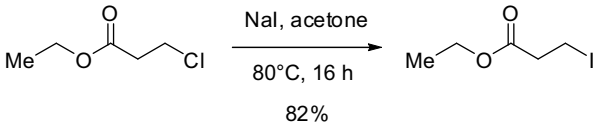
1.5.1 Attack by Halides at Alkyl Carbon or Silicon

1.5.1.1 Halide Exchange The exchange of one halide for another, known as the Finkelstein reaction,[157] is a thermodynamically driven process that can be influenced by the stoichiometric ratio of the two halides as well as relative solubilities of halide salts in the reaction medium. A halogen exchange reaction is commonly used to convert more stable, accessible, and inexpensive alkyl chlorides to their more reactive bromide or iodide analogs prior to an alkylation reaction. The Finkelstein reaction can frequently be carried out during an alkylation reaction, by adding a bromide or iodide salt to the reaction mixture. In the example below, an α-chloroamide is converted to the corresponding iodide through treatment with super-stoichiometric sodium iodide in acetone.[158]

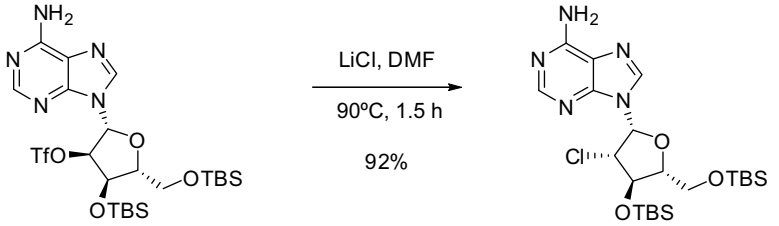
[155]Magnus, N. A.; Confalone, P. N.; Storace, L.; Patel, M.; Wood, C. C.; Davis, W. P.; Parsons, R. L., Jr., *J. Org. Chem.* **2003**, *68*, 754–761.
[156]Young, W. G.; Webb, I. D.; Goering, H. L. *J. Am. Chem. Soc.* **1951**, *73*, 1076–1083.
[157]Finkelstein, H. *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 1528–1532.
[158]Kropf, J. E.; Meigh, I. C.; Bebbington, M. W. P.; Weinreb, S. M. *J. Org. Chem.* **2006**, *71*, 2046–2055.



With the activated halide highlighted in the example above, exchange occurs at an acceptable rate at ambient temperature; however, moderate heating is commonly employed to accelerate the conversion. In the example below, the less-activated substrate required considerable heating and an extended reaction time to accomplish complete halide exchange.[159]

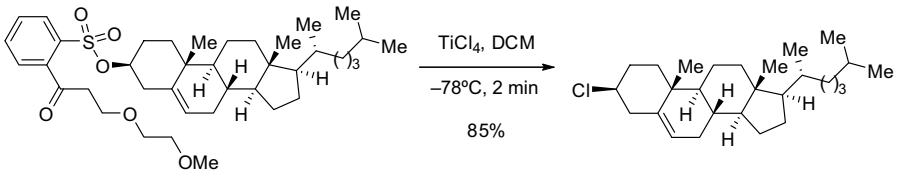


1.5.1.2 Preparation of Halides from Sulfonic Acid Esters Alkyl halides can be prepared from aliphatic alcohol precursors via the intermediacy of sulfonic acid esters such as mesylates, tosylates, or triflates. Preferred conditions involve heating the sulfonate with a halide salt in a polar aprotic solvent such as acetone, acetonitrile, or dimethylformamide. The reaction generally proceeds via direct S_N2 displacement to provide the product of stereochemical inversion, although subsequent halide–halide exchange may occur to yield an epimeric mixture. In the example below from Robins and coworkers, clean inversion was achieved with lithium chloride in dimethylformamide.[160] The corresponding bromide could be prepared in 85% yield under analogous conditions with lithium bromide.

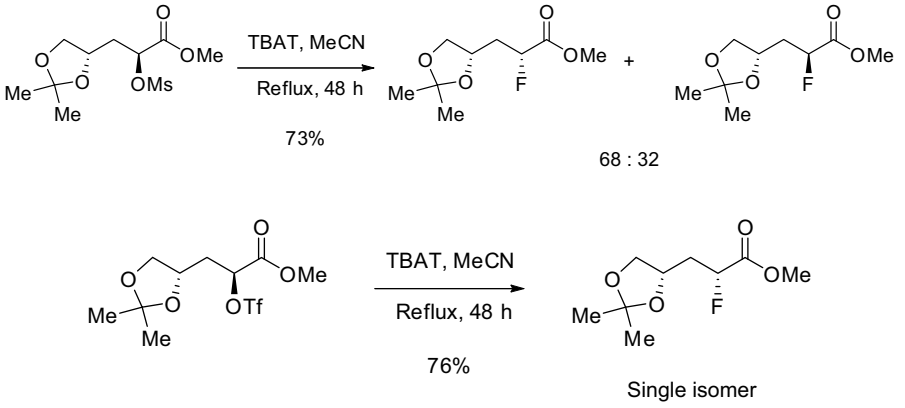


Interestingly, Lepore and coworkers have reported that certain sterically bulky arenesulfonates can be converted to the corresponding chlorides with retention of configuration by treatment with titanium tetrachloride in dichloromethane at −78°C.[161] The method requires the use of an aryl sulfonic acid derivative that is capable of strong coordination to titanium. The authors propose an S_Ni-type mechanism to explain the observed stereochemical outcome.

[159]Jensen, A. E.; Kneisel, F.; Knochel, P. *Org. Synth.* **2003**, *79*, 35–42.
[160]Robins, M. J.; Nowak, I.; Wnuk, S. F.; Hansske, F.; Madej, D. *J. Org. Chem.* **2007**, *72*, 8216–8221.
[161]Lepore, S. D.; Bhunia, A. K.; Mondal, D.; Cohn, P. C.; Lefkowitz, C. *J. Org. Chem.* **2006**, *71*, 3285–3286.



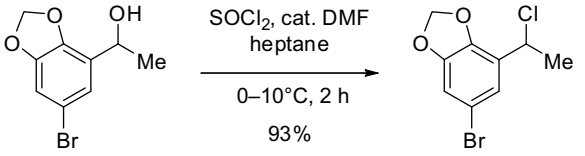
With the steady increase in the number of fluorinated compounds being investigated in the pharmaceutical industry, numerous methods for the nucleophilic introduction of fluorine in a stereo- and regioselective manner have appeared.[162] Both alkali metal fluorides and tetra-*n*-butylammonium fluoride (TBAF) have been utilized successfully, but these reagents suffer from poor solubility and/or high basicity. A more general, albeit expensive, method for the direct nucleophilic displacement of halides (chlorides, bromides, and iodides) and sulfonates was introduced by DeShong and coworkers.[163] As highlighted by the example below, treatment of a diastereomerically pure secondary mesylate with tetra-*n*-butylammonium (triphenylsilyl) difluorosilicate (TBAT) in refluxing acetonitrile provided the secondary fluoride in good yield, albeit as a mixture of diastereomers. Interestingly, when the triflate-leaving group was utilized under identical conditions, the fluoride was obtained as a single syn-diastereoisomer in a slightly improved 76% yield. This result demonstrates that the substitution reaction occurs with clean inversion of stereochemistry and that erosion of diastereomeric purity does not occur via epimerization of the product under the reaction conditions.



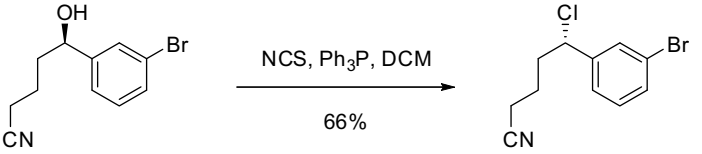
1.5.1.3 Preparation of Alkyl Halides from Alcohols Alcohols can serve as convenient precursors to halides, although direct displacement using hydrohalic acids is not always a practical operation due to competitive elimination and/or incompatibility with common functional groups. Instead, an activation step is carried out that renders the oxygen more reactive toward nucleophilic displacement. For large scale applications, the reagents of choice for conversion of an aliphatic alcohol to its corresponding chloride are typically thionyl chloride, oxalyl chloride, or methanesulfonyl chloride. Each reagent has advantages and disadvantages when cost, atom economy, and handling issues are considered. As a result,

[162]Bohm, H.-J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Muller, K.; Obst-Sander, U.; Stahl, M. *Chembiochem* **2004**, *5*, 637–643.
[163]Pilcher, A. S.; Ammon, H. L.; DeShong, P. *J. Am. Chem. Soc.* **1995**, *117*, 5166–5167.

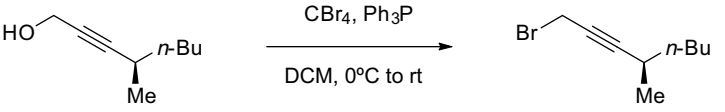
reagent choice is often determined on a case by case basis. The example below highlights the use of thionyl chloride in the presence of catalytic *N,N*-dimethylformamide (DMF) for the high-yielding conversion of a secondary benzylic alcohol to its chloride.[164] The reaction proceeds cleanly in heptane to afford the desired product with minimal manipulation. The workup for this reaction generally involves a slow, cautious addition of water to carefully quench residual thionyl chloride (HCl generation), followed by neutralization, phase separation, and concentration to remove volatiles.



Alternatively, *N*-chlorosuccinimide (NCS) in combination with triphenylphosphine can be used to convert an alcohol to a chloride. The reaction on the chiral secondary alcohol shown below proceeded with inversion of stereochemistry and minimal erosion of enantiomeric excess.[165] In contrast, the use of the more common reagents described above would likely degrade the stereochemical integrity of the chiral center via reaction of the product with excess chloride.



For the simple preparation of alkyl halides from alcohols, few methods are as straightforward and reliable as the Appel reaction.[166] Thus, treatment of an alcohol with carbon tetrabromide and triphenylphosphine provides the corresponding bromide, along with the stoichiometric triphenylphosphine oxide byproduct.[167] However, drawbacks associated with the use of this method include low atom economy, higher relative expense and additional challenges in purging phosphines and phosphine oxides from products. The latter can typically be accomplished via chromatography on silica gel or selective precipitation from a non-polar solvent.



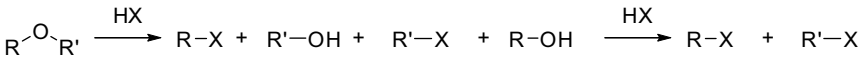
[164]Jacks, T. E.; Belmont, D. T.; Briggs, C. A.; Horne, N. M.; Kanter, G. D.; Karrick, G. L.; Krikke, J. J.; McCabe, R. J.; Mustakis, J. G.; Nanninga, T. N.; Risedorph, G. S.; Seamans, R. E.; Skeean, R.; Winkle, D. D.; Zennie, T. M. *Org. Process Res. Dev.* **2004**, *8*, 201–212.

[165]Merschaert, A.; Boquel, P.; Van Hoeck, J.-P.; Gorissen, H.; Borghese, A.; Bonnier, B.; Mockel, A.; Napora, F. *Org. Process Res. Dev.* **2006**, *10*, 776–783.

[166]Appel, R. *Angew. Chem., Int. Ed. Engl.* **1975**, *87*, 863–874.

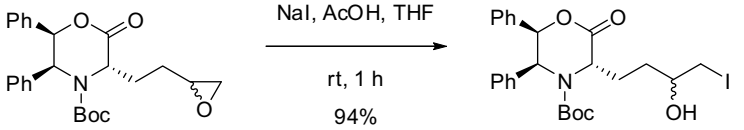
[167]Woodin, K. S.; Jamison, T. F. *J. Org. Chem.* **2007**, *72*, 7451–7454.

1.5.1.4 Preparation of Alkyl Halides from Ethers The action of the strong acids HI[92] and HBr[168] upon ethers provides one molar equivalent of an alkyl halide and another equivalent of an alcohol. If a stoichiometric excess of the acid is employed, the alcohol product is usually converted to its corresponding alkyl halide as well. This method is not commonly utilized to prepare alkyl halides from mixed ethers due to the lack of selectivity in the cleavage to halide and alcohol.

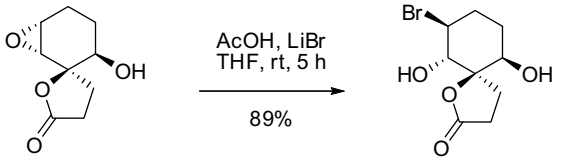


Conversely, there is broad utility for this method in the cleavage of alkyl aryl ethers (anisole derivatives), which liberate the alkyl halide and phenol preferentially (see Section 1.5.1.6). In this case, the goal is deprotection of the phenol rather than synthesis of the alkyl halide, although the latter is a consequence.

1.5.1.5 Preparation of Alkyl Halides from Epoxides Epoxides are commonly prepared via intramolecular nucleophilic displacement of halides by vicinal alcohols (see Section 1.2.2.8). The inverse reaction can also be carried out; epoxides can be opened via nucleophilic attack by halide ions. Allevi reported that the treatment of a terminal epoxide with sodium iodide and acetic acid in tetrahydrofuran provides the primary alkyl iodide (via anti-Markovnikov attack) in high yield at room temperature.[169]

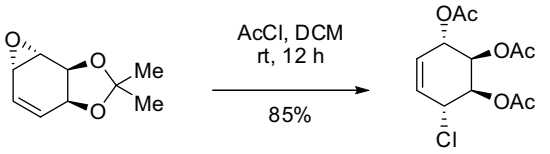


The ring-opening of epoxides with halide salts to produce halohydrins can also be promoted by either Lewis or Brønsted acids. The example below is representative of the stereochemical course of the reaction, which obeys the Fürst-Plattner rule,[170] providing the anti-halohydrin via backside attack on the epoxide.[171] The selectivity for the favored constitutional isomer is controlled in this case by steric factors, although electronic factors can also strongly influence the product distribution. The latter is especially true when strong Lewis or Brønsted acids are employed.

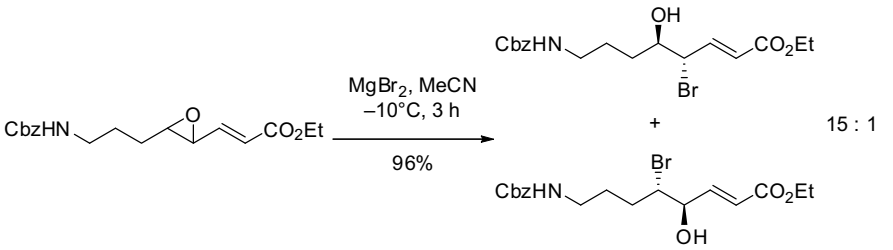


[168]Giles, M. E.; Thomson, C.; Eyley, S. C.; Cole, A. J.; Goodwin, C. J.; Hurved, P. A.; Morlin, A. J. G.; Tornos, J.; Atkinson, S.; Just, C.; Dean, J. C.; Singleton, J. T.; Longton, A. J.; Woodland, I.; Teasdale, A.; Gregertsen, B.; Else, H.; Athwal, M. S.; Tatterton, S.; Knott, J. M.; Thompson, N.; Smith, S. J. *Org. Process Res. Dev.* **2004**, *8*, 628–642.
[169]Allevi, P.; Anastasia, M. *Tetrahedron: Asymmetry* **2004**, *15*, 2091–2096.
[170]Furst, A.; Plattner, P. A. *Helv. Chim. Acta* **1949**, *32*, 275–283.
[171]Eipert, M.; Maichle-Moessmer, C.; Maier, M. E. *Tetrahedron* **2003**, *59*, 7949–7960.

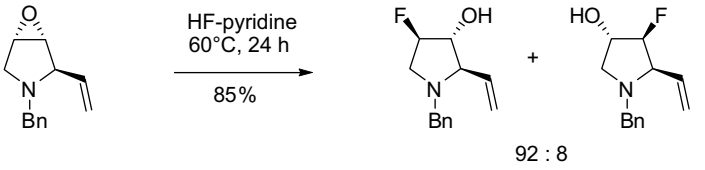
In the interesting example below, from Seçen and coworkers, a cyclic epoxide was opened in a highly stereoselective manner to afford the 1,4-*syn*-haloacetate.[172] The authors proposed that this reaction may proceed through a semi-concerted transition state, where partial acylation of the epoxide occurs concurrently with S_N2' attack of halide ion. Note that under these reaction conditions the acetonide was also converted to a diacetate.



Another example of opening an allylic epoxide with halide ions is shown below.[173] In this case, halohydrin formation was promoted by magnesium bromide in cold acetonitrile. The ratio of isomers is presumably a reflection of increased carbocation stabilization at the allylic position, since sterics would appear to offer little influence.

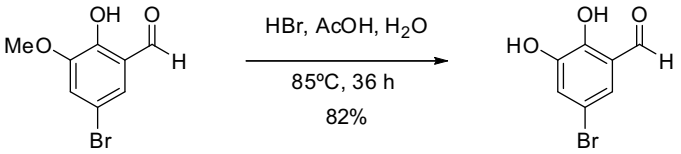


Epoxides can also be ring-opened in a highly stereoselective manner by hydrogen fluoride–pyridine complex.[174] It is notable that preferential attack by fluoride occurred away from the vinyl substituent in this example.

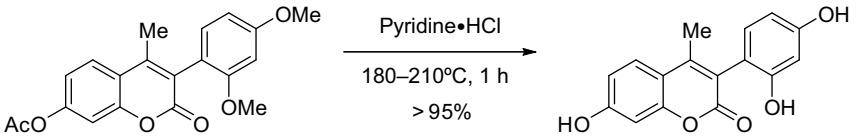


1.5.1.6 Cleavage of Alkyl Ethers with Halide Ion The cleavage of arylmethyl ethers with halide ion to form the corresponding phenols is a common practice in the pharmaceutical industry. In the example below from Jacks and coworkers, hydrogen bromide in acetic acid gave good conversion and high yield of a catechol intermediate.[164]

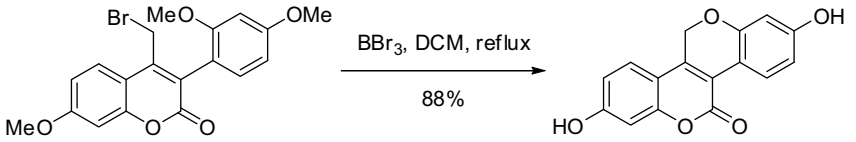
[172]Baran, A.; Kazaz, C.; Secen, H. *Tetrahedron* **2004**, *60*, 861–866.
[173]Ha, J. D.; Kim, S. Y.; Lee, S. J.; Kang, S. K.; Ahn, J. H.; Kim, S. S.; Choi, J.-K. *Tetrahedron Lett*. **2004**, *45*, 5969–5972.
[174]Ayad, T.; Genisson, Y.; Broussy, S.; Baltas, M.; Gorrichon, L. *Eur. J. Org. Chem.* **2003**, 2903–2910.



Hydrogen chloride is generally less effective than hydrogen iodide or hydrogen bromide, although when used as a pyridine salt, high yields have been reported for demethylation of certain anisole derivatives. In the example below, the starting coumarin derivative was treated with pyridine hydrochloride in the absence of solvent at high temperature. The reagent cleaves two methyl ethers and an acetyl-protecting group in excellent yield, although the required reaction temperature was quite high.[175]

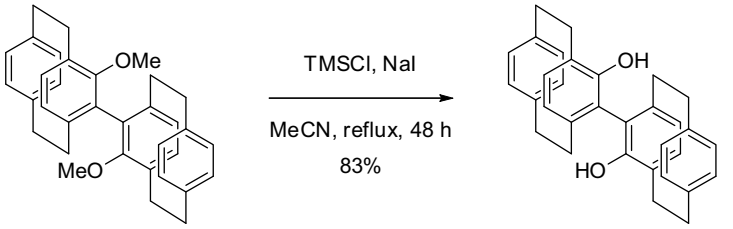


However, the use of strong mineral acids is often incompatible with organic substrates. Therefore, preferable methods for large scale applications often utilize reagents such as boron tribromide,[176] boron trichloride,[177] or aluminum trichloride[164,178] despite the challenges associated with safe handling of these materials. In these reactions, ionization of the departing alcohol is promoted by complexation of the boron or aluminum to the ether oxygen. The use of BBr_3 in dichloromethane has proven to be effective for the cleavage of a range of arylmethyl ethers.[179]



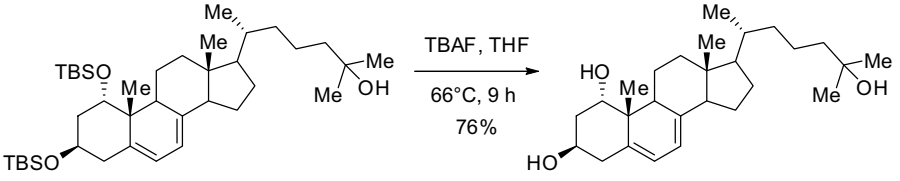
Arylmethyl ethers can also be converted to phenols by treatment with iodotrimethylsilane, which liberates iodomethane as a stoichiometric byproduct. This mild method can be further improved by utilizing the less expensive chlorotrimethylsilane in combination with sodium iodide.[180]

[175]Li, X.; Jain, N.; Russell, R. K.; Ma, R.; Branum, S.; Xu, J.; Sui, Z. *Org. Process Res. Dev.* **2006**, *10*, 354–360.
[176]Lim, C. W.; Tissot, O.; Mattison, A.; Hooper, M. W.; Brown, J. M.; Cowley, A. R.; Hulmes, D. I.; Blacker, A. J. *Org. Process Res. Dev.* **2003**, *7*, 379–384.
[177]Cai, S.; Dimitroff, M.; McKennon, T.; Reider, M.; Robarge, L.; Ryckman, D.; Shang, X.; Therrien, J. *Org. Process Res. Dev.* **2004**, *8*, 353–359.
[178]Haight, A. R.; Bailey, A. E.; Baker, W. S.; Cain, M. H.; Copp, R. R.; DeMattei, J. A.; Ford, K. L.; Henry, R. F.; Hsu, M. C.; Keyes, R. F.; King, S. A.; McLaughlin, M. A.; Melcher, L. M.; Nadler, W. R.; Oliver, P. A.; Parekh, S. I.; Patel, H. H.; Seif, L. S.; Staeger, M. A.; Wayne, G. S.; Wittenberger, S. J.; Zhang, W. *Org. Process Res. Dev.* **2004**, *8*, 897–902.
[179]Zhang, W.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 286–287.
[180]Wack, H.; France, S.; Hafez, A. M.; Drury, W. J., III; Weatherwax, A.; Lectka, T. *J. Org. Chem.* **2004**, *69*, 4531–4533.

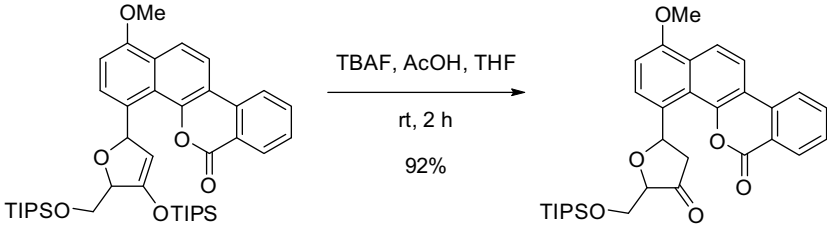


Perhaps the most attractive protocol for demethylation on large scale involves nucleophilic attack on the methyl group by a mild sulfur nucleophile such as methionine[93] or a simple aliphatic thiol.[92] This reaction is discussed in Section 1.3.1.2.

1.5.1.7 Cleavage of Silyl Ethers and Silyl Enol Ethers with Halide Ion Silicon-based protecting groups play a central role in complex target-oriented synthesis. As a result, numerous mild and effective methods have been developed for efficient cleavage of silicon oxygen bonds. Nevertheless, the use of tetra-*n*-butylammonium fluoride (TBAF) remains the most commonly employed reagent for this task. In their multi-kilogram scale preparation of vitamin D_3 analogs, Shimizu and coworkers were successful in removing two TBS-protecting groups in high yield with TBAF in refluxing THF.[181]



If mild reaction temperatures and appropriate stoichiometry are utilized, more labile silyl enol ethers may be selectively cleaved in the presence of a silyl ether with TBAF. The following example is particularly impressive, as the bulky triisopropylsilyl (TIPS) group resides at each position in the starting material.[182]

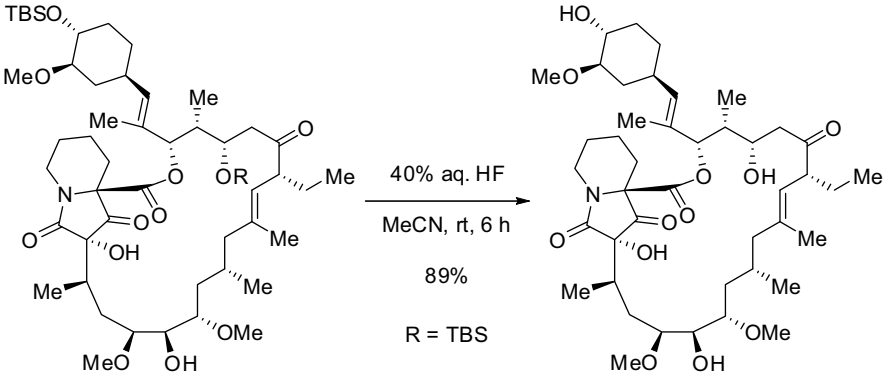


It should be noted that TBAF is strongly basic and is manufactured as a water-wet substance. As a result, the addition of a suitable acid (often acetic acid) is typical when

[181]Shimizu, H.; Shimizu, K.; Kubodera, N.; Mikami, T.; Tsuzaki, K.; Suwa, H.; Harada, K.; Hiraide, A.; Shimizu, M.; Koyama, K.; Ichikawa, Y.; Hirasawa, D.; Kito, Y.; Kobayashi, M.; Kigawa, M.; Kato, M.; Kozono, T.; Tanaka, H.; Tanabe, M.; Iguchi, M.; Yoshida, M. *Org. Process Res. Dev.* **2005**, *9*, 278–287.
[182]Outten, R. A.; Daves, G. D., Jr., *J. Org. Chem.* **1987**, *52*, 5064–5066.

base-sensitive substrates are involved. Furthermore, hydrogen fluoride is a highly toxic and corrosive substance, so extreme caution should be taken to minimize exposure during handling of TBAF or related materials.

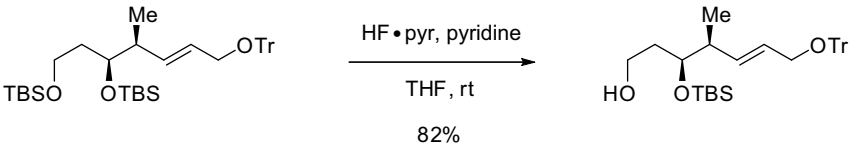
For the desilylation of compounds where high pH must be avoided, the use of aqueous hydrofluoric acid may be considered. In the example below, two secondary TBS ethers are cleaved with high efficiency by utilizing 40% aqueous hydrofluoric acid in acetonitrile at ambient temperature.[183]



It should be noted that HF has been demonstrated to etch glass at low concentrations,[184–187] so care must be taken when choosing equipment for the laboratory or plant. Fluorinated polymers (e.g., Teflon-PTFE) have been shown to offer good corrosion resistance, and are generally the preferred materials of construction for HF-resistant laboratory equipment, while alloys of nickel and copper (e.g., Alloy 400, C71500, C70600, etc.) comprise the preferred materials of construction for commercial reactors that are routinely exposed to hydrofluoric acid.[188]

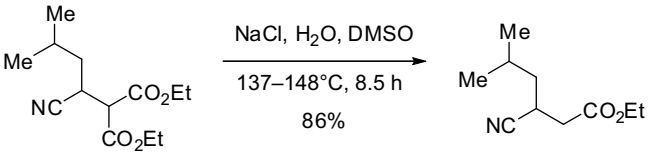
Other attractive options for large scale silyl ether cleavage are triethylamine trihydrofluoride,[189] ammonium bifluoride,[190,191] and hydrogen fluoride–pyridine complex.[65,192] As described in the example below, hydrogen fluoride–pyridine complex has been utilized for the selective cleavage of a primary silyl ether in the presence of a secondary silyl ether in high yield under very mild conditions. The cleavage of silyl ethers with acids or bases in an aqueous or alcoholic environment is discussed in Sections 1.2.1.8 and 1.2.2.6, respectively.

[183]Baumann, K.; Bacher, M.; Steck, A.; Wagner, T. *Tetrahedron* **2004**, *60*, 5965–5981.
[184]Spierings, G. A. C. M. *J. Mater. Sci.* **1993**, *28*, 6261–6273.
[185]Spierings, G. A. C. M. *J. Mater. Sci.* **1991**, *26*, 3329–3336.
[186]Spierings, G. A. C. M.; Van Dijk, J. *J. Mater. Sci.* **1987**, *22*, 1869–1874.
[187]Tso, S. T.; Pask, J. A. *J. Am. Ceram. Soc.* **1982**, *65*, 360–362.
[188]Schillmoller, C. M. *Chem. Eng. Prog.* **1998**, *94*, 49–54.
[189]Joubert, N.; Pohl, R.; Klepetarova, B.; Hocek, M. *J. Org. Chem.* **2007**, *72*, 6797–6805.
[190]Hu, X. E.; Kim, N. K.; Grinius, L.; Morris, C. M.; Wallace, C. D.; Mieling, G. E.; Demuth, T. P., Jr., *Synthesis* **2003**, 1732–1738.
[191]Seki, M.; Kondo, K.; Kuroda, T.; Yamanaka, T.; Iwasaki, T. *Synlett* **1995**, 609–611.
[192]Shin, Y.; Fournier, J.-H.; Brueckner, A.; Madiraju, C.; Balachandran, R.; Raccor, B. S.; Edler, M. C.; Hamel, E.; Sikorski, R. P.; Vogt, A.; Day, B. W.; Curran, D. P. *Tetrahedron* **2007**, *63*, 8537–8562.



1.5.1.8 Cleavage of Carboxylic Acid and Sulfonic Acid Esters with Halide Ion In a series of seminal publications, Krapcho and coworkers reported that heating β-ketoesters, malonate esters, or α-cyanoesters in water-wet dimethylsulfoxide in the presence of chloride or cyanide ions provided the products of dealkoxycarbonylation.[193] A $B_{AL}2$ type mechanism (i.e., nucleophilic attack by chloride on the alkyl group of the ester to provide a sodium carboxylate) is generally accepted, although Krapcho demonstrated that certain dealkoxycarbonylations are more likely to proceed through a $B_{AC}2$ pathway. Dealkoxycarbonylation in the absence of salts was also reported, although both rate and yield improve with added chloride ion for most substrates.[194]

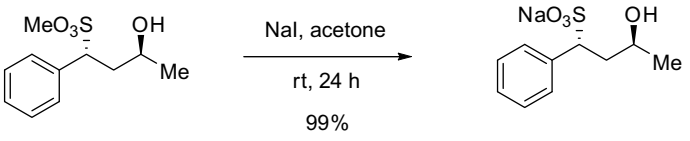
Nonetheless, the "Krapcho decarboxylation" has demonstrated utility in synthetic organic chemistry, as highlighted by the example below from Hoekstra and coworkers during development of a multi-kilogram synthesis of the anticonvulsant pregabalin.[153] The major disadvantage of the classic Krapcho conditions is that a temperature in excess of 130°C is generally required, which presents challenges for substrate compatibility and worker safety on large scale.



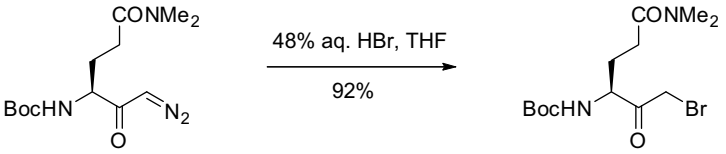
Through related transformations, nucleophilic cleavage of aliphatic esters has also been reported with cyanide[195–198] or thiolate anions.[199–203] These latter methods are typically employed for the ring-opening of cyclic esters (lactones) and therefore incorporate the nucleophiles into the product as nitriles or thioethers, respectively.

Sulfonic acid esters may also be converted to the parent sulfonic acids through nucleophilic attack by halide ion at carbon. In the example below, sodium iodide in acetone solvent provided the sodium sulfonate via a mild, high-yielding transformation.[8]

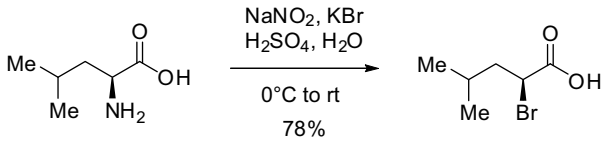
[193]Krapcho, A. P. *Synthesis* **1982**, 893–914.
[194]Krapcho, A. P.; Weimaster, J. F.; Eldridge, J. M.; Jahngen, E. G. E., Jr., ; Lovey, A. J.; Stephens, W. P. *J. Org. Chem.* **1978**, *43*, 138–147.
[195]Stanetty, P.; Froehlich, H.; Sauter, F. *Monatsh. Chem.* **1986**, *117*, 69–88.
[196]Anjanamurthy, C.; Rai, K. M. L. *Indian J. Chem. B Org* **1985**, *24B*, 502–504.
[197]Goya, S.; Takadate, A.; Tanaka, T.; Tsuruda, Y.; Ogata, H. *Yakugaku Zasshi*. **1980**, *100*, 819–825.
[198]Miller, A. W.; Stirling, C. J. M. *J. Chem. Soc., C* **1968**, 2612–2617.
[199]Kelly, T. R.; Dali, H. M.; Tsang, W. G. *Tetrahedron Lett*. **1977**, 3859–3860.
[200]Traynelis, V. J.; Love, R. F. *J. Org. Chem.* **1961**, *26*, 2728–2733.
[201]Kresze, G.; Schramm, W.; Cleve, G. *Chem. Ber.* **1961**, *94*, 2060–2072.
[202]Farrar, M. W. *J. Org. Chem.* **1958**, *23*, 1065–1066.
[203]Gresham, T. L.; Jansen, J. E.; Shaver, F. W.; Bankert, R. A.; Beears, W. L.; Prendergast, M. G. *J. Am. Chem. Soc.* **1949**, *71*, 661–663.



1.5.1.9 Preparation of Halides from α-Diazo Carbonyl Compounds Treatment of α-diazo carbonyl compounds with a haloacid can efficiently provide the α-halo derivative. In the example below, a diazoketone is reacted with aqueous HBr in THF at 0°C to yield the corresponding bromoketone in high yield.[204]



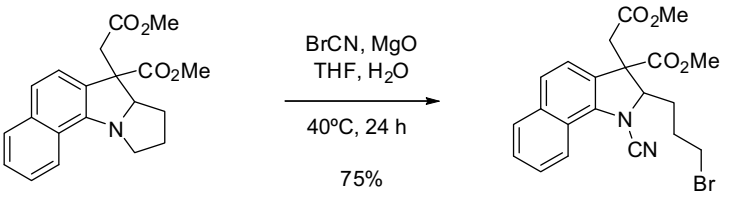
α-Halo carbonyl compounds can also be prepared from α-amine precursors via diazotization *in situ* followed by reaction with a halide. Treatment of the amino carbonyl compound with a halide salt in the presence of sodium nitrite and in aqueous sulfuric acid provides the product at or near room temperature. When applied to α-amino carboxylic acids, this transformation has been shown to proceed in high yields, and with net retention of configuration, as illustrated in the example that follows.[205]



This stereochemical outcome is specific to α-amino acids, as the mechanism involves the intermediacy of an α-lactone. The analogous reaction with amino ketones, esters, or amides would proceed with less stereoselectivity. Complementary methods for the synthesis of α-halo carbonyl compounds are discussed in Section 10.3.3.

1.5.1.10 Preparation of Cyanamides The reaction of an amine with cyanogen bromide yields cyanamide products of the general formula $R^1R^2N{-}CN$. When the reaction is carried out on a tertiary amine, one of the C−N bonds of the initially formed quaternary amine is cleaved through nucleophilic attack at carbon by bromide ion (von Braun reaction).[206] The reaction may be carried out with a wide range of tertiary amines, although at least one substituent on the amine must be aliphatic, as aromatic groups are not cleaved after amine quaternization.[207,208] An illustrative example from Reinhoudt and coworkers is provided below.[209]

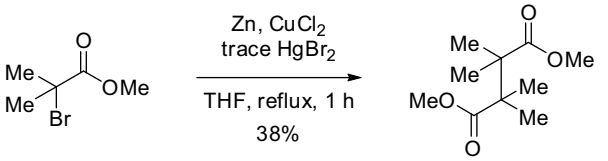
[204]Ramtohul, Y. K.; James, M. N. G.; Vederas, J. C. *J. Org. Chem.* **2002**, *67*, 3169–3178.
[205]Dutta, A. S.; Giles, M. B.; Gormley, J. J.; Williams, J. C.; Kusner, E. J. *J. Chem. Soc., Perkin Trans.* **1987**, *1*, 111–120.
[206]von Braun, J. *Ber. Dtsch. Chem. Ges.* **1900**, *33*, 1438–1452.
[207]Cooley, J. H.; Evain, E. J. *Synthesis* **1989**, 1–7.
[208]Hageman, H. *Organic Reactions (New York)* **1953**, *VII*, 198–262.
[209]Verboom, W.; Visser, G. W.; Reinhoudt, D. N. *Tetrahedron* **1982**, *38*, 1831–1835.



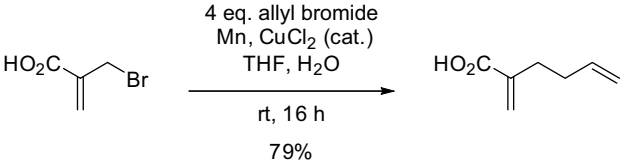
1.6 CARBON NUCLEOPHILES

1.6.1 Attack by Carbon at Alkyl Carbon

1.6.1.1 Direct Coupling of Alkyl Halides The direct coupling of alkyl halides via treatment with a metal or mixture of metals is known as the Wurtz reaction. Although it has been suggested that the initial stages of the Wurtz reaction are radical in nature,[210] the bond formation step is believed to consist of an S_N2 displacement of an alkyl halide with an aliphatic anion.[211] The reaction is not typically amenable to large scale applications, since specialized equipment is required. Furthermore, substrate scope is generally limited to homocoupling of activated halides and yields are typically low to moderate due to competitive alkene formation of the presumed radical intermediate. However, the homocoupled products can be useful, and might otherwise require multi-step synthesis.[212]

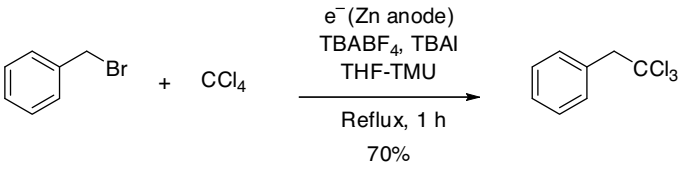


Unsymmetrical Wurtz couplings can be promoted by manganese and copper co-catalysts, as reported by Chan and Ma.[213] It is noteworthy that these reactions are carried out in an aqueous solvent system, thus avoiding the challenges associated with handling moisture sensitive reagents and intermediates. In addition, this methodology proved applicable to unactivated aliphatic alkyl bromides and iodides. In the following example, a significant quantity of 1,5-hexadiene byproduct was formed, which called for a stoichiometric excess of allyl bromide. However, the desired acid could be easily separated from this non-polar hydrocarbon. Note that for this particular substrate, a copper promoted S_N2' displacement of the allylic bromide cannot be ruled out.



[210]Richards, R. B. *Trans. Faraday Soc.* **1940**, *36*, 956–960.
[211]LeGoff, E.; Ulrich, S. E.; Denney, D. B. *J. Am. Chem. Soc.* **1958**, *80*, 622–625.
[212]Fouquey, C.; Jacques, J. *Synthesis* **1971**, 306.
[213]Ma, J.; Chan, T.-H. *Tetrahedron Lett.* **1998**, *39*, 2499–2502.

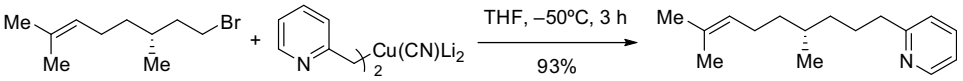
For small scale applications, electrochemical Wurtz coupling methods may be applicable, although specialized equipment is required.[214] For more on the coupling of allylic halides, see Section 1.6.1.3.



1.6.1.2 Reactions of Organometallic Reagents with Alkyl Halides The nucleophilic displacement of an alkyl halide with an organometallic reagent has been the subject of considerable research by the synthetic organic community. A wide variety of organometallic reagents have proven effective for this transformation, and their preparation is the subject of Chapter 12. A concern when choosing the appropriate methodology for a given system is the ability of many organometallic reagents to act as bases; deprotonation of the electrophile can lead to undesired elimination products. The relatively high basicity of alkyl lithium compounds makes their use in halide displacement reactions quite challenging. As a result, transmetallation from readily accessible but somewhat capricious alkyl lithiums to more predictable organometallic derivatives is common.

Perhaps the most highly utilized method was co-developed by the laboratories of Corey, House, Posner, and Whitesides.[215] This method consists of the reaction of a lithium dialkylcuprate (Gilman reagent), formed by treatment of an alkyl lithium with copper iodide in THF at −78°C, with a suitable alkyl halide to afford the desired product. The scope of this methodology is generally limited to primary or activated alkyl halides. A notable drawback to the use of Gilman reagents is that two equivalents of the alkyl lithium are required, but only one equivalent is incorporated into the product.

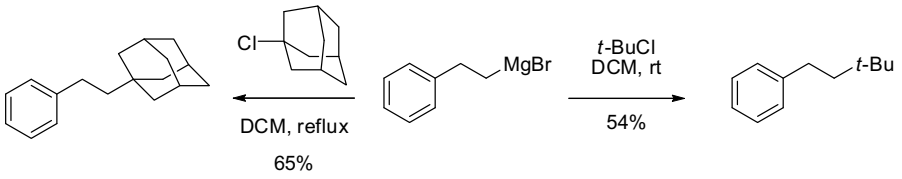
In 1983, Lipshutz and coworkers reported a valuable extension of this method: the facile coupling of higher order cyanocuprates with a range of alkyl halide electrophiles.[216] These reagents have an advantage over traditional Gilman reagents in that they can be prepared from more stable, easily accessible alkyl bromides or chlorides. However, they are somewhat less reactive, so higher than cryogenic temperatures are often utilized for the coupling step. For more on the use of cyanocuprates as nucleophiles, see Section 1.6.1.7. In the example below, a high yield of the substituted pyridine product is obtained after three hours at −50°C in tetrahydrofuran.



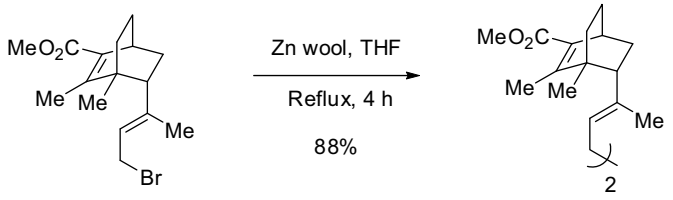
The displacement of alkyl halides with aliphatic Grignard reagents has also been reported, however these methods are often complicated by functional group incompatibility and/or elimination. The use of the non-Lewis basic solvent dichloromethane allowed Eguchi and coworkers to couple Grignard reagents with tertiary halides with

[214]Nedelec, J. Y.; Mouloud, H. A. H.; Folest, J. C.; Perichon, J. *J. Org. Chem.* **1988**, *53*, 4720–4724.
[215]Posner, G. H. *Organic Reactions (New York)* **1975**, *22*, 253–400.
[216]Lipshutz, B. H.; Parker, D.; Kozlowski, J. A.; Miller, R. D. *J. Org. Chem.* **1983**, *48*, 3334–3336.

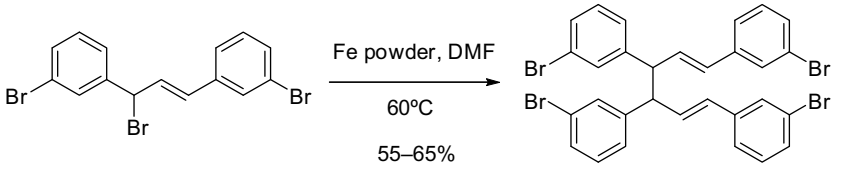
moderate success.[217] The authors suspect competitive elimination was responsible for the lower yield observed with *t*–butyl chloride; elimination is prohibited by Bredt's rule for adamantyl chloride. A single electron transfer (radical) mechanism likely competes with an S_N2 pathway for these substrates.



1.6.1.3 Couplings of Allylic and Propargylic Halides Allylic and propargylic halides are reactive electrophiles due to their ability to offer resonance stabilization to growing positive charge at the allylic/propargylic carbon during ionization of the carbon−halogen bond. This effect also allows for insertion of low valent metals into the carbon−halogen bond, which produces nucleophilic organometallic compounds. As a result, the addition of a metal in its lowest oxidation state, such as zinc, magnesium, or iron, to a solution of an allylic or propargylic halide will typically yield significant quantities of dimerization products (Wurtz coupling).[218]



The example below illustrates that this reductive dimerization is also effective with secondary allylic halides, although the rate and yield often decline for such systems.[219]

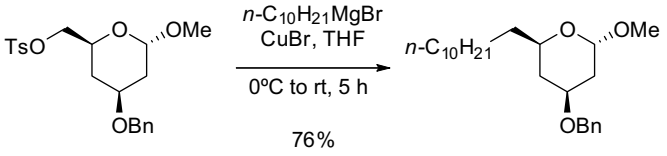


For an additional example of the Wurtz coupling of an allylic halide, see Section 1.6.1.1.

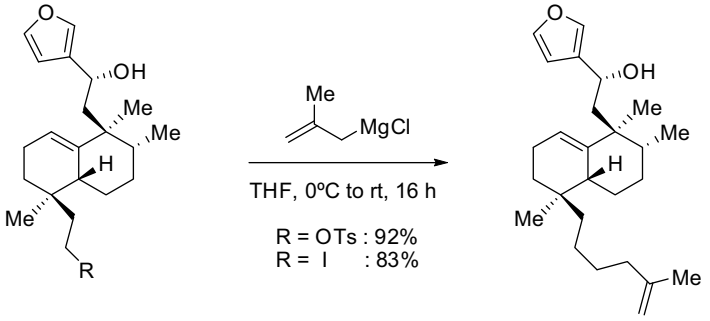
1.6.1.4 Couplings of Organometallic Reagents with Sulfonate Esters Most organometallic carbon nucleophiles (Grignards, cuprates, etc.) react with aliphatic sulfonate ester electrophiles in a manner analogous to that observed with alkyl halides

[217]Ohno, M.; Shimizu, K.; Ishizaki, K.; Sasaki, T.; Eguchi, S. *J. Org. Chem.* **1988**, *53*, 729–733.
[218]Rao, G. S. R. S.; Bhaskar, K. V. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2813–2816.
[219]Voegtle, F.; Eisen, N.; Franken, S.; Buellesbach, P.; Puff, H. *J. Org. Chem.* **1987**, *52*, 5560–5564.

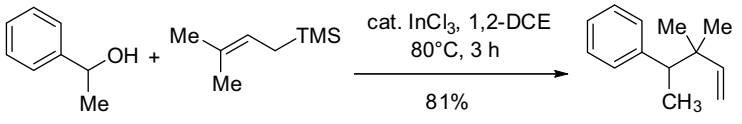
(see Section 1.6.1.2). In the example below, an aliphatic Grignard reagent is modified by the addition of copper(I) bromide to allow smooth displacement of a primary tosylate in tetrahydrofuran at ambient temperature.[220]



Grignard reagents are frequently used without conversion to copper complexes in cases where allylic or propargylic carbon nucleophiles are involved. In the example below, a high yield of the alkylation product was obtained under mild conditions when an excess of 2-methallylmagnesium chloride was allowed to react with either the primary tosylate or iodide.[221] Benzenesulfonate derivatives typically outperform mesylates, as the latter contain acidic α-protons that may quench basic carbon nucleophiles.



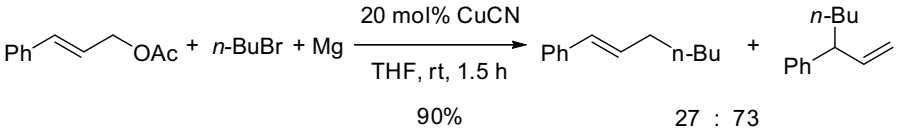
1.6.1.5 Couplings Involving Alcohols Because hydroxide ion is a relatively poor leaving group, the direct S_N2 displacement at an alcohol-bearing carbon center is rare. Instead, alcohols are typically subjected to an activation step such as conversion to the corresponding halide[164] or inorganic ester[50–52,222](see Sections 1.5.1.3 and 1.7.1.2). A few methods for direct alcohol displacement have been reported, however. One particularly mild method, the treatment of benzylic alcohols with a catalytic quantity of $InCl_3$ (5 mol%) in the presence of allyl, propargyl, or alkynyl silanes, was reported by Baba and coworkers.[223]



[220]Yadav, J. S.; Rao, K. V.; Prasad, A. R. *Synthesis* **2006**, 3888–3894.
[221]Marcos, I. S.; Pedrero, A. B.; Sexmero, M. J.; Diez, D.; Basabe, P.; Garcia, N.; Moro, R. F.; Broughton, H. B.; Mollinedo, F.; Urones, J. G. *J. Org. Chem.* **2003**, *68*, 7496–7504.
[222]Shan, Z.; Xiong, Y.; Zhao, D. *Tetrahedron* **1999**, *55*, 3893–3896.
[223]Yasuda, M.; Saito, T.; Ueba, M.; Baba, A. *Angew. Chem., Int. Ed. Engl.* **2004**, *43*, 1414–1416.

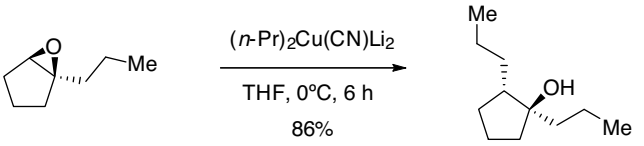
Aliphatic Grignard reagents have also been coupled with alcohols in the presence of titanium(IV) isopropoxide, although scope appears to be limited to activated (e.g. allylic) alcohols.[224]

1.6.1.6 Reactions of Organometallic Reagents with Allylic Esters and Carbonates Allylic esters and carbonates possess unique reactivity amongst aliphatic electrophiles in that they may be alkylated at either the 1- or 3-position of the allylic system via formal S_N2 or S_N2' displacement of the leaving group. In the absence of a catalyst, the two modes of attack may be competitive, resulting in a product distribution that varies with substrate. In the example below, an allylic acetate was reacted with *n*-butyl magnesium bromide in the presence of CuCN to yield a mixture of regioisomers favoring the branched (S_N2'-type) alkylation product.[225]



More commonly, reactions of allylic electrophiles are catalyzed by an organometallic complex that provides a π-allyl intermediate via oxidative addition. The choice of metal and ligand set influences the sterics and electronics of the π-allyl intermediate, and therefore, the product distribution. The metal-catalyzed allylic substitution reaction falls outside the scope of this chapter, but is discussed thoroughly within Section 6.8.

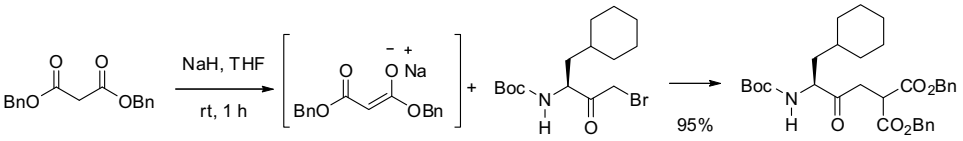
1.6.1.7 Reactions of Organometallic Reagents with Epoxides The opening of epoxides with non-enolate carbon nucleophiles is most reliably carried out with higher order mixed organocuprate reagents "$R_2Cu(CN)Li_2$" generated *in situ* from two equivalents of the corresponding organolithium and one equivalent of copper cyanide, as reported by Lipshutz and coworkers. These reagents often outperform the related Gilman-type reagents "R_2CuLi" and "RCu(CN)Li", presumably due to decreased basicity and enhanced nucleophilicity. Furthermore, cyanocuprates exhibit increased thermal stability compared to classical Gilman reagents, which allows reactions to be carried out at or above ambient temperature. In the example below, the reagent generated from *n*-propyllithium and copper cyanide provided the desired ring-opened product in high yield under mild conditions in THF. The same transformation carried out with *n*-PrCu(CN)Li proceeded in only 15% to 30% yield, and required ethyl ether solvent to minimize competitive reagent complexation with the THF solvent.[226]



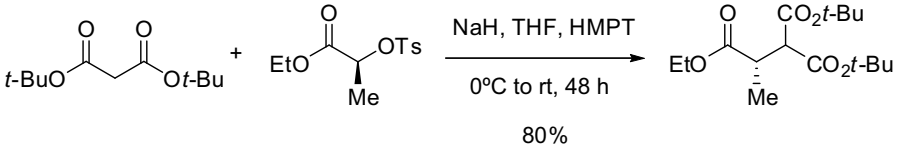
[224]Kulinkovich, O. G.; Epstein, O. L.; Isakov, V. E.; Khmel'nitskaya, E. A. *Synlett* **2001**, 49–52.
[225]Erdik, E.; Kocoglu, M. *Tetrahedron Lett*. **2007**, *48*, 4211–4214.
[226]Lipshutz, B. H.; Kozlowski, J.; Wilhelm, R. S. *J. Am. Chem. Soc.* **1982**, *104*, 2305–2307.

1.6.1.8 Alkylation of Malonate and Acetoacetate Derivatives A carbon bearing at least one hydrogen atom and two to three electronegative substituents can be deprotonated to provide a stabilized carbanion that may be alkylated with a broad range of electrophiles under very mild conditions. The most common examples in this class are resonance stabilized salts of malonic acid derivatives (e.g., dimethylmalonate) and acetoacetate esters (e.g., ethyl acetoacetate). These compounds have found broad utility in transition metal-catalyzed allylic alkylation methodology pioneered by Tsuji[227,228] and Trost[229] as well as in the Knoevenagel condensation[230] to provide α,β-unsaturated carbonyl compounds. These reactions fall outside the scope of this chapter, but are discussed in Chapters 2 and 6, respectively.

Salts of β-dicarbonyl compounds can also be alkylated with alkyl halides,[231] epoxides,[232] and alkyl sulfonates.[233] In the representative example below, dibenzyl malonate was treated with sodium hydride in THF to provide a sodio-malonate that reacted with an alkyl bromide in high yield.[231]



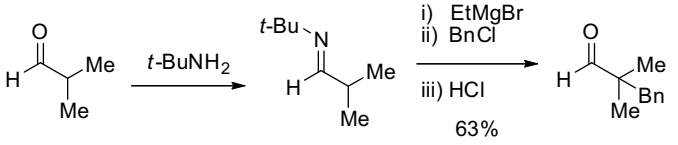
In the second example, an enantiomerically enriched secondary tosylate is displaced by the sodium salt of di-*tert*-butyl malonate to provide the alkylation product in good yield. The product was formed with clean inversion of stereochemistry, in support of an S_N2 mechanism.



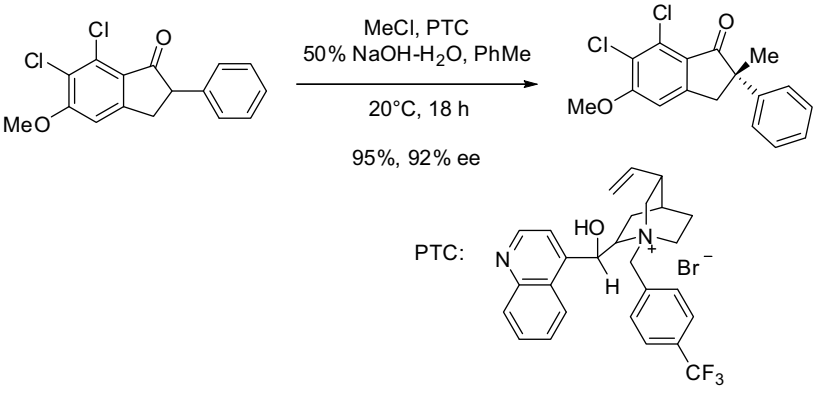
1.6.1.9 Alkylation of Aldehydes, Ketones, Nitriles, and Carboxylic Esters The α-alkylation of aldehyde enolates is plagued by self condensation byproducts, as aldehydes are reactive electrophiles. An elegant solution was introduced by Stork, as highlighted by the example below.[234] Condensation of an enolizable aldehyde with a primary amine provides the corresponding imine, which is far less prone to self condensation. Subjecting the imine to reaction with a base provides the metalated enamine, which can be reacted with mild electrophiles such as alkyl halides. Of

[227]Minami, I.; Shimizu, I.; Tsuji, J. *J. Organomet. Chem.* **1985**, *296*, 269–280.
[228]Tsuji, J. *Organic Synthesis with Palladium Compounds*; Springer-Verlag: Berlin, **1980**.
[229]Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4730–4743.
[230]Davis, A. P.; Egan, T. J.; Orchard, M. G.; Cunningham, D.; McArdle, P. *Tetrahedron* **1992**, *48*, 8725–8738.
[231]Kaltenbronn, J. S.; Hudspeth, J. P.; Lunney, E. A.; Michniewicz, B. M.; Nicolaides, E. D.; Repine, J. T.; Roark, W. H.; Stier, M. A.; Tinney, F. J.;et al. *J. Med. Chem.* **1990**, *33*, 838–845.
[232]Takasu, H.; Tsuji, Y.; Sajiki, H.; Hirota, K. *Tetrahedron* **2005**, *61*, 8499–8504.
[233]Larcheveque, M.; Petit, Y. *Synthesis* **1991**, 162–164.
[234]Stork, G.; Dowd, S. R. *Org. Synth.* **1974**, *54*, 46–49.

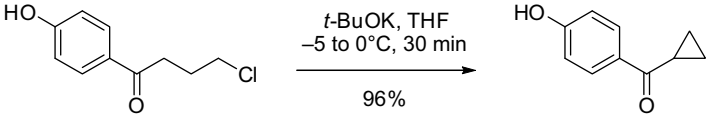
particular note is that ethyl magnesium bromide is employed as a base in this particular example, and no addition of the Grignard reagent to the imine is observed. The resulting bromomagnesium counterion works in combination with the bulky *t*-butyl substituent on the imine nitrogen to provide excellent C- versus N-alkylation selectivity. A simple aqueous hydrochloric acid workup hydrolyzes the imine to release the aldehyde function for further elaboration.



In what has become the definitive example of stereocontrolled enolate alkylation under chiral phase transfer catalysis, Dolling and coworkers reported the following enantioselective methylation of an aryl ketone enolate.[235] The cinchona alkaloid-derived phase transfer catalyst blocks one face of the enolate to provide a substantial rate advantage over the racemic background alkylation. In their account of this work, Dolling and coworkers reported that several variables, including solvent polarity, reaction concentration, sodium hydroxide concentration, and catalyst loading were critical to optimizing yield and enantioselectivity.

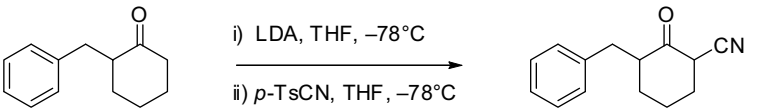


Ketone enolates are readily generated by treatment with strong base.[68,69] When only one enolate is possible, as is the case with aryl ketones, a wide variety of bases can be used. In the example below, a chloroketone was treated with two equivalents of potassium *t*-butoxide in THF, to promote intramolecular alkylation and provide the cyclopropyl ketone in excellent yield.[236]



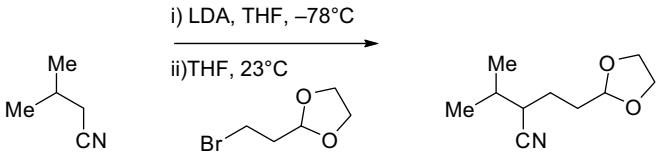
[235]Dolling, U. H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1984**, *106*, 446–447.
[236]Chang, S.-J.; Fernando, D. P.; King, S. *Org. Process Res. Dev.* **2001**, *5*, 141–143.

The generation and cyanation of ketone enolates obtained by treatment with lithium diisopropylamide in THF at −78°C has been reported by Kahne and Collum.[237] The use of *p*-toluenesulfonyl cyanide as the cyanide source proved to be critical, as did inverse addition of the enolate into a cold THF solution of *p*-TsCN. For more on the addition of carbon-based nucleophiles to nitriles see Section 2.39.



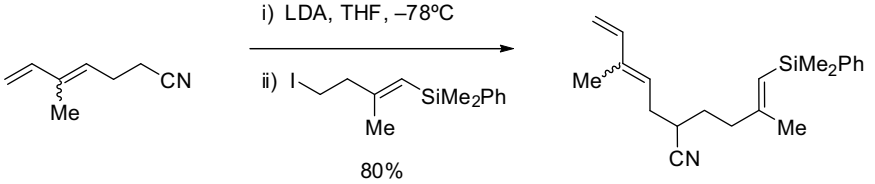
67%

It is also possible to deprotonate the position α to an aliphatic nitrile with LDA. In the example below, reaction of the deprotonated nitrile with an alkyl bromide provided the expected alkylation product in good yield.[238]



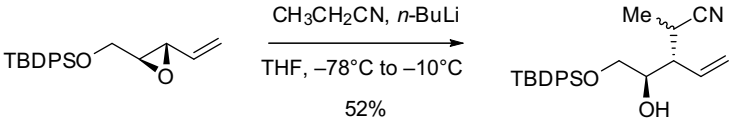
85%

The alkylation of nitriles is often complicated by incomplete conversion and over-alkylation. In the following example from Taber and coworkers, however, a rather complex nitrile is further elaborated via deprotonation with LDA at −78°C, and subsequent treatment with an alkyl iodide.[239]



80%

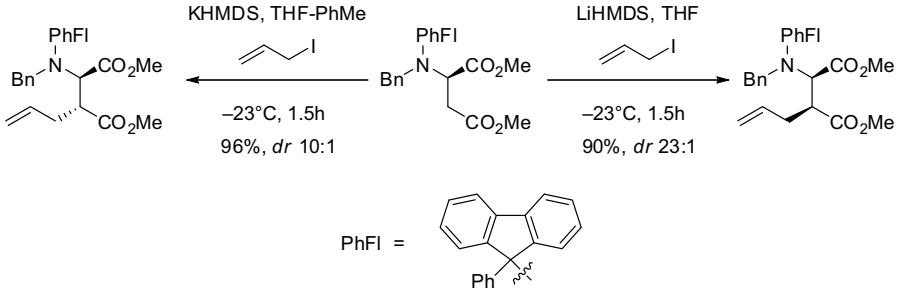
Taber and coworkers have also reported on the use of epoxides for the alkylation of nitrile enolates. In the example shown below, *n*-butyllithium is utilized for the deprotonation step, and an allylic epoxide serves as the electrophile. Of note is the apparent lack of regioisomeric products that could arise from attack at the other epoxide-bearing carbon or the less-substituted allylic terminus (S_N2').[240]



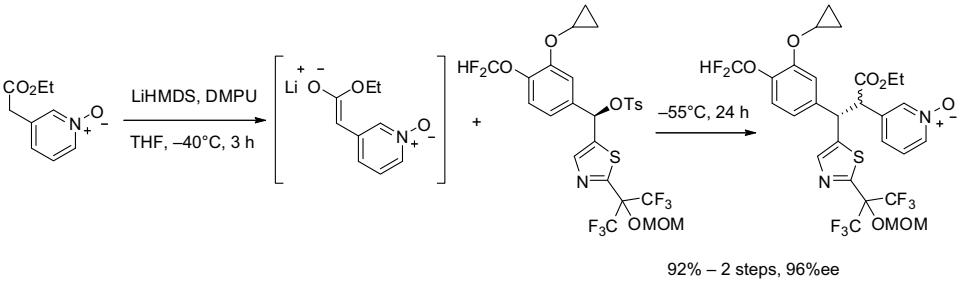
52%

[237]Kahne, D.; Collum, D. B. *Tetrahedron Lett.* **1981**, *22*, 5011–5014.
[238]Wu, L.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 15824–15832.
[239]Taber, D. F.; Bhamidipati, R. S.; Yet, L. *J. Org. Chem.* **1995**, *60*, 5537–5539.

The use of strong bases derived from hexamethyldisilazane is becoming increasingly popular for both small and large scale applications. The lithium, sodium, and potassium hexamethyldisilazides are relatively stable, commercially available materials, and provide a convenient option for investigating counterion effects on rate and/or selectivity in a given reaction. In the example below, lithium hexamethyldisilazide (LiHMDS) in THF was employed for the selective formation of the kinetically favored (*Z*)-ester enolate at a temperature of −23°C. The subsequent addition of allyl iodide provided a 23:1 ratio of diastereoisomers in excellent yield.[241] Interestingly, potassium hexamethyldisilazide (KHMDS) also provided the (*Z*)-ester enolate, although the opposite diastereoisomer was favored during the alkylation. The authors propose an internal ester chelation mechanism for the potassium enolate that is not operable for the lithium enolate.

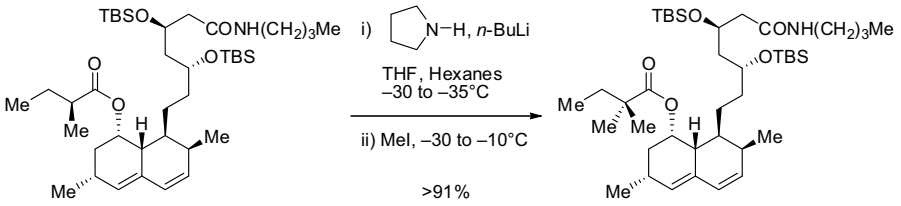


LiHMDS in THF/DMPU has been used for an ester enolate formation on multi-kilogram scale. The enolization and subsequent tosylate displacement were carried out below −40°C in order to conserve the stereochemical integrity of the benzylic chiral center.[242]

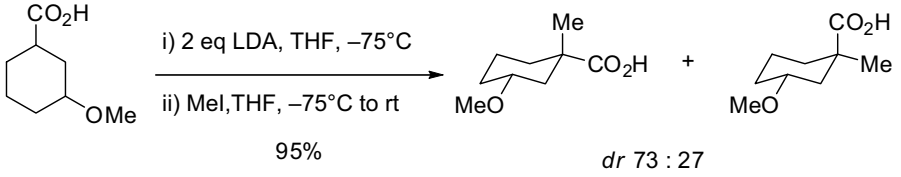


In a process to the HMG CoA reductase inhibitor simvastatin, lithium pyrrolidide has been used as a base for ester enolization, which allowed for the introduction of a challenging acyclic geminal methyl substituent.[243] Of significance is the lack of competitive amide methylation observed under these conditions. The authors were able to optimize reaction temperature and methyl iodide stoichiometry to minimize this side reaction, presumably aided by the high pK_a of the amide α-protons after initial lithium imidate formation.

[241]Humphrey, J. M.; Bridges, R. J.; Hart, J. A.; Chamberlin, A. R. *J. Org. Chem.* **1994**, *59*, 2467–2472.
[242]O'Shea, P. D.; Chen, C.-Y.; Chen, W.; Dagneau, P.; Frey, L. F.; Grabowski, E. J. J.; Marcantonio, K. M.; Reamer, R. A.; Tan, L.; Tillyer, R. D.; Roy, A.; Wang, X.; Zhao, D. *J. Org. Chem.* **2005**, *70*, 3021–3030.
[243]Askin, D.; Verhoeven, T. R.; Liu, T. M. H.; Shinkai, I. *J. Org. Chem.* **1991**, *56*, 4929–4932.



1.6.1.10 Alkylation of Carboxylic Acid Salts The action of two equivalents of strong base on carboxylic acids produces a dianion that is capable of reaction with electrophiles to provide α-substitution products (the Krapcho method).[244] Although the second deprotonation is considerably more challenging than the initial carboxylate salt formation, aggregate effects render the effective pK_a of lithium carboxylates in THF solvent just a few units higher than the corresponding carboxylic esters.[245] In the example below, treatment of an enolizable carboxylic acid with two equivalents of lithium diisopropylamide (LDA) at −75°C in THF provided the dianion. Subsequent addition of methyl iodide, followed by a hydrolytic workup, afforded the α-methylation products in high yield as a mixture of diastereoisomers favoring axial substitution.[246]

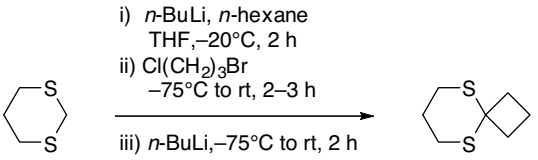


1.6.1.11 Alkylation α to a Heteroatom In a series of seminal publications, Corey and Seebach described the use of 1,3-dithianes as acyl anion synthons.[247–249] Soon after, Seebach introduced the term *umpolung* (German for "reversed polarity"), whereby a chemical transformation carried out on a functional group changes the inherent reactive polarity of that group. The use of dithianes as umpolung synthons has been reviewed.[250,251]

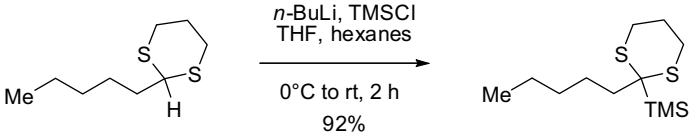
The example below clearly illustrates the umpolung concept, as the carbon in the 2-position of the starting 1,3-dithiane is derived from formaldehyde, which is typically electrophilic at carbon. Through conversion to the dithiane and deprotonation with *n*-butyllithium, this carbon becomes a nucleophilic center. Subsequent addition of 1-bromo-3-chloropropane provides the 3-chloropropyl alkylation product. In this example, another charge of *n*-BuLi addition led to intramolecular alkylation, which afforded dithiane-protected cyclobutanone in good yield. One major drawback of this methodology is the typical use of mercury(II) salts to promote conversion of the dithiane to the free

[244]Krapcho, A. P.; Dundulis, E. A. *Tetrahedron Lett.* **1976**, 2205–2208.
[245]Gronert, S.; Streitwieser, A. *J. Am. Chem. Soc.* **1988**, *110*, 4418–4419.
[246]Krapcho, A. P.; Dundulis, E. A. *J. Org. Chem.* **1980**, *45*, 3236–3245.
[247]Corey, E. J.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 1075–1077.
[248]Corey, E. J.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 1077–1078.
[249]Corey, E. J.; Seebach, D. *Org. Synth.* **1970**, *50*, 72–74.
[250]Groebel, B. T.; Seebach, D. *Synthesis* **1977**, 357–402.
[251]Seebach, D. *Synthesis* **1969**, *1*, 17–36.

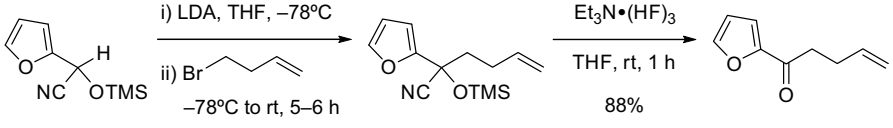
carbonyl.[252,253] However, a handful of alternative methods for this conversion have been reported.[254,255] For more on the oxidation of sulfides, see Section 10.8.5.



The dithiane alkylation reaction can also be used for the preparation of acyl silanes for further elaboration.[256] As described in the following scheme, the dithiane was deprotonated at the 2-position by *n*-BuLi in THF-hexanes and then reacted with chlorotrimethylsilane to afford the quaternary silane product in excellent yield.



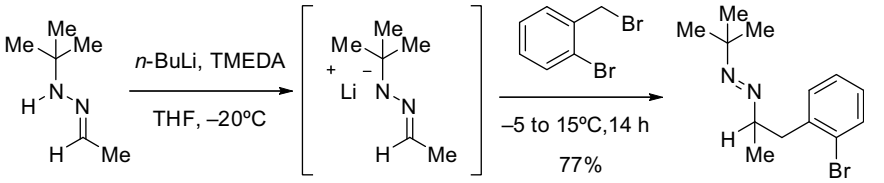
C-alkylation of trimethylsilyl cyanohydrins has emerged as an excellent method for homologation of aldehydes at the carbonyl carbon. As described in the example below, the TMS cyanohydrin prepared from furfuraldehyde and trimethylsilyl cyanide was treated with LDA at low temperature in THF to afford the carbon-centered anion. The addition of 4-bromo-1-butene followed by warming to room temperature provided the C-alkylated product in excellent yield. The cyanohydrin product was then subjected to triethylamine trihydrofluoride, which led to desilylation and loss of cyanide, and provide the ketone in high yield.[257]



Hydrazones have also been shown to be effective acyl anion equivalents, as highlighted by the pioneering work of Baldwin[258–260] and coworkers. In the example below, the *t*-butyl

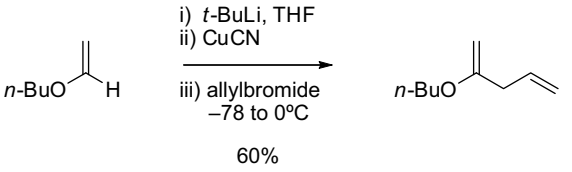
[252]Seebach, D.; Beck, A. K. *Org. Synth.* **1971**, *51*, 76–81.
[253]Manaviazar, S.; Frigerio, M.; Bhatia, G. S.; Hummersone, M. G.; Aliev, A. E.; Hale, K. J. *Org. Lett.* **2006**, *8*, 4477–4480.
[254]Firouzabadi, H.; Hazarkhani, H.; Hassani, H. *Phosphorus, Sulfur Silicon Relat. Elem.* **2004**, *179*, 403–409.
[255]Walsh, L. M.; Goodman, J. M. *Chem. Commun.* **2003**, 2616–2617.
[256]Huckins, J. R.; Rychnovsky, S. D. *J. Org. Chem.* **2003**, *68*, 10135–10145.
[257]Fischer, K.; Huenig, S. *J. Org. Chem.* **1987**, *52*, 564–569.
[258]Baldwin, J. E.; Adlington, R. M.; Bottaro, J. C.; Jain, A. U.; Kohle, J. N.; Perry, M. W. D.; Newington, I. M. *J. Chem. Soc., Chem. Commun.* **1984**, 1095–1096.
[259]Baldwin, J. E.; Adlington, R. M.; Bottaro, J. C.; Kolhe, J. N.; Perry, M. W. D.; Jain, A. U. *Tetrahedron* **1986**, *42*, 4223–4234.
[260]Baldwin, J. E.; Adlington, R. M.; Newington, I. M. *J. Chem. Soc., Chem. Commun.* **1986**, 176–178.

hydrazone of acetaldehyde was treated with *n*-butyllithium in THF to provide the expected lithiated intermediate at −20°C. Subsequent reaction with *o*-bromobenzylbromide at 15°C provided exclusively the product of C-alkylation in 77% yield.[261] Use of the sterically bulky *tert*-butyl substituent minimizes competitive N-alkylation.



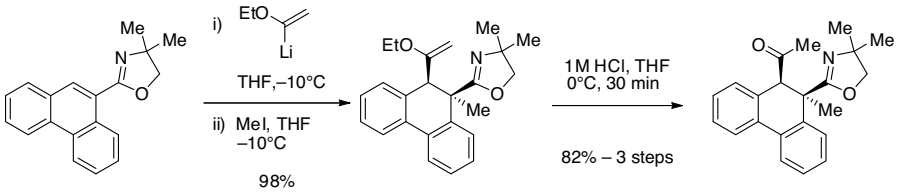
Dieter and coworkers have extended this methodology through the use of organocuprates derived from lithiated hydrazones in reactions with Michael acceptors. This reaction is useful for the preparation of β-substituted carbonyl compounds.[262] The use of copper additives enhances the selectivity for C- versus N-alkylation of these ambident nucleophiles, and expands the substrate scope to include cyclic α,β-unsaturated ketones.

Alkoxy vinyl lithium reagents are another useful class of acyl anion equivalents. First reported by Baldwin and coworkers, the methyl enol ether of acetaldehyde can be deprotonated with *tert*-butyl lithium at the vinyl carbon-bearing oxygen.[263] The resulting vinyl anions can be alkylated with various electrophiles. Both *tert*-butyl lithium and alkoxy vinyl lithium reagents are highly reactive substances, which may limit practical use on a large scale; however a number of improvements to the original synthesis of these reagents have been made and several useful applications have been reported. In the example below from Denmark and coworkers, *n*-butyl vinyl ether is deprotonated with *tert*-butyllithium in tetrahydrofuran. Following transmetallation with CuCN the resulting vinyl cuprate was treated with allyl bromide to afford the alkylation product in good yield.[264]



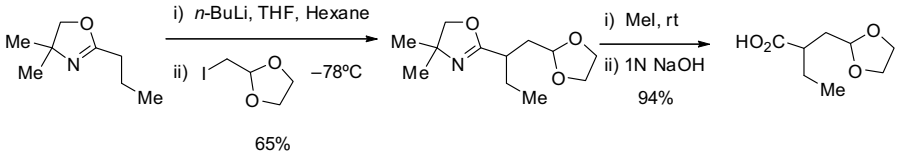
Meyers and coworkers have communicated that the use of tetrahydropyran (THP) is superior to THF for the efficient preparation of these reagents via deprotonation by *t*-BuLi.[265] Meyers' group has also demonstrated the utility of α-ethoxyvinyl lithium in a diastereoselective conjugate addition to α,β-unsaturated oxazolines. Although not an aliphatic nucleophilic substitution reaction, an example is provided below for illustrative purposes.[266] The addition of carbon nucleophiles to polarized carbon−carbon multiple bonds is the subject of Section 3.5.

[261]Wang, S. F.; Warkentin, J. *Can. J. Chem.* **1988**, *66*, 2256–2258.
[262]Alexander, C. W.; Lin, S.-Y.; Dieter, R. K. *J. Organomet. Chem.* **1995**, *503*, 213–220.
[263]Baldwin, J. E.; Hoefle, G. A.; Lever, O. W., Jr., *J. Am. Chem. Soc.* **1974**, *96*, 7125–7127.
[264]Denmark, S. E.; Guagnano, V.; Dixon, J. A.; Stolle, A. *J. Org. Chem.* **1997**, *62*, 4610–4628.
[265]Shimano, M.; Meyers, A. I. *Tetrahedron Lett*. **1994**, *35*, 7727–7730.
[266]James, B.; Meyers, A. I. *Tetrahedron Lett*. **1998**, *39*, 5301–5304.



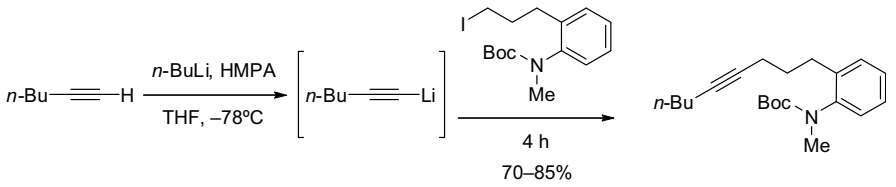
Alkoxyvinyl lithium derivatives have also found utility in nucleophilic additions to carbonyl centers such as carboxylic esters.[267]

1.6.1.12 Alkylation α to a Masked Carboxylic Acid Elaboration at the α-position of carboxylic acid derivatives has been the subject of considerable research. Although much has been reported on the direct alkylation of carboxylate dianions, it is often preferable to employ carboxylic acid surrogates in bond forming operations and then deprotect later in a multi-step synthesis. In a series of seminal publications, Meyers and coworkers introduced 2-substituted–4,4-dimethyloxazolines as carboxylic acid synthons that can be easily elaborated via alkylation of their stabilized anion derivatives. The following example illustrates the deprotonation of 2-propyl oxazoline by *n*-butyllithium, followed by reaction with an alkyl iodide to provide the alkylated product.[268] The carboxylic acid moiety can be conveniently liberated under either acidic (3N HCl) or alkaline (MeI, then 1N NaOH) conditions. The latter method was utilized here to preserve the acid sensitive acetal functionality.

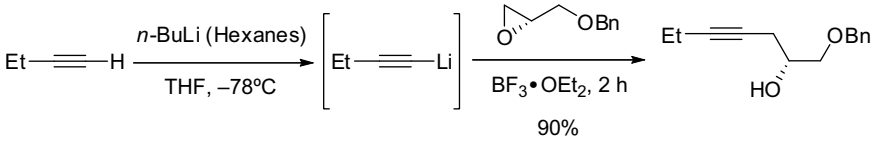


1.6.1.13 Alkylation at Alkynyl Carbon Terminal alkynes can be converted to their acetylide anions by deprotonation with a strong base such as *n*-butyllithium. The acetylide formation and subsequent reaction with electrophiles are typically carried out in THF at temperatures near −78°C. In a few cases, additives such as HMPA or DMPU[269] are included to accelerate the overall reaction rate via coordination to lithium cations, resulting in deaggregation. An interesting study on the implications of HMPA additives on solution kinetics has been reported.[270] It should be noted that HMPA is a demonstrated health hazard and extreme care should be taken to avoid exposure during handling. If a strongly coordinating additive is desired, DMPU should be used preferentially, due to a superior safety profile. The following example is demonstrative of typical conditions for deprotonation and alkylation of terminal alkynes.[271]

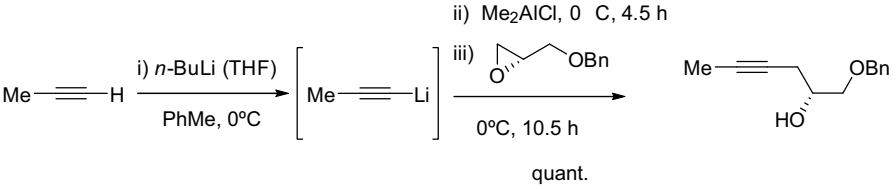
[267]Li, Y.; Drew, M. G. B.; Welchman, E. V.; Shirvastava, R. K.; Jiang, S.; Valentine, R.; Singh, G. *Tetrahedron* **2004**, *60*, 6523–6531.
[268]Meyers, A. I.; Temple, D. L.; Nolen, R. L.; Mihelich, E. D. *J. Org. Chem.* **1974**, *39*, 2778–2783.
[269]Mukhopadhyay, T.; Seebach, D. *Helv. Chim. Acta* **1982**, *65*, 385–391.
[270]Collum, D. B.; McNeil, A. J.; Ramirez, A. *Angew. Chem., Int. Ed. Engl.* **2007**, *46*, 3002–3017.
[271]Patil, N. T.; Wu, H.; Yamamoto, Y. *J. Org. Chem.* **2007**, *72*, 6577–6579.



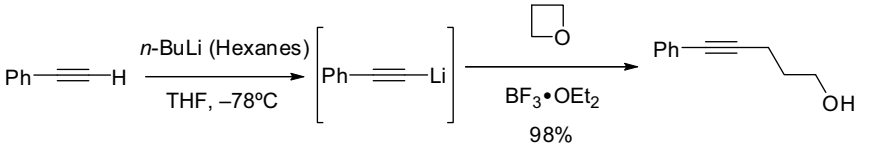
Epoxides are also suitable alkylating agents for lithium acetylides when the reaction is carried out in the presence of an oxophilic Lewis acid. In the example below, nucleophilic attack occurred at the less sterically encumbered position in the presence of boron trifluoride diethyl etherate.[272]



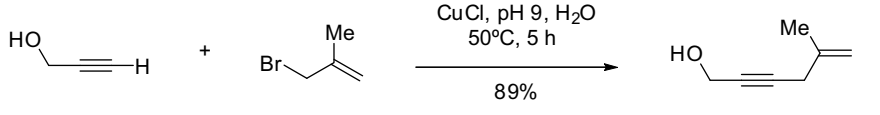
Trost and coworkers reported the use of catalytic diethylaluminum chloride as a Lewis acid on a closely related system to obtain the enantiomerically enriched alcohol in quantitative yield.[273]



Under analogous conditions, acetylides can be alkylated with oxetane via catalysis by BF_3•OEt_2, as described by Wessig and coworkers.[274]

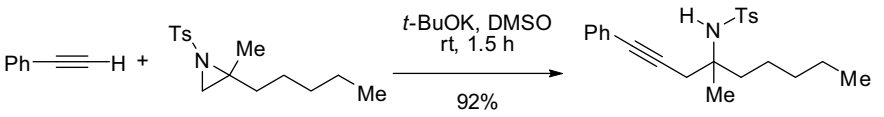


Copper-promoted acetylinic alkylation reactions have also been reported. The mild conditions described in the example below are advantageous compared to methods that require cryogenic temperatures and pyrophoric reagents.[275]



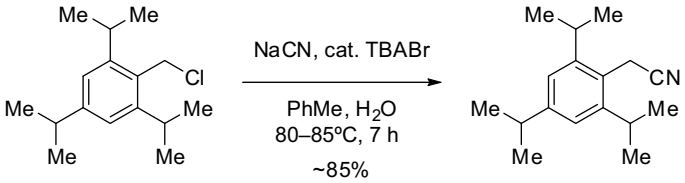
[272]Reddy, M. S.; Narender, M.; Rao, K. R. *Tetrahedron* **2007**, *63*, 11011–11015.
[273]Trost, B. M.; Ball, Z. T.; Laemmerhold, K. M. *J. Am. Chem. Soc.* **2005**, *127*, 10028–10038.
[274]Wessig, P.; Mueller, G.; Kuehn, A.; Herre, R.; Blumenthal, H.; Troelenberg, S. *Synthesis* **2005**, 1445–1454.
[275]Alegret, C.; Santacana, F.; Riera, A. *J. Org. Chem.* **2007**, *72*, 7688–7692.

Acetylenes can be reacted with activated aziridines to afford homopropargylic amine derivatives in good yield.[276] It has been reported that potassium *tert*-butoxide base in dimethylsulfoxide is optimal for these systems.

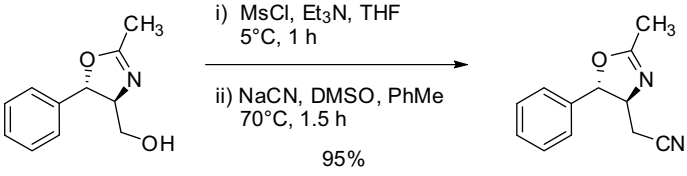


1.6.1.14 Alkylation of Cyanide Ion—Preparation of Nitriles The use of cyanide anion for the preparation of nitriles (or amines via nitrile reduction) is a useful and commonly employed operation in target-directed synthesis. Despite the serious health hazards presented by hydrogen cyanide, sodium and potassium cyanide salts are utilized extensively as nucleophiles under basic conditions. Highly sensitive HCN detection monitors are available to provide an early warning to scientists working in the vicinity of cyanide-containing reactions. Diligence in the use of these detectors, in addition to personal protective equipment and proper engineering controls, is essential to maintaining a safe working environment.

In the example below, 2,4,6-triisopropylbenzyl chloride was converted to the corresponding benzylic nitrile in a biphasic solvent system via phase transfer catalysis.[277] This nucleophilic substitution reaction requires heating, presumably due to considerable steric obstruction from the isopropyl substituents. For some substrates, the more expensive, but also commercially available, tetrabutylammonium cyanide may provide a rate advantage over the catalytic method described here. However, this reagent is exceedingly hygroscopic, which complicates storage and handling.

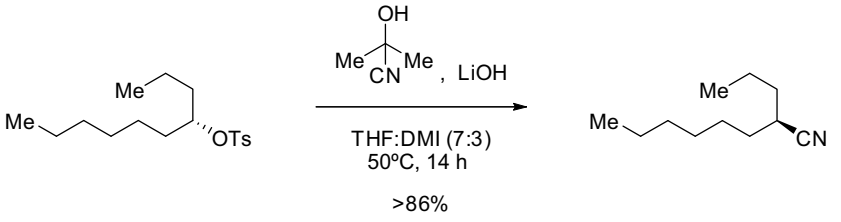


Cyanide salts can also be reacted with alkyl sulfonates to provide the expected nitriles in high yield. In the example below, a primary alcohol was converted to its mesylate under standard conditions. The subsequent reaction of sodium cyanide in dimethylsulfoxide-toluene provided the nitrile in excellent overall yield on multi-gram scale.[278]

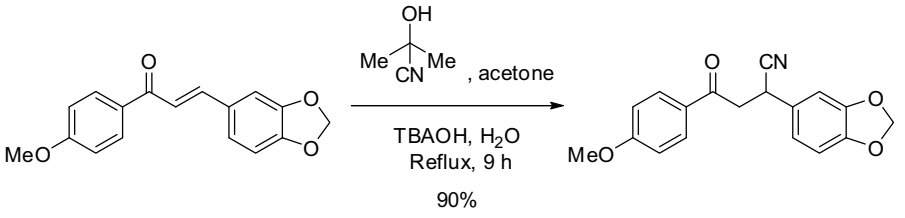


[276]Ding, C.-H.; Dai, L.-X.; Hou, X.-L. *Tetrahedron* **2005**, *61*, 9586–9593.
[277]Dozeman, G. J.; Fiore, P. J.; Puls, T. P.; Walker, J. C. *Org. Process Res. Dev.* **1997**, *1*, 137–148.
[278]Wu, G.; Wong, Y.; Steinman, M.; Tormos, W.; Schumacher, D. P.; Love, G. M.; Shutts, B. *Org. Process Res. Dev.* **1997**, *1*, 359–364.

Acetone cyanohydrin can also be employed as a convenient source of nucleophilic cyanide in the presence of a base. In the following example, an enantiomerically enriched secondary tosylate is converted to the corresponding nitrile in high yield and with clean inversion of stereochemistry. The authors reported that proper choice of base and solvent were critical to achieving high yield and reaction rate while preserving the stereochemical integrity of the product.[279] Optimal conditions included lithium hydroxide in a mixture of THF and 1,3-dimethyl-2-imidazolidinone (DMI).



In the example below, the action of tetrabutylammonium hydroxide on acetone cyanohydrin produced tetrabutylammonium cyanide *in situ*. This underwent a smooth, high-yielding conjugate addition to the enone to afford the β-cyanoketone in high yield.[280] This methodology was successfully scaled to approximately 10 kilograms during the preparation of an endothelin antagonist candidate. Although this example does not satisfy the definition of a nucleophilic aliphatic substitution reaction, it is included here to illustrate the utility of *in situ* derived tetrabutylammonium cyanide, as the isolated compound is exceedingly hygroscopic and difficult to handle. For more discussion on the nucleophilic addition of cyanide to polarized carbon−carbon multiple bonds, see Section 3.5.6.

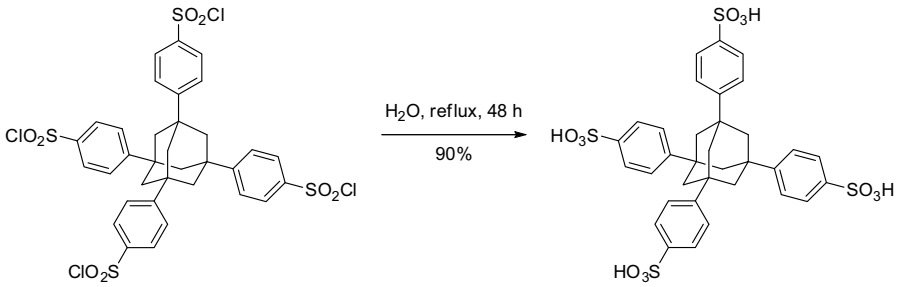


1.7 NUCLEOPHILIC SUBSTITUTION AT A SULFONYL SULFUR ATOM

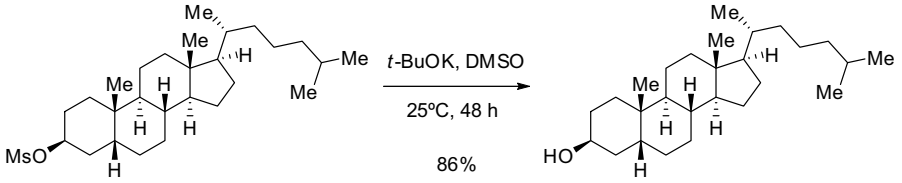
1.7.1 Attack by Oxygen

1.7.1.1 Hydrolysis of Sulfonic Acid Derivatives Sulfonyl halides are readily hydrolyzed to the parent sulfonic acids or sulfonate salts under acidic or basic conditions, respectively. In fact, most sulfonyl halides will hydrolyze in an aqueous environment in the absence of an additive, as the acidic products are themselves catalysts.[281]

[279]Hasegawa, T.; Kawanaka, Y.; Kasamatsu, E.; Ohta, C.; Nakabayashi, K.; Okamoto, M.; Hamano, M.; Takahashi, K.; Ohuchida, S.; Hamada, Y. *Org. Process Res. Dev.* **2005**, *9*, 774–781.
[280]Ellis, J. E.; Davis, E. M.; Brower, P. L. *Org. Process Res. Dev.* **1997**, *1*, 250–252.
[281]Hoffart, D. J.; Cote, A. P.; Shimizu, G. K. H. *Inorg. Chem.* **2003**, *42*, 8603–8605.

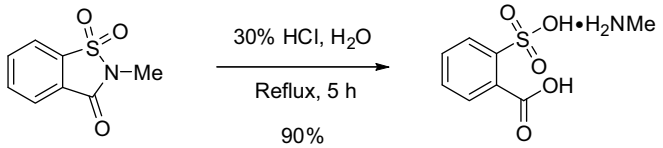


Sulfonic acid esters are also susceptible to hydrolysis. However, nucleophilic attack by water generally takes place at the carbon center, with concomitant displacement of the sulfonate moiety, as discussed in Section 1.2.1.4. Basic conditions are typically employed, and elimination is a concern. In a few rare cases, nucleophilic attack may occur at the sulfur center, as evidenced by net stereochemical retention at carbon in the following example.[282] The product is consistent with hydrolysis of the sulfonate, although steps were taken to ensure that water was not present in the reaction mixture.



Attack by water at the sulfur center is likely also operative during the hydrolysis of aryl sulfonate esters, although examples of this reaction are rare.[283,284]

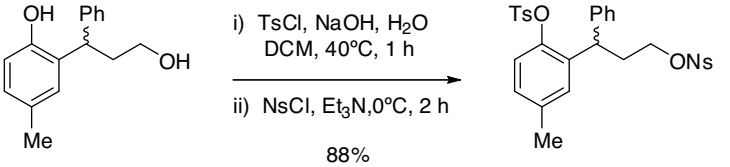
Sulfonamides can be converted to the corresponding sulfonic acids via hydrolysis promoted by strong acids. Alkaline hydrolysis is typically ineffective, although a few special exceptions have been reported.[285] In the example below, *N*-methyl saccharin was treated with hydrochloric acid at reflux temperature to provide the methylammonium salt of the sulfonic acid resulting from complete hydrolysis of the mixed sulfonamide. The authors advise that the initial hydrolysis product is the *N*-methylsulfonamide, which reacts further with water to provide the sulfonic acid.[286]



1.7.1.2 Formation of Sulfonate Esters Sulfonic acid esters are most commonly prepared by reaction of alcohols with sulfonyl halides under basic conditions. The use

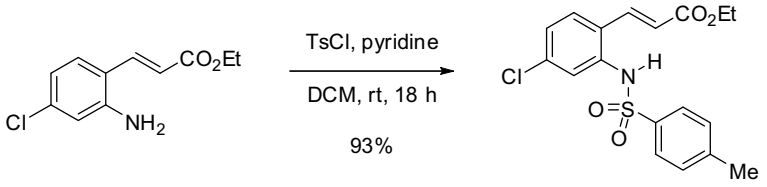
[282]Chang, F. C. *Tetrahedron Lett*. **1964**, 305–309.
[283]Suh, J.; Suh, M. K.; Cho, S. H. *J. Chem. Soc., Perkin Trans.* **1990**, *2*, 685–688.
[284]Kano, K.; Nishiyabu, R.; Asada, T.; Kuroda, Y. *J. Am. Chem. Soc.* **2002**, *124*, 9937–9944.
[285]Cuvigny, T.; Larcheveque, M. *J. Organomet. Chem.* **1974**, *64*, 315–321.
[286]Meadow, J. R.; Cavagnol, J. C. *J. Org. Chem.* **1951**, *16*, 1582–1587.

of methanesulfonyl chloride (MsCl) and *p*-toluenesulfonyl chloride (TsCl) is commonplace, as these reagents are employed in the activation step during conversion of alcohols to other functionalities (for example, see Section 1.6.1.4). In the following example, a diol intermediate was differentially protected with TsCl and *p*-nitrobenzenesulfonyl chloride (NsCl) by taking advantage of the relative acidities of the two alcohols.[287] This selective protection sequence was used in the authors' synthesis of the muscarinic receptor antagonist tolterodine.

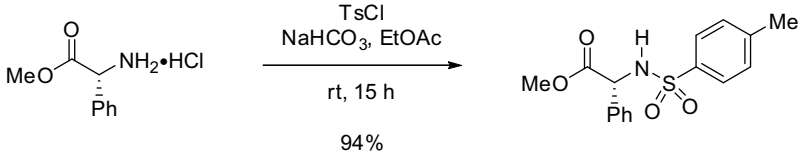


1.7.2 Attack by Nitrogen

1.7.2.1 Formation of Sulfonamides The reaction of primary and secondary amines with sulfonyl halides is analogous to the corresponding reaction with oxygen nucleophiles, although the superior nucleophilicity of most amines makes the formation of sulfonamides a milder, more efficient transformation.[288] During the development of novel COX-2 inhibitors for the treatment of pain and related inflammatory disorders, Caron and coworkers reported the preparation of an aryl sulfonamide via treatment of an aniline derivative with tosyl chloride and pyridine in dichloromethane.



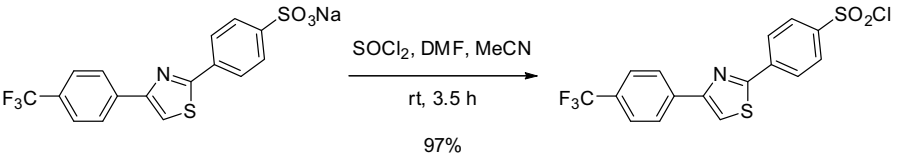
In the example below from Han and coworkers, the hydrochloride salt of (*R*)-phenylglycine methyl ester was treated with tosyl chloride in the presence of the mild base sodium bicarbonate to afford the sulfonamide in excellent yield at room temperature.[289] The authors were able to employ ethyl acetate as the solvent in this example, which is preferred for large scale applications due to its decreased environmental impact.



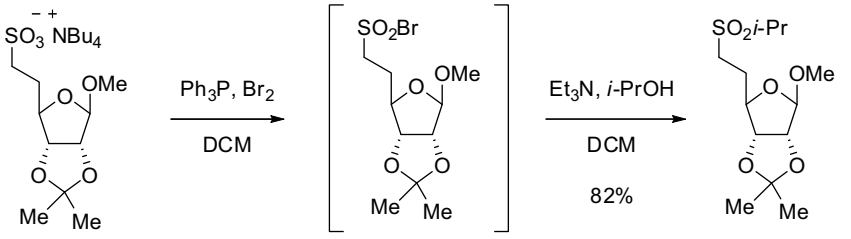
[287]De Castro, K. A.; Ko, J.; Park, D.; Park, S.; Rhee, H. *Org. Process Res. Dev.* **2007**, *11*, 918–921.
[288]Caron, S.; Vazquez, E.; Stevens, R. W.; Nakao, K.; Koike, H.; Murata, Y. *J. Org. Chem.* **2003**, *68*, 4104–4107.
[289]Han, Z.; Krishnamurthy, D.; Senanayake, C. H. *Org. Process Res. Dev.* **2006**, *10*, 327–333.

1.7.3 Attack by Halogen

1.7.3.1 Formation of Sulfonyl Halides Sulfonic acids or their salts can be converted to the corresponding sulfonyl halides with methods analogous to the conversion of carboxylic acids or carboxylate salts to carboxylic acid halides (see Section 2.24). Sulfonyl chlorides are most commonly prepared by treatment with thionyl chloride[290] or phosphorus pentachloride,[291] with the former preferred for large scale applications due to the ease of reagent removal by distillation. In the example below, treatment of an acetonitrile suspension of a sulfonic acid sodium salt with thionyl chloride in the presence of DMF provided the sulfonyl chloride in excellent yield.[292]

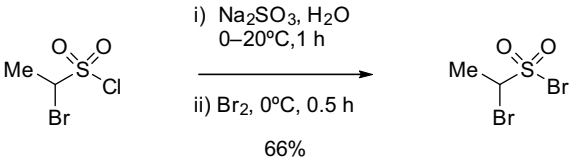


Likewise, sulfonyl bromides can be prepared from sulfonic acid salts by utilizing phosphorous pentabromide,[293] or preferably, via treatment with triphenylphosphine and bromine or *N*-bromosuccinimide.[294] In the example below, the tetrabutylammonium salt of a sulfonic acid was converted to the corresponding sulfonyl bromide with triphenylphosphine and bromine. As sulfonyl bromides are generally unstable, the product was not isolated, but rather converted immediately to the isopropyl sulfonate ester by quenching the reaction with isopropanol and triethylamine.

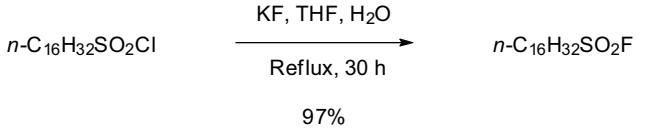


A less frequently utilized method involves treatment of sulfonyl hydrazines with bromine.[295] As a relatively large number of sulfonyl chlorides are commercially available, a convenient method for the preparation of sulfonyl bromides involves treatment of sulfonyl chlorides with sodium sulfite, followed by bromine, as described in the example below.[293]

[290]Morikawa, A.; Sone, T.; Asano, T. *J. Med. Chem.* **1989**, *32*, 42–46.
[291]Ponticello, G. S.; Freedman, M. B.; Habecker, C. N.; Lyle, P. A.; Schwam, H.; Varga, S. L.; Christy, M. E.; Randall, W. C.; Baldwin, J. J. *J. Med. Chem.* **1987**, *30*, 591–597.
[292]Ikemoto, N.; Liu, J.; Brands, K. M. J.; McNamara, J. M.; Reider, P. J. *Tetrahedron* **2003**, *59*, 1317–1325.
[293]Block, E.; Aslam, M.; Eswarakrishnan, V.; Gebreyes, K.; Hutchinson, J.; Iyer, R.; Laffitte, J. A.; Wall, A. *J. Am. Chem. Soc.* **1986**, *108*, 4568–4580.
[294]Huang, J.; Widlanski, T. S. *Tetrahedron Lett*. **1992**, *33*, 2657–2660.
[295]Palmieri, G. *Tetrahedron* **1983**, *39*, 4097–4101.

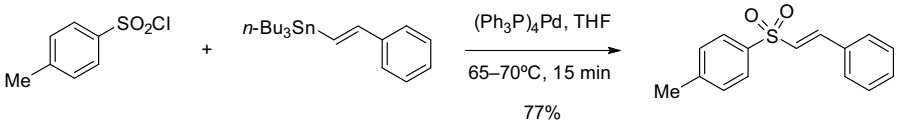


Sulfonyl fluorides are also most easily prepared from their sulfonyl chloride analogs through halogen exchange with potassium fluoride[296] or TBAF.[297] In the representative example below, a sulfonyl fluoride was obtained in high yield via treatment of a sulfonyl chloride with KF in refluxing THF. The sulfonyl fluoride products typically require purification through distillation, which can be damaging to glass and is better carried out in specialized equipment.



1.7.4 Attack by Carbon

1.7.4.1 Preparation of Sulfones The range of carbon-centered nucleophiles that can react with sulfonyl halide electrophiles to afford sulfone products with reasonable efficiency is rather limited. One complicating factor is that sulfone products typically have a lower pKa than the carbanion nucleophiles used to prepare them. Although stoichiometry may be adjusted to address this issue, the synthesis of alkyl sulfones is best accomplished via oxidation of sulfide or sulfoxide precursors (see Section 10.8.5). Nevertheless, the addition of certain carbon nucleophiles to sulfonyl halides has been accomplished under transition metal catalysis.[298] The example below from Labadie is representative and involves the use of a stoichiometric organostannane.



[296]Hyatt, J. A.; White, A. W. *Synthesis* **1984**, 214–217.
[297]Sun, H.; DiMagno, S. G. *J. Am. Chem. Soc.* **2005**, *127*, 2050–2051.
[298]Labadie, S. S. *J. Org. Chem.* **1989**, *54*, 2496–2498.